血管（静脈血栓症）に関連する有害事象

日本人のポサコナゾール新錠剤及び静注用溶液投与集団での血管（静脈血栓症）に関連する有害事象の要約を[表 2.7.4-85]に示す。

血管（静脈血栓症）に関連する有害事象は、ポサコナゾール群では認められなかった[付録 2.7.4-91]。

表 2.7.4-85　血管（静脈血栓症）に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Adverse Event Summary
for Vascular Disorders - Venous Thrombosis
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	77		38		115	
with one or more adverse events	0	(0.0)	1	(2.6)	1	(0.9)
with no adverse event	77	(100.0)	37	(97.4)	114	(99.1)
with drug-related† adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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血管（動脈血栓症）に関連する有害事象

日本人のポサコナゾール新錠剤及び静注用溶液投与集団での血管（動脈血栓症）に関連する有害事象の要約を[表 2.7.4-86]に示す。

血管（動脈血栓症）に関連する有害事象は認められなかった。

表 2.7.4-86　血管（動脈血栓症）に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Adverse Event Summary
for Vascular Disorders - Arterial Thrombosis
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	77		38		115	
with one or more adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with no adverse event	77	(100.0)	38	(100.0)	115	(100.0)
with drug-related† adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

2.7.4.2.2.6.11　新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象

2.7.4.2.2.6.11.1　経口懸濁液を投与した海外患者対象試験併合（計4試験）

非日本人のポサコナゾール経口懸濁液投与集団での新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象の要約を[表 2.7.4-87]に示す。

新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象（発現割合0%超）は、副腎腫瘤及び肝癌 各0.1%（1/1,033例）で[付録 2.7.4-92]、副作用は認められなかった。

表 2.7.4-87　新生物［新生物・悪性腫瘍の発現
（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］
に関連する有害事象の要約
ポサコナゾール経口懸濁液を投与した海外試験併合
（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）
Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Adverse Event Summary for
Neoplasm/Malignancy

	Posaconazole n = 1033	
Treatment-Emergent Adverse Events	2	(0.2)
Treatment-Related, Treatment-Emergent Adverse Events†	0	(0.0)
Serious Adverse Events	1	(0.1)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	1	(0.1)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	1	(0.1)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	0	(0.0)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.

2.7.4.2.2.6.11.2　　新錠剤及び静注用溶液を投与した海外患者対象試験併合（計2試験）

非日本人のポサコナゾール新錠剤及び静注用溶液投与集団での新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象の要約を[表 2.7.4-88]に示す。

新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象は認められなかった。

表 2.7.4-88　新生物［新生物・悪性腫瘍の発現
（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］
に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）
（All Treated Subjects）
Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Adverse Event Summary for
Neoplasm/Malignancy

	Posaconazole n = 509	
Treatment-Emergent Adverse Events	0	(0.0)
Treatment-Related, Treatment-Emergent Adverse Events†	0	(0.0)
Serious Adverse Events	0	(0.0)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	0	(0.0)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	0	(0.0)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

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2.7.4.2.2.6.11.3　　新錠剤及び静注用溶液を投与した国内患者対象試験（P101試験）

日本人のポサコナゾール新錠剤及び静注用溶液投与集団での新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象の要約を[表 2.7.4-89]に示す。

新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象は認められなかった。

表 2.7.4-89　新生物［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Adverse Event Summary
for Neoplasm/Malignancy
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	77		38		115	
with one or more adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with no adverse event	77	(100.0)	38	(100.0)	115	(100.0)
with drug-related† adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

2.7.4.2.2.6.12　　視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象

2.7.4.2.2.6.12.1　　経口懸濁液を投与した海外患者対象試験併合（計4試験）

非日本人のポサコナゾール経口懸濁液投与集団での視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約を[表 2.7.4-90]に示す。

視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象（発現割合0%超）は、視力障害0.2%（2/1,033例）で[付録 2.7.4-93]、副作用は認められなかった。

表 2.7.4-90　視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約
ポサコナゾール経口懸濁液を投与した海外試験併合
（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）
Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Adverse Event Summary for
Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances

	Posaconazole n = 1033	
Treatment-Emergent Adverse Events	2	(0.2)
Treatment-Related, Treatment-Emergent Adverse Events†	0	(0.0)
Serious Adverse Events	1	(0.1)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	1	(0.1)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	0	(0.0)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	0	(0.0)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.

2.7.4.2.2.6.12.2　　新錠剤及び静注用溶液を投与した海外患者対象試験併合（計2試験）

非日本人のポサコナゾール新錠剤及び静注用溶液投与集団での視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約を[表 2.7.4-91]に示す。

視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象（発現割合0%超）は、視力障害0.6%（3/509例）で[付録 2.7.4-94]、副作用は認められなかった。

表 2.7.4-91　視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）

（All Treated Subjects）
Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Adverse Event Summary for
Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances

	Posaconazole n = 509	
Treatment-Emergent Adverse Events	3	(0.6)
Treatment-Related, Treatment-Emergent Adverse Events†	0	(0.0)
Serious Adverse Events	0	(0.0)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	0	(0.0)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	0	(0.0)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

2.7.4.2.2.6.12.3　　新錠剤及び静注用溶液を投与した国内患者対象試験（P101試験）

日本人のポサコナゾール新錠剤及び静注用溶液投与集団での視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約を[表 2.7.4-92]に示す。

視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象は、ポサコナゾール群では認められなかった[付録 2.7.4-95] [付録 2.7.4-96]。

表 2.7.4-92　視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の要約
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Adverse Event Summary
for Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	77		38		115	
with one or more adverse events	0	(0.0)	4	(10.5)	4	(3.5)
with no adverse event	77	(100.0)	34	(89.5)	111	(96.5)
with drug-related† adverse events	0	(0.0)	4	(10.5)	4	(3.5)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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2.7.4.2.2.6.13　　注入部位反応に関連する有害事象

ポサコナゾール静注用溶液の注入部位反応に関連する安全性は、末梢静脈内投与及び中心静脈内投与の投与経路別に評価した。

2.7.4.2.2.6.13.1　　静注用溶液を投与した海外第Ⅰ相試験（P04985、P06356及びP07783）

本項では、ポサコナゾール静注用溶液を末梢静脈内投与した際の安全性を評価するために、非日本人健康被験者を対象に注入時間90分間で末梢静脈内投与したP04985試験、並びに注入時間30分間で末梢静脈内投与したP06356試験及びP07783試験の結果を記載する。なお、注入部位反応は、P04985試験では圧痛、紅斑、腫脹、硬結、触知可能な静脈索の症状及び明らかな静脈血栓症の有無に基づきGradeを評価し、P06356試験ではShort peripheral catheter thrombophlebitis（SPCT）スコアを用いて評価した（[資料5.3.3.1.8: P04985] 9.5.1.2.6項、[資料5.3.3.1.9: P06356] 9.5.1.2項）。

本項では、以下の基準に合致する注入部位反応を特に注目した有害事象と定義し、評価した。

1) P04985及びP06356試験で発現した注入部位反応のうち、重症度がGrade（又は総スコア）2を超えるもの
2) 有害事象として報告されている
3) 血栓性静脈炎と診断されているか又は血栓性静脈炎に関連する症状（紅斑、圧痛、熱感、硬結又は腫脹など）である

なお、「注入部位」又は「血栓性静脈炎／静脈炎」の文字を含む事象を注入部位反応とし、注入部位血腫及び錯感覚は、注入部位反応には含めなかった。また、「カテーテル留置部位」又は「適用部位」の文字を含む有害事象は、採血用のカニューレ留置部位反応を意味することから注入部位反応に含めなかった。さらに、P04985試験では、特に注目した有害事象に加え、有害事象として報告されなかった注入部位反応も評価に含めた。

以下に、試験ごとの結果を示す。

2.7.4.2.2.6.13.1.1　　P04985試験：90分間単回末梢静脈内投与（コホート１）

P04985試験のコホート1では、Treatment Aでポサコナゾール静注用溶液200 mgを90分かけて単回末梢静脈内投与し、安全性を確認した後、コホート2のTreatment Bでポサコナゾール静注用溶液400 mgを90分かけて単回末梢静脈内投与する計画であった。

本試験のコホート1には、12例が組み入れられた［200 mg群：9例、プラセボ（5%ブドウ糖溶液）群：3例］。

ポサコナゾール静注用溶液200 mgを単回投与された被験者9例のうち6例で注入部位反応が発現した。このうち2例（22%）の注入部位反応が、特に注目した有害事象の基準に合致した。2例とも単回投与後（注入から約5時間後）に発現し、1例は末梢性浮腫（被験者番号[redacted]）、もう1例は注入部位疼痛（被験者番号[redacted]）であった。いずれもGrade 3の注入部位反応と評価され、4日後（被験者番号[redacted]）及び11日後（被験者番号[redacted]）に回復した。

注入部位反応が発現した6例のうち、特に注目した有害事象の基準に合致しなかった4例（44%）で発現した注入部位反応は、いずれも単回投与後に認められ、程度が Grade 1の紅斑、腫脹、硬結及び触知可能な静脈索を伴わない注入部位の圧痛が2例、Grade 2の紅斑及び一定程度の腫脹を伴い、硬結及び触知可能な静脈索を伴わない注入部位の圧痛が1例、Grade 3の紅斑、腫脹、硬結又は触知可能な静脈索を伴う注入部位の圧痛が1例であった。これらの事象は投与から6～22時間後に発現し、2～19日目に回復した。

本試験は、これらの注入部位反応により、早期中止（コホート1の Treatment A の200 mg 単回投与後）することとなった。

2.7.4.2.2.6.13.1.2　　P06356試験：30分間単回末梢静脈内投与（パート1）

P06356試験では、P04985試験の結果から、注入部位反応の発現を抑えるために、注入時間を90分から30分に短縮して末梢静脈内投与を実施した。また、本試験は、ポサコナゾール静注用溶液（0～300 mg）を単回投与するパート1と反復投与するパート2からなるものの、パート2の100 mg の反復投与時に注入部位反応のため試験は中止された。パート1の結果は本項に記載し、パート2の100 mg 反復末梢静脈内投与時の結果は[2.7.4.2.2.6.13.1.4 項]に記載する。

P06356試験のパート1は、6つのコホートからなり、各コホートに12例［実薬0～300 mg 群 : 9例、プラセボ（5%ブドウ糖溶液）群：3例］が組み入れられた。なお、0 mg 群にはポサコナゾールを含まない静注用溶媒のみが投与された（以下、静注用溶媒群）。

P06356試験の単回投与（パート1）で認められた血栓性静脈炎及び注入部位反応の要約を[表2.7.4-93]に示す。

ポサコナゾール静注用溶液（50～300 mg）を30分かけて単回末梢静脈内投与した45例（各群9例）のうち、4%（2/45例）で血栓性静脈炎が報告された（被験者番号[redacted]及び[redacted]）。その内訳は、ポサコナゾール200 mg 群9例中1例及びポサコナゾール300 mg 群9例中1例であった。いずれの被験者でも、注入部位反応が投与1日目に報告され、1日目（被験者番号[redacted]）及び3日目（被験者番号[redacted]）に血栓性静脈炎に進行した［血栓性静脈炎の総スコアは重症度判定基準で2を超えた（判定基準については[資料5.3.3.1.9: P06356]を参照）］。1件が中等度、1件が軽度と判断された。これらの事象は無処置で、6日目及び8日目に回復した。

血栓性静脈炎以外の注入部位反応の有害事象が13%（9/72例）で報告された（静注用溶媒群：2例、50 mg 群：1例、200 mg 群：1例、250 mg 群：2例及び300 mg 群：3例）。これらの注入部位反応は1日目又は2日目に発現し、1～8日目に回復した。

表 2.7.4-93　　血栓性静脈炎及び注入部位反応の要約
健康被験者へのポサコナゾール静注用溶液末梢静脈内投与試験（P06356 試験）
（単回投与集団）（All Treated Subjects）

単回投与	Summary of Adverse Experiences (number (%) of subjects)							
用量	Placebo	0 mg†	50 mg	100 mg	200 mg	250 mg	300 mg	Total
例数	18	9	9	9	9	9	9	72
血栓性静脈炎 n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (11)	2 (3)
注入部位反応 n (%)	0 (0)	2 (22)	1 (11)	0 (0)	1 (11)	2 (22)	3 (33)	9 (13)

†静注用溶媒（ポサコナゾール非含有）群

[資料5.3.3.1.9: P06356]
治験薬の用法・用量
ポサコナゾール静注用溶液50、100、200、250及び300 mg、静注用溶媒（ポサコナゾール非含有）及びプラセボ（5%ブドウ糖溶液）を30分かけて単回末梢静脈内投与

2.7.4.2.2.6.13.1.3　　P07783試験：30分間単回末梢静脈内投与（パート1）

P07783試験のパート1では、Treatment B でポサコナゾール静注用溶液300 mg を30分かけて単回末梢静脈内投与した。

ポサコナゾール静注用溶液300 mg を単回投与した13例のうち1例（7%）（被験者番号[redacted]）で血栓性静脈炎（報告事象名：静脈炎）が報告された。当該事象は、投与1日目（投与から約8時間後）に軽度の紅斑、疼痛、腫脹及び温感が認められたが、3日後に無処置で回復した。

2.7.4.2.2.6.13.1.4　　P06356試験、30分間反復末梢静脈内投与（パート2）

P06356試験のパート2では、18例の被験者が2つのコホートに組み入れられた（コホート7：静注用溶媒群9例及びプラセボ群3例、コホート8：100 mg 群5例及びプラセボ群1例）。

ポサコナゾール静注用溶液100 mg を30分かけて反復末梢静脈内投与した5例のうち3例に血栓性静脈炎が報告された。また、プラセボ（5%ブドウ糖溶液）群及び静注用溶媒群で各1例血栓性静脈炎が報告された。これらの結果に基づき、本試験は中止された。血栓性静脈炎を発現した5例中4例では、本事象発現前（投与1日目又は2日目）に注入部位反応が発現した。血栓性静脈炎の発現時期は、プラセボ（5%ブドウ糖溶液）群及び静注用溶媒群で投与9日目、100 mg 群で投与2日目、3日目及び4日目であった。血栓性静脈炎の程度は5例中4例で中等度、1例（プラセボ群）で軽度であった。血栓性静脈炎が認められた被験者は、いずれも投与を中止した（血栓性静脈炎のため：4例、治験中止のため：1例）。1例がアセトアミノフェン、別の1例がフルクロキサシリンによる治療を受けた。いずれも投与5～17日目に回復した。

血栓性静脈炎以外の注入部位反応は7例（39%）で報告され、その内訳は、静注用溶媒群3例（33%）及び100 mg 群4例（80%）であった。注入部位反応の発現時期は、投与1～5日目であった。上述したように、注入部位反応が認められた7例中4例で2日目、3日目、4日目及び9日目に血栓性静脈炎（血栓性静脈炎の総スコアが重症度判定基準で2を超えた）が発現した。なお、被験者番号[redacted]（静注用溶媒群）は注入部位反応が5日目に回復し、血栓性静脈炎が9日目に発現した。それ以外の注入部位反応は3～10日目に回復した。

P06356試験の反復投与（パート2）で認められた血栓性静脈炎及び注入部位反応の概要を[表2.7.4-94]に示す。

表 2.7.4-94　　血栓性静脈炎及び注入部位反応の要約
健康被験者へのポサコナゾール静注用溶液末梢静脈内投与試験（P06356 試験）
（反復投与集団）（All Treated Subjects）

反復投与	Summary of Adverse Experiences (number (%) of subjects)			
用量	Placebo	0 mg†	100 mg	Total
例数	4	9	5	18
血栓性静脈炎 n (%)	1 (25)	1 (11)	3 (60)	5 (28)
注入部位反応 n (%)	0 (0)	3 (33)	4 (80)	7 (39)

†静注用溶媒（ポサコナゾール非含有）群

[資料5.3.3.1.9: P06356]
治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール静注用溶液100、200及び300 mg、静注用溶媒（ポサコナゾール非含有）及びプラセボ（5%ブドウ糖溶液）を30分かけて QD（1日目は BID）10日間反復末梢静脈内投与

2.7.4.2.2.6.13.2　　静注用溶液を投与した国内第Ⅰ相試験（P067試験）

日本人健康被験者を対象に、ポサコナゾール静注用溶液300 mg を30分かけて単回末梢静脈内投与した P067試験の結果を記載する。注入部位反応の重症度は、P06356試験と同様の SPCT スコアを用いて評価した。

P067試験のパート1の第3期には、300 mg 群6例、静注用溶媒群6例及びプラセボ群4例が組み入れられた。いずれの投与群でも注入部位反応は認められなかった。

2.7.4.2.2.6.13.3　　静注用溶液を投与した海外患者対象試験（P05520試験）

侵襲性真菌症のハイリスク患者を対象に、ポサコナゾール静注用溶液200 mg 又は300 mg を90分間かけて中心静脈内投与した P05520試験の結果を記載する。特に注目した注入部位反応の有害事象の定義は[表 2.7.4-6]に示す。

ポサコナゾール静注用溶液を投与した集団での注入部位反応に関連する有害事象の要約を[表 2.7.4-95]に示す。

よくみられた注入部位反応に関連する有害事象（発現割合1%以上）は、カテーテル留置部位疼痛2.2%（6/268例）、注入部位血栓1.5%（4/268例）、カテーテル留置部位紅斑、カテーテル留置部位炎症及び注入部位疼痛 各1.1%（3/268例）であった[付録 2.7.4-97]。副作用（発現割合0%超）は、注入部位血栓0.7%（2/268例）及び注入部位静脈炎0.4%（1/268例）であった[付録 2.7.4-98]。

なお、本試験のコホート3では、同一の末梢静脈カテーテルからの投与は1回のみ許容されており、9例の被験者（被験者番号[redacted]）が末梢静脈内投与された。このうち、1例の被験者で、末梢静脈内投与時に中等度のカテーテル留置部位疼痛が発現したが、治験薬との因果関係は考えにくいと判断された。また、コホート1の被験者1例が、治験実施計画書違反によりポサコナゾール静注用溶液を9日間連続で末梢静脈内投与された。当該被験者では血栓性静脈炎が発現した[2.7.4.2.2.6.10.2 項]。

表 2.7.4-95　注入部位反応に関連する有害事象の要約
ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）
（All Treated Subjects）
Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Adverse Event Summary for
Infusion Site Reactions after Central Line Infusion of Intravenous Posaconazole

	Posaconazole n = 268	
Treatment-Emergent Adverse Events	32	(11.9)
Treatment-Related, Treatment-Emergent Adverse Events†	3	(1.1)
Serious Adverse Events	0	(0.0)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	0	(0.0)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	2	(0.7)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.

注：本表は、全コホート（コホート0～3）の静脈内投与期のデータを示す。
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート0：　ポサコナゾール静注用溶液200 mg 又はプラセボを単回中心静脈内投与し、その約12時間後にポサコナゾール経口懸濁液400 mg を単回経口投与、その後 BID にて合計11回経口投与
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

2.7.4.2.2.6.13.4　　静注用溶液を投与した国内患者対象試験（P101試験）

日本人深在性真菌症患者を対象に、ポサコナゾール静注用溶液300 mg を90分かけて中心静脈内投与した P101試験の結果を記載する。特に注目した注入部位反応の有害事象の定義は[表 2.7.4-6]に示す。

ポサコナゾール静注用溶液を投与した集団での注入部位反応に関連する有害事象の要約を[表 2.7.4-96]に示す。注入部位反応に関連する有害事象は認められなかった。

表 2.7.4-96　注入部位反応に関連する有害事象の要約
ポサコナゾール静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）
ポサコナゾール群（ASaT）
Adverse Event Summary
in MK-5592 Treatment Group
for Infusion Site Reactions after Central Line Infusion of Intravenous Posaconazole
Cohort 1 and 2 (ASaT)

	MK-5592	
	n	(%)
Subjects in population	19	
with one or more adverse events	0	(0.0)
with no adverse event	19	(100.0)
with drug-related† adverse events	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで 300 mg を QD にて投与

2.7.4.2.2.6.14　　腎機能障害に関連する有害事象

2.7.4.2.2.6.14.1　　静注用溶液を投与した海外第Ⅰ相試験（P04985、P06356及びP07783）

非日本人健康被験者を対象にポサコナゾール静注用溶液を末梢静脈内投与した72例において、腎機能障害に関連する有害事象は報告されなかった。

2.7.4.2.2.6.14.2　　静注用溶液を投与した国内第Ⅰ相試験（P067試験）

日本人健康被験者を対象に、ポサコナゾール静注用溶液（300 mg）を単回末梢静脈内投与したP067試験のパート1の第3期には、300 mg 群6例、静注用溶媒群6例及びプラセボ群4例が組み入れられた。いずれの投与群でも腎機能障害に関連する有害事象は認められなかった。

2.7.4.2.2.6.14.3　　静注用溶液を投与した海外患者対象試験（P05520試験）

非日本人のポサコナゾール静注用溶液投与集団での腎機能障害に関連する有害事象の要約を[表 2.7.4-97]に示す。

腎機能障害に関連する有害事象（発現割合0%超）は、急性腎障害1.5%（4/268例）、腎不全及び腎機能障害 各0.4%（1/268例）で[付録 2.7.4-99]、副作用（発現割合0%超）は、急性腎障害0.4%（1/268例）であった[付録 2.7.4-100]。

表 2.7.4-97　　腎機能障害に関連する有害事象の要約
ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）
（All Treated Subjects）
Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Adverse Event Summary for
Renal Effects of Cyclodextrin with Intravenous Infusion of Posaconazole

	Posaconazole n = 268	
Treatment-Emergent Adverse Events	6	(2.2)
Treatment-Related, Treatment-Emergent Adverse Events†	1	(0.4)
Serious Adverse Events	3	(1.1)
Treatment-Related Serious Adverse Events	0	(0.0)
Severe/Life-Threatening Treatment-Emergent Adverse Events	3	(1.1)
Severe/Life-Threatening Treatment-Related, Treatment-Emergent Adverse Events	0	(0.0)
Adverse Events Leading to Death	2	(0.7)
Treatment-Related, Adverse Events Leading to Death	0	(0.0)
Adverse Events Leading to Study Drug Discontinuation‡	1	(0.4)
Treatment-Related, Adverse Events Leading to Study Drug Discontinuation	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study Medication Withdrawn.

注：本表は、全コホート（コホート0～3）の静脈内投与期のデータを示す。
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート0：　ポサコナゾール静注用溶液200 mg 又はプラセボを単回中心静脈内投与し、その約12時間後にポサコナゾール経口懸濁液400 mg を単回経口投与、その後 BID にて合計11回経口投与
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

2.7.4.2.2.6.14.4　　静注用溶液を投与した国内患者対象試験（P101試験）

日本人のポサコナゾール静注用溶液投与集団での腎機能障害に関連する有害事象の要約を[表2.7.4-98]に示す。

腎機能障害に関連する有害事象は認められなかった。

表 2.7.4-98　腎機能障害に関連する有害事象の要約
ポサコナゾール静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）
ポサコナゾール群（ASaT）
Adverse Event Summary
in MK-5592 Treatment Group
for Renal Effects of Cyclodextrin with Intravenous Infusion of Posaconazole
Cohort 1 and 2 (ASaT)

	MK-5592	
	n	(%)
Subjects in population	19	
with one or more adverse events	0	(0.0)
with no adverse event	19	(100.0)
with drug-related† adverse events	0	(0.0)
with toxicity grade 3-5 adverse events	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)
with serious adverse events	0	(0.0)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)
† Determined by the investigator to be related to the drug.		
‡ Study medication withdrawn.		

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで 300 mg を QD にて投与

2.7.4.2.3　　個別有害事象の文章による説明

重篤な有害事象（死亡に至った有害事象を含む）及びその他の重要な有害事象の個別症例の叙述は各治験総括報告書に示す。このうち、ポサコナゾール群で認められた重篤な副作用（死亡に至った副作用を含む）の叙述については、[付録 2.7.6.2.22-3]、[付録 2.7.6.2.23-4]（P05615及び P05520試験）及び[付録 2.7.6.3.2-3]、[付録 2.7.6.3.1-3]、[付録 2.7.6.4.1-6]、[付録 2.7.6.3.5-14]（C/I98-316、P01899、P00041及び P101試験）にも示す。

2.7.4.3　　臨床検査値の評価

本項では、健康被験者を対象とした試験結果の要約を[2.7.4.3.1 項]に、患者を対象とした予防投与試験及び治療試験の結果を[2.7.4.3.2 項]及び[2.7.4.3.3 項]に示す。

臨床検査値の程度分類は CTC 又は CTCAE を用いた[付録 2.7.4-101] [付録 2.7.4-102]。

2.7.4.3.1　　健康被験者を対象とした試験結果の要約

2.7.4.3.1.1　　経口懸濁液（旧錠剤又は旧カプセルを含む）を投与した第 I 相試験（非日本人）

健康被験者を対象としたポサコナゾール経口懸濁液（旧錠剤又は旧カプセルを含む）の第 I 相試験では、血液学的検査、血液生化学検査及び尿検査をスクリーニング時、ベースライン時及びポサコナゾール経口懸濁液投与後に実施した。

血液学的検査及び尿検査では、臨床的に意義のある所見は認められなかった。血液生化学検査では、肝酵素（ALT、AST 及び GGT）の一過性で軽度の増加［基準値上限（ULN）の1倍超～5倍］が一部の被験者に認められたが、CTC Grade 3又は4への変動は認められなかった。そのほかに血液生化学検査で臨床的に意義のある所見は認められなかった[資料5.3.3.1.12: C96_104] [資料5.3.3.1.13: P02418] [資料5.3.3.3.1: P02810] [資料5.3.3.3.2: P02811] [資料5.3.1.1.2: P02812] [資料5.3.3.1.5: I95_098] [資料5.3.1.2.1: I95_099] [資料5.3.3.1.6: I96_089] [資料5.3.1.2.2: I96_099] [資料5.3.3.1.10: P04547] [資料5.3.3.1.11: P05270] [資料5.3.3.3.5: I97_195] [資料5.3.3.3.4: P01940] [資料5.3.3.4.10: P02489] [資料5.3.3.4.6: P02862] [資料5.3.3.4.12: C96_120] [資料5.3.3.4.2: C96_173] [資料5.3.3.4.4: C96_201] [資料5.3.3.4.3: I96_207] [資料5.3.3.4.1: I97_016]。

また、初期のポサコナゾール臨床開発プログラム（I95-098及び I96-089試験）では、腎機能への影響を評価するため、ポサコナゾール経口懸濁液の単回又は反復投与後に特別な尿検査（尿比重、クレアチニン、ナトリウム、カリウム、カルシウム、N-アセチルグルコサミニダーゼ及び β_2ミクログロブリンの尿排泄）を実施した。その結果、持続する異常又は臨床的に意義のある所見は認められなかった。さらに、播種性血管内凝固症候群を評価する目的で、フィブリノゲン、フィブリンーフィブリノゲン分解産物、トロンビン／アンチトロンビンⅢ複合体及びハプトグロビンの濃度をポサコナゾール経口懸濁液の単回又は反復投与後に測定した結果、臨床的に意義のある所見は認められなかった[資料5.3.3.1.5: I95_098] [資料5.3.3.1.6: I96_089]。

2.7.4.3.1.2　　新錠剤を投与した第 I 相試験（計5試験）（非日本人）

健康被験者を対象としたポサコナゾール新錠剤の第 I 相試験では、血液学的検査、血液生化学検査及び尿検査をスクリーニング時、ベースライン時及びポサコナゾール新錠剤投与後に実施した。

1)　単回投与試験（P04975、P07691、P07764試験及び P07783試験パート1）

ポサコナゾール新錠剤を単回投与した健康被験者73例で、血液学的検査、血液生化学検査及び

尿検査に臨床的に意義のある所見は認められなかった[資料5.3.1.2.3: P04975] [資料5.3.1.2.4: P07691] [資料5.3.3.4.13: P07764] [資料5.3.1.1.1: P07783]。

なお、P07764試験の1例でメトクロプラミドの4回目の投与後（ポサコナゾールの投与開始前日）に臨床検査値の有害事象（CPK の増加：4386 U/L）が報告されたものの、ポサコナゾール新錠剤投与前に認められていたことからポサコナゾールとの因果関係はなしと判定された。

2)　反復投与試験（P05637試験及び P07783試験パート2）

ポサコナゾール新錠剤を反復投与した健康被験者31例で、血液学的検査及び尿検査に臨床的に意義のある所見は認められなかった。血液生化学検査では、軽度から中等度の一過性の肝酵素（ALT 及び AST）の増加が認められたものの、Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者はいなかった。また、これ以外に臨床的に意義のある臨床検査値の変化は認められなかった[2.7.4.2.1.2 項] [資料5.3.3.1.7: P05637] [資料5.3.1.1.1: P07783]。

2.7.4.3.1.3　　静注用溶液を投与した第Ⅰ相試験（計3試験）（非日本人）

健康被験者を対象としたポサコナゾール静注用溶液の第Ⅰ相試験（P04985、P07783及び P06356試験）では、血液学的検査、血液生化学検査及び尿検査をスクリーニング時、ベースライン時及びポサコナゾール静注用溶液投与後に実施した。なお、静注用溶液を反復投与した被験者数は少なく、反復投与期間も短い（2～4日）ことから、臨床検査値の経時的な変動は評価しなかった。

ポサコナゾール静注用溶液を投与した健康被験者72例で、血液学的検査及び尿検査に臨床的に意義のある所見は認められなかった[資料5.3.3.1.8: P04985] [資料5.3.1.1.1: P07783] [資料5.3.3.1.9: P06356]。

血液生化学検査では、200 mg を単回投与した1例（P04985試験）で有害事象として AST、ALT、ALP 及び GGT の増加を伴う「肝機能検査異常」が報告された。当該事象は投与3日目に発現、14日目に回復し、程度は中等度で治験薬との因果関係はありと判定された。当該事象の他に臨床的に意義のある所見は認められなかった。また、Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者はいなかった。

2.7.4.3.1.4　　新錠剤及び静注用溶液を投与した第Ⅰ相試験（P067試験）（日本人）

日本人の健康被験者を対象としたポサコナゾール新錠剤及び静注用溶液の第Ⅰ相試験（P067試験）では、血液学的検査、血液生化学検査及び尿検査をスクリーニング時、ベースライン時及び治験薬投与後に実施した。

1)　単回経口投与及び単回静脈内投与（パート1）

パート1の健康被験者16例（ポサコナゾール投与12例、プラセボ投与4例）で、血液学的検査、血液生化学検査及び尿検査に臨床的に意義のある所見は認められなかった[資料5.3.3.1.4: P067]。

2)　反復経口投与（パート2）

パート2の健康被験者16例（ポサコナゾール投与12例、プラセボ投与4例）のうち、副作用と判定された ALT 増加がプラセボ群で1例認められたが、血液学的検査、血液生化学検査及び尿検査に臨床的に意義のある所見は認められなかった[資料5.3.3.1.4: P067]。

2.7.4.3.2　　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.3.2.1　　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及び P01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）では、血液学的検査及び血液生化学検査をベースライン時、治験薬投与中及びフォローアップ時に実施した。臨床検査値の程度分類は CTC を用いた。

臨床検査値は、肝機能検査の4項目（ALP、ALT、AST 及び総ビリルビン）、カリウムの2項目（高カリウム血症及び低カリウム血症）及び腎機能検査の1項目（クレアチニン）を評価した。これらの臨床検査項目の、C/I98-316試験は投与開始から16週間、P01899試験は無作為割付から治験薬の最終投与7日後までの最終測定時点のベースラインからの値の変動を[付録 2.7.4-103]に示した。また、ベースライン値の Grade から試験期間中の最も重い Grade への変動を[付録 2.7.4-104]に、ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-99]にそれぞれ示す。

<u>肝機能関連の臨床検査値</u>

ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者の割合は、いずれの臨床検査項目でも、ポサコナゾール群とフルコナゾール群で類似していた[表 2.7.4-99]。なお、いずれの投与群でも変動した被験者の割合が高かった ALT では、共に半数近い被験者の ALT のベースライン値が高値であった[付録 2.7.4-105]。

<u>代謝機能関連の臨床検査値</u>

低カリウム血症のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者の割合は、ポサコナゾール群13%（73/560例）とフルコナゾール群10%（52/507例）で類似していた[表 2.7.4-99]。また、高カリウム血症の Grade が1以上の被験者の割合は両投与群で類似していた[付録 2.7.4-104]。

<u>腎機能関連の臨床検査値</u>

ポサコナゾール経口懸濁液を投与した被験者で、クレアチニンのベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者の割合は、ポサコナゾール群2%（10/575例）とフルコナゾール群2%（8/515例）で、いずれも2%であった[表 2.7.4-99]。

表 2.7.4-99　血液生化学検査項目のベースライン値が CTC Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

	Number (%) of Subjects		
Laboratory Parameter	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Aspartate Aminotransferase (AST)	21/552 (4)	17/490 (3)	2/58 (3)
Alanine Aminotransferase (ALT)	65/560 (12)	54/502 (11)	1/56 (2)
Alkaline Phosphatase	13/552 (2)	9/491 (2)	1/57 (2)
Total Bilirubin	44/561 (8)	39/505 (8)	7/57 (12)
Hyperkalemia	6/560 (1)	8/507 (2)	0/56
Hypokalemia	73/560 (13)	52/507 (10)	14/56 (25)
Creatinine	10/575 (2)	8/515 (2)	1/58 (2)

CTC：共通毒性基準、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ
注：　データは X/Y として示す。X は定義を満たす被験者数、Y はベースライン後の1時点以上で該当する検査値が得られた被験者数を示す。
治験薬の用法・用量（TID：1日3回、QD：1日1回、BID：1日2回）
C/I98-316試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾールカプセル剤400 mg を QD 経口投与
P01899試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾール経口懸濁液400 mg を QD 経口投与
イトラコナゾール群：イトラコナゾール内用液200 mg を BID 経口投与

2.7.4.3.2.2　　新錠剤を投与した後期第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

ポサコナゾール新錠剤の予防投与試験（P05615試験）では、血液学的検査及び血液生化学検査をベースライン時、治験薬投与中、治験薬の最終投与6日後までの最終測定時点及びフォローアップ時に実施した。臨床検査値の程度分類はCTCAEを用いた。

なお、200 mg コホートには、パート1A（ポサコナゾール新錠剤200 mg を投与1日目に BID、2日目以降はQD経口投与）の被験者のデータを含めた。300 mg コホートには、パート1B及びパート2（ポサコナゾール新錠剤300 mg を投与1日目に BID、2日目以降はQD経口投与）の被験者のデータを含めた。

1)　200 mg コホート

臨床検査項目のうち、クレアチニン、AST、ALT、ALP 及び総ビリルビンの平均値及びベースラインからの平均変化量を[表 2.7.4-100]に示す。

クレアチニンの平均値は14日目に増加した後、フォローアップ時にはベースライン値に戻る傾向を示した。AST の平均値は14日目以降に増加したが、フォローアップ時にはベースライン値に戻った。ALT の平均値は14日目以降に増加したが、フォローアップ時にはベースライン値に戻った。ALP の平均値は8日目以降に増加したが、フォローアップ時にはベースライン値に戻る傾向を示した。総ビリルビンの平均値は投与後にわずかに増加したが、フォローアップ時にはベースライン値に戻る傾向を示した。

表 2.7.4-100　来院別の血液生化学検査項目の平均値及びベースラインからの変化量
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（200 mg コホート）（All Treated Subjects）

Visit	Number of Subjects, All Treated Subjects 200 mg Cohort														
	Creatinine (μmol/L)			AST (U/L)			ALT (U/L)			ALP (U/L)			Total Bilirubin (μmol/L)		
	n	Mean Creatinine Con	Chg from BL	n	Mean AST Con	Chg from BL	n	Mean ALT Con	Chg from BL	n	Mean ALP Con	Chg from BL	n	Mean TBILI Con	Chg from BL
Baseline	20	72.8	-------	20	28.5	-------	20	39.7	-------	20	110.1	-------	20	9.6	-------
Day 3	20	66.4	-6.4	20	18.7	-9.8	20	28.5	-11.3	20	99.5	-10.6	20	13.0	3.3
Day 8	20	65.3	-7.5	18	19.5	-6.3	20	33.2	-6.5	20	148.7	38.6	20	15.5	5.8
Day 14	19	101.0	28.1	18	29.9	0.7	18	47.3	5.9	19	185.8	78.2	18	15.8	6.1
Day 21	17	96.5	23.8	16	33.4	8.1	16	62.2	32.3	15	266.1	151.7	16	12.8	2.8
Day 28	8	79.3	7.5	8	37.9	14.9	8	71.3	43.4	8	338.9	176.4	8	20.6	9.4
Endpoint	20	96.1	23.3	20	29.2	0.8	20	47.3	7.6	20	190.9	80.8	20	14.2	4.6
FW	16	86.1	14.1	15	27.1	0.2	15	38.7	3.4	14	189.9	65.9	16	13.3	4.1

ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、BL：ベースライン、Chg：変化量、Con：濃度、Endpoint：治験薬の最終投与6日後までに測定した最終時点、FW：フォローアップ、n：被験者数、TBILI：総ビリルビン
注：ベースライン時及び投与期間中の1時点以上で検査値がある被験者のみを対象とした。時間区分ごとに最大値を示した。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
200 mg コホート：ポサコナゾール新錠剤200 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

肝機能関連の臨床検査値

肝機能毒性を評価する目的で AST、ALT、ALP 及び総ビリルビンを評価した。

ポサコナゾール新錠剤200 mg を投与した被験者で、肝機能関連の臨床検査項目（AST、ALT、ALP 及び総ビリルビン）のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-101]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者がみられた項目は ALT 及び ALP であり、発現割合は各5%（1/20例）であった。

Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者はいなかった[2.7.6.2.22.5.1.5 項]。

表 2.7.4-101　肝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（200 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 200 mg
Chemistry	AST (U/L)	0/20
	ALT (U/L)	1/20 (5)
	ALP (U/L)	1/20 (5)
	Total Bilirubin (µmol/L)	0/20

CTCAE：有害事象共通用語基準、ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
200 mg コホート：ポサコナゾール新錠剤200 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

代謝機能関連の臨床検査値

代謝機能毒性を評価する目的で、カリウムの2項目（高カリウム血症及び低カリウム血症）及びナトリウムの2項目（高ナトリウム血症及び低ナトリウム血症）を評価した。

ポサコナゾール新錠剤200 mg を投与した被験者で、代謝機能関連の臨床検査項目（カリウム及びナトリウム）のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-102]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は低カリウム血症であり、発現割合は25%（5/20例）であった。

表 2.7.4-102　代謝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（200 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 200 mg
Chemistry	Hyperkalaemia (mmol/L)	1/20 (5)
	Hypokalaemia (mmol/L)	5/20 (25)
	Hypernatraemia (mmol/L)	0/20
	Hyponatraemia (mmol/L)	1/20 (5)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
200 mg コホート：ポサコナゾール新錠剤200 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

腎機能関連の臨床検査値

腎機能毒性を評価する目的で、クレアチニンを評価した。

ポサコナゾール新錠剤200 mg を投与した被験者で、クレアチニンのベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者は5%（1/20例）であった[表 2.7.4-103]。当該被験者（被験者番号[redacted]）では、腎不全の重篤な副作用が報告された。この被験者の叙述は[付録 2.7.6.2.22-3]に示す。

表 2.7.4-103　クレアチニンのベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（200 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 200 mg
Chemistry	Creatinine	1/20 (5)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
200 mg コホート：ポサコナゾール新錠剤200 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

2)　300 mg コホート

臨床検査項目のうち、クレアチニン、AST、ALT、ALP 及び総ビリルビンの平均値及びベースラインからの平均変化量を[表 2.7.4-104]に示す。

クレアチニンの平均値は投与後に増加したが、フォローアップ時にはベースライン値に戻る傾向を示した。AST の平均値は3日目以降に増加したが、フォローアップ時にはベースライン値に戻った。ALT の平均値は3日目以降に増加したが、フォローアップ時にはほぼベースライン値に戻った。ALP の平均値は8日目以降に増加したが、28日目から減少した。総ビリルビンの平均値は投与後にわずかに増加したが、フォローアップ時にはベースライン値に戻った。

表 2.7.4-104　来院別の血液生化学検査項目の平均値及びベースラインからの変化量
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（300 mg コホート）（All Treated Subjects）

Visit	Number of Subjects, All Treated Subjects 300 mg Cohort														
	Creatinine (μmol/L)			AST (U/L)			ALT (U/L)			ALP (U/L)			Total Bilirubin (μmol/L)		
	n	Mean Creatinine Con	Chg from BL	n	Mean AST Con	Chg from BL	n	Mean ALT Con	Chg from BL	n	Mean ALP Con	Chg from BL	n	Mean TBILI Con	Chg from BL
Baseline	209	74.8	-------	208	25.8	-------	209	35.3	-------	209	78.3	-------	209	12.7	-------
Day 1	7	88.4	10.1	6	18.8	-3.2	7	24.4	-0.3	7	79.1	7.1	7	17.0	1.3
Day 3	205	79.6	4.7	197	26.6	0.5	199	36.4	0.8	204	78.6	-0.2	200	13.5	0.8
Day 8	197	79.6	4.2	192	38.7	12.3	196	57.7	21.7	197	87.0	8.0	196	15.5	3.0
Day 14	184	78.6	2.9	180	32.7	8.3	182	55.8	22.9	184	101.1	21.7	184	14.3	2.0
Day 21	162	83.7	7.7	159	31.0	6.0	162	46.3	14.4	162	102.8	24.1	162	13.0	1.0
Day 28	137	89.6	12.3	134	30.1	4.0	135	41.3	7.4	136	98.5	16.4	136	11.8	0.1
Endpoint	209	84.2	9.4	208	34.2	8.3	208	56.3	20.9	209	104.2	25.8	208	13.9	1.2
FW	165	82.6	7.2	159	25.9	-1.3	161	40.4	3.6	164	97.0	19.3	162	12.2	-0.2

ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、BL：ベースライン、Chg：変化量、Con：濃度、Endpoint：治験薬の最終投与6日後までに測定した最終時点、FW：フォローアップ、n：被験者数、TBILI：総ビリルビン
注：ベースライン時及び投与期間中の1時点以上で検査値がある被験者のみを対象とした。時間区分ごとに最大値を示した。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
300 mg コホート：ポサコナゾール新錠剤300 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

肝機能関連の臨床検査値

肝機能毒性を評価する目的で AST、ALT、ALP 及び総ビリルビンを評価した。

ポサコナゾール新錠剤300 mg を投与した被験者で、肝機能関連の臨床検査項目（AST、ALT、ALP 及び総ビリルビン）のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-105]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は、ALT であり、発現割合は5%（11/208例）であった。

表 2.7.4-105　肝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（300 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg
Chemistry	AST (U/L)	4/208 (2)
	ALT (U/L)	11/208 (5)
	ALP (U/L)	1/209 (<1)
	Total Bilirubin (µmol/L)	5/208 (2)

CTCAE：有害事象共通用語基準、ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
300 mg コホート：ポサコナゾール新錠剤300 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者は2例（被験者番号[redacted]及び[redacted]）であった[2.7.6.2.22.5.2.5 項]。これらの被験者の叙述は[付録 2.7.6.2.22-3]に記載した。

なお、別の1例（被験者番号[redacted]）では、既往歴及び併用薬に基づいて慢性 B 型肝炎の発症が疑われた。当該被験者は5日目にトランスアミナーゼ上昇、黄疸及び血中ビリルビン増加の重篤な有害事象を報告し、同日に治験薬の投与を中止した。ALP の値が ULN の2倍以上あったため、Hy's Law の基準に合致しないと判定された。治験担当医師はこれらの事象とポサコナゾールとの因果関係を考えにくいと判定し、データカットオフ日の時点でこれらの事象は未回復と報告された。この被験者の叙述は[資料5.3.3.2.2: P05615] 14.8.4 項に示す。

代謝機能関連の臨床検査値

代謝機能毒性を評価する目的で、カリウムの2項目（高カリウム血症及び低カリウム血症）及びナトリウムの2項目（高ナトリウム血症及び低ナトリウム血症）を評価した。

ポサコナゾール新錠剤300 mg を投与した被験者で、代謝機能関連の臨床検査項目（カリウム及びナトリウム）のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-106]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は低カリウム血症であり、発現割合は12%（26/209例）であった。

表 2.7.4-106　代謝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（300 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/ Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg
Chemistry	Hyperkalaemia (mmol/L)	6/209 (3)
	Hypokalaemia (mmol/L)	26/209 (12)
	Hypernatraemia (mmol/L)	0/209
	Hyponatraemia (mmol/L)	6/209 (3)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
300 mg コホート：ポサコナゾール新錠剤300 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

腎機能関連の臨床検査値

腎機能毒性を評価する目的で、クレアチニンを評価した。

ポサコナゾール新錠剤300 mg を投与した被験者で、クレアチニンのベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者は1例（1%未満）であった[表 2.7.4-107]。

表 2.7.4-107　クレアチニンのベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（300 mg コホート）（All Treated Subjects）

Laboratory Group	Laboratory Parameter	Number of Subjects/ Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg
Chemistry	Creatinine	1/209 (<1)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
300 mg コホート：ポサコナゾール新錠剤300 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

2.7.4.3.2.3　静注用溶液を投与した後期第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）では、血液学的検査及び血液生化学検査をベースライン時、治験薬投与中、治験薬の最終投与6日後までの最終測定時点及びフォローアップ時に実施した。臨床検査値の程度分類は CTCAE を用いた。

本項では、コホート1（ポサコナゾール静注用溶液200 mg 反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID 経口投与）の結果を最初に提示し、その後コホート2（ポサコナゾール静注用溶液300 mg 反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID 経口投与）及びコホート3（ポ

サコナゾール静注用溶液300 mg 反復静脈内投与+ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID 経口投与）の併合結果を示す。なお、コホート0（ポサコナゾール静注用溶液200 mg 単回投与）の結果は[資料5.3.3.2.3: P05520]に示す。

1)　200 mg 反復静脈内投与（コホート1）

臨床検査項目のうち、クレアチニン、AST、ALT、ALP 及び総ビリルビンの平均値及びベースラインからの平均変化量を[表 2.7.4-108]に示す。

クレアチニンの平均値は3日目以降に減少した後、14日目からわずかに増加したが、フォローアップ時にはベースライン値に戻った。AST の平均値は14日目にはベースライン値より高い値であったが、その他の測定時点ではベースライン値に近い値であった。ALT の平均値は14日目にはベースライン値より高い値であったが、フォローアップ時にはベースライン値に戻った。ALP の平均値は7日目以降に増加し、フォローアップ時まで増加と減少を繰り返した。総ビリルビンの平均値は3日目以降に増加したが、フォローアップ時にはベースライン値に戻った。

表 2.7.4-108　来院別の血液生化学検査項目の平均値及びベースラインからの変化量
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（200 mg 反復静脈内投与：コホート 1）（All Treated Subjects）

Visit	Creatinine (μmol/L)			AST (U/L)			ALT (U/L)			ALP (U/L)			Total Bilirubin (μmol/L)		
	n	Mean Creatinine Con	Chg from BL	n	Mean AST Con	Chg from BL	n	Mean ALT Con	Chg from BL	n	Mean ALP Con	Chg from BL	N	Mean Total Bilirubin Con	Chg from BL
Baseline	20	72.2	-------	20	27.7	-------	20	35.3	-------	20	66.8	-------	20	14.2	-------
Day 1	0	-------	-------	0	-------	-------	0	-------	-------	0	-------	-------	0	-------	-------
Day 3	20	72.1	-0.1	20	24.4	-3.3	20	36.5	1.2	20	66.3	-0.5	20	14.8	0.6
Day 7	20	67.2	-5.0	19	23.5	-4.7	20	39.0	3.7	20	79.6	12.8	20	18.6	4.4
Day 14	20	74.4	2.2	20	46.3	18.6	20	58.9	23.6	20	103.7	36.9	20	22.5	8.3
Day 21	17	78.0	6.4	16	20.4	-5.3	17	38.8	5.6	17	88.2	22.4	17	32.1	18.8
Day 28	17	78.1	6.5	17	26.4	1.6	17	40.6	7.5	17	94.4	28.5	17	15.7	2.4
Endpoint	20	77.6	5.5	20	27.0	-0.8	20	47.4	12.1	20	88.7	22.0	20	29.0	14.8
FW	14	70.3	-1.7	14	23.4	-2.1	14	33.5	3.2	14	91.4	22.3	14	11.7	-2.0

ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、BL：ベースライン、Chg：変化量、Con：濃度、Endpoint：治験薬の最終投与6日後までに測定した最終時点、FW：フォローアップ、n：被験者数
注：ベースライン時及び投与期間中の1時点以上で検査値がある被験者のみを対象とした。時間区分ごとに最大値を示した。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

肝機能関連の臨床検査値

肝機能毒性を評価する目的で AST、ALT、ALP 及び総ビリルビンを評価した。

ポサコナゾール静注用溶液200 mg を投与した被験者で、肝機能関連の臨床検査項目（AST、ALT、ALP 及び総ビリルビン）のベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-109]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は総ビリルビンであり、発現割合は15%（3/20例）であった。

表 2.7.4-109　肝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、静脈内投与期のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（200 mg 反復静脈内投与：コホート 1）（All Treated Subjects）

		Cohort 1	
Laboratory Group	Laboratory Parameter	n/N	(%)
CHEMISTRY	AST (U/L)	1/ 20	(5)
	ALT (U/L)	1/ 20	(5)
	ALP	0/ 20	
	Total Bilirubin (µmol/L)	3/ 20	(15)

CTCAE：有害事象共通用語基準
ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、
n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者は1例（被験者番号[redacted]）であった[2.7.6.2.23.5.1.5 項]。この被験者の簡潔な叙述を以下に、詳細な叙述は[資料5.3.3.2.3: P05520] 14.6.1 項に示す。

- 被験者番号[redacted]：当該被験者は AML の既往歴がある[redacted]歳の[redacted]人[redacted]性で、治験薬投与開始の前日（Baseline）に軽度の発汗、7日目に中等度で間欠性の下肢痙攣及び股関節／下肢の疼痛（アセトアミノフェン、マグネシウム、モルヒネ、tetrazepam 及びトラマドールで治療）、11日目に軽度で間欠性の錯乱、14日目に中等度の肝酵素上昇、18日目に中等度で間欠性の咳嗽（デキストロメトルファンで治療）を呈した。14日目より血液生化学検査の値が上昇し、Hy's Law の臨床検査基準に合致した。重要な臨床検査値を[表 2.7.4-110]に示す。28日目に重度で進行性の白血病が認められ、被験者は治療を受けるため入院した。白血病に対して29～35日目にシタラビン、32～34日目に amsacrine が投与された。また、被験者は1日目より発熱性好中球減少症に対してアセトアミノフェンの投与を継続中で、11日目及び30日目以降スルピリン水和物を投与中であった。治験担当医師は、これらのすべての事象と治験薬との因果関係は考えにくいと判断した。治験薬に対して取られた処置はなかった。

表 2.7.4-110　Hy's Law に合致した被験者番号 [redacted] の臨床検査値
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（200 mg 反復静脈内投与：コホート 1）

Visit	Alanine Aminotransferase (6-35 U/L)	Alkaline Phosphatase (35-130 U/L)	Total Bilirubin (3-21 µmol/L)
Baseline	68	185	9
1日目：静注用溶液投与時	75	200	12
3日目：静注用溶液投与時	85	162	13
7日目：静注用溶液投与時	103	164	18
14日目：静注用溶液投与時	**488**	**230**	**75**
21日目：経口懸濁液投与時	**184**	**221**	**46**
28日目：経口懸濁液投与時	218	241	33
Follow-up	97	302	64

14日目（静注用溶液投与時）及び21日目（経口懸濁液投与時）の検査結果が Hy's Law に合致している
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

代謝機能関連の臨床検査値

代謝機能毒性を評価する目的で、カリウムの2項目（高カリウム血症及び低カリウム血症）及びナトリウムの2項目（高ナトリウム血症及び低ナトリウム血症）を評価した。

ポサコナゾール静注用溶液200 mg を投与した被験者で、代謝機能関連の臨床検査項目（カリウム及びナトリウム）のベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-111]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は低カリウム血症であり、発現割合は10%（2/20例）であった。

表 2.7.4-111　代謝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、静脈内投与期のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（200 mg 反復静脈内投与：コホート 1）（All Treated Subjects）

		Cohort 1	
Laboratory Group	Laboratory Parameter	n/N	(%)
CHEMISTRY	Hyperkalemia (mmol/L)	1/ 20	(5)
	Hypokalemia (mmol/L)	2/ 20	(10)
	Hypernatremia (mmol/L)	0/ 20	
	Hyponatremia (mmol/L)	1/ 20	(5)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

腎機能関連の臨床検査値

腎機能毒性を評価する目的で、クレアチニンを評価した。ポサコナゾール静注用溶液200 mg を投与した被験者で、クレアチニンのベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者はいなかった（[資料5.3.3.2.3: P05520] Table 12-28）。

2)　300 mg 反復静脈内投与（コホート2及び3併合）

臨床検査項目のうちクレアチニン、AST、ALT、ALP 及び総ビリルビンの平均値及びベースラインからの平均変化量を[表 2.7.4-112]に示す。

クレアチニンの平均値は7日目にはベースライン値より高い値であったが、その他の測定時点ではベースライン値に近い値が多く、フォローアップ時にはベースライン値に戻る傾向を示した。AST の平均値は7日目に増加したものの、フォローアップ時にはほぼベースライン値に戻った。ALT の平均値は7日目に増加したものの、フォローアップ時にはほぼベースライン値に戻った。ALP の平均値は7日目から増加し、フォローアップ時までには増加と減少を繰り返した。総ビリルビンの平均値は投与期間中に増加と減少を繰り返し、フォローアップ時にはベースライン値に戻った。

表 2.7.4-112　来院別の血液生化学検査項目の平均値及びベースラインからの変化量
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 2 及び 3 併合）（All Treated Subjects）

Visit	Creatinine (μmol/L)			AST (U/L)			ALT (U/L)			ALP (U/L)			Total Bilirubin (μmol/L)		
	n	Mean Creatinine Con	Chg from BL	n	Mean AST Con	Chg from BL	n	Mean ALT Con	Chg from BL	n	Mean ALP Con	Chg from BL	n	Mean Total Bilirubin Con	Chg from BL
Baseline	237	66.3	---	235	25.8	---	236	36.2	---	237	73.5	---	237	14.4	---
Day 1	19	65.4	2.8	20	36.4	-4.4	20	40.3	-6.9	20	71.4	1.2	21	15.3	-0.9
Day 3	229	68.0	1.6	219	26.8	1.0	221	38.5	1.7	228	73.4	-0.6	224	16.5	1.9
Day 6	200	66.8	0.2	186	25.8	-0.2	186	38.5	1.4	196	74.3	0.1	191	17.9	3.2
Day 7	24	84.2	17.8	24	317.9	285.1	24	183.1	143.6	24	76.5	14.8	24	26.0	12.5
Day 8	187	67.1	0.6	183	23.1	-2.6	184	35.0	-1.9	186	81.8	6.1	186	20.0	5.8
Day 10	39	70.9	6.0	46	36.9	6.2	53	46.3	5.5	45	97.0	11.0	46	27.2	8.5
Day 14	20	64.2	-0.1	20	32.9	-2.5	20	51.2	11.0	20	102.9	42.4	20	35.5	22.7
Day 15	129	71.3	5.4	130	36.9	10.9	133	42.1	2.6	131	97.8	21.5	130	18.6	3.7
Day 21	189	75.3	9.8	185	36.7	10.7	186	50.8	14.8	189	112.0	39.4	191	14.2	-0.2
Day 28	170	78.0	11.0	169	31.6	6.0	168	45.7	11.1	170	108.8	36.5	171	12.4	-1.4
Endpoint	237	78.2	11.9	235	65.1	39.3	236	57.0	20.8	237	103.3	29.7	237	18.3	4.0
FW	113	77.7	10.9	112	28.1	3.4	110	40.6	3.6	113	103.9	29.5	111	11.3	-2.7

ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、BL：ベースライン、Chg：変化量、Con：濃度、Endpoint：治験薬の最終投与6日後までに測定した最終時点、FW：フォローアップ、n：被験者数
注：ベースライン時及びベースライン後の1時点以上で検査値がある被験者のみを対象とした。時間区分ごとに最大値を示した。
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

肝機能関連の臨床検査値

肝機能毒性を評価する目的で AST、ALT、ALP 及び総ビリルビンを評価した。

ポサコナゾール静注用溶液300 mg を投与した被験者で、肝機能関連の臨床検査項目（AST、ALT、ALP 及び総ビリルビン）のベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-113]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は総ビリルビンであり、発現割合は6%（14/237例）であった。

表 2.7.4-113　肝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、静脈内投与期のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 2 及び 3 併合）（All Treated Subjects）

		Cohort 2/Cohort 3	
Laboratory Group	Laboratory Parameter	n/N	(%)
CHEMISTRY	AST (U/L)	7/235	(3)
	ALT (U/L)	9/236	(4)
	ALP (U/L)	0/237	
	Total Bilirubin (µmol/L)	14/237	(6)

CTCAE：有害事象共通用語基準、ALP：アルカリホスファターゼ、ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

Hy's Law（ALT 又は AST が ULN の3倍以上かつ ALP が ULN の2倍以下、総ビリルビンが ULN の2倍以上、胆管閉塞のエビデンスがない）に合致した被験者はコホート2で3例（被験者番号[redacted]）及びコホート3で4例（被験者番号[redacted]）であった[2.7.6.2.23.5.2.5 項]。これらの被験者は Hy's Law の臨床検査基準に合致したが、各種トランスアミナーゼ及び総ビリルビンの上昇を引き起こす敗血症又は GVHD の既往歴、若しくは肝損傷を引き起こす可能性がある別の薬剤の使用など、治験薬以外の理由がそれぞれ存在した。これらの被験者の簡潔な叙述を[資料5.3.3.2.3: P05520] 12.2.4.3 項に示す。

代謝機能関連の臨床検査値

代謝機能毒性を評価する目的で、カリウムの2項目（高カリウム血症及び低カリウム血症）及びナトリウムの2項目（高ナトリウム血症及び低ナトリウム血症）を評価した。

ポサコナゾール静注用溶液300 mg を投与した被験者で、代謝機能関連の臨床検査項目（カリウム及びナトリウム）のベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-114]に示す。

これらの臨床検査項目のうち、ベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者が最もよくみられた項目は低カリウム血症であり、発現割合は9%（22/237例）であった。

表 2.7.4-114　代謝機能検査項目のベースライン値が CTCAE Grade 0、1 又は 2 で、静脈内投与期のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 2 及び 3 併合）（All Treated Subjects）

		Cohort 2/Cohort 3	
Laboratory Group	Laboratory Parameter	n/N	(%)
CHEMISTRY	Hyperkalemia (mmol/L)	1/237	(<1)
	Hypokalemia (mmol/L)	22/237	(9)
	Hypernatremia (mmol/L)	0/237	
	Hyponatremia (mmol/L)	3/237	(1)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

腎機能関連の臨床検査値

腎機能毒性を評価する目的で、クレアチニンを評価した。

ポサコナゾール静注用溶液300 mg を投与した被験者で、クレアチニンのベースライン値が Grade 0、1又は2で、静脈内投与期のいずれかの時点で Grade 3又は4に変動した被験者は3例（1%）であった[表 2.7.4-115]。

表 2.7.4-115　クレアチニンのベースライン値が CTCAE Grade 0、1 又は 2 で、静脈内投与期のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 2 及び 3 併合）（All Treated Subjects）

		Cohort 2/Cohort 3	
Laboratory Group	Laboratory Parameter	n/N	(%)
CHEMISTRY	Creatinine (μmol/L)	3/237	(1)

CTCAE：有害事象共通用語基準、n：被験者数、N：各臨床検査パラメータについてベースライン時及び投与期間中の1時点以上で検査値がある被験者数
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

2.7.4.3.3　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.3.3.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及びP00041試験）（rIFI併合集団）では、血液学的検査及び血液生化学検査をベースライン時、治験薬投与中及びフォローアップ時に実施した。臨床検査値の程度分類はCTCを用いた。

これらの臨床検査項目のベースライン値のGradeから試験期間中の最も重いGradeへの変動を[付録2.7.4-106]に、検査値ごとのベースラインからの中央値の変動を[付録2.7.4-107]に示す。

血液学的検査項目のベースライン時からの変化量（中央値）は、概して小さかった[付録2.7.4-107]。このうち、ヘマトクリット、ヘモグロビン及び血小板数では、大多数の被験者のベースライン値が異常値であり、好中球数及び白血球数では約半数が異常値であった。血小板数は非造血幹細胞移植患者の約半数、造血幹細胞移植患者の約90%がベースライン時に異常低値であったが、それ以外のこれらの検査値のベースライン時の異常値の割合は、造血幹細胞移植患者と非造血幹細胞移植患者で概して類似していた。

血液学的検査項目のベースライン値がGrade 0又は1であった被験者の大多数は、試験期間中の最も重いGradeもGrade 0又は1であった。血液学的検査項目のベースライン値がGrade 0、1又は2で、試験期間中のいずれかの時点でGrade 3又は4に変動した被験者数を[表2.7.4-116]に示す。

ヘマトクリット、ヘモグロビン及び血小板数の減少が認められ、かつ、ベースライン値がCTC Grade 0、1又は2で、試験期間中のいずれかの時点でGrade 3又は4に変動した被験者は非造血幹細胞移植患者よりも造血幹細胞移植患者の方が多く、これは造血幹細胞移植後に一般的にみられる変動であった。なお、造血幹細胞移植患者の被験者の大部分では、これらの検査項目のベースライン値はGrade 2以上であった。好中球数の減少が認められた被験者が少なかったが、これは造血幹細胞移植後に骨髄増殖因子を投与したことによるもので、ヘマトクリット、ヘモグロビン及び血小板数の異常値からの回復は、好中球数の回復後に認められるものと考えられる[付録2.7.4-106]。

表 2.7.4-116　血液学的検査項目のベースライン値が CTC Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

Laboratory Parameter	Number (%) of Subjects		
	BMT (n = 124)	Non-BMT (n = 304)	Overall rIFI Pool (n = 428)
Hematocrit	36/110 (33)	53/271 (20)	89/381 (23)
Hemoglobin	33/110 (30)	53/272 (19)	86/382 (23)
Platelet Count	24/109 (22)	31/271 (11)	55/380 (14)
Leukocyte Count	15/110 (14)	26/271 (10)	41/381 (11)
Neutrophil Count	13/100 (13)	26/250 (10)	39/350 (11)

CTC：共通毒性基準、rIFI：難治性侵襲性真菌症
注：データは X/Y (%)として示す。X は定義を満たす被験者数、Y はベースライン後の1時点以上で該当する検査値が得られた被験者数を示す。
BMT：　造血幹細胞移植［P00041試験の治験総括報告書[資料5.3.5.2.1: P00041]では、治験薬投与前の病歴から侵襲性真菌症の発症リスクが存在する被験者集団を特定するための用語の一つとして「骨髄移植：Bone marrow transplant（BMT）」の表現が用いられたが、より適切な表現は造血幹細胞移植であったため、P01893及び P00041試験の併合解析では、BMT を造血幹細胞移植として示す。］
治験薬の用法・用量（QID：1日4回、BID：1日2回、QD：1日1回）
P01893試験
400 mg BID 群：負荷用量200 mg QID を2日間経口投与後、維持用量400 mg BID を経口投与
600 mg BID 群：負荷用量400 mg QID を2日間経口投与後、維持用量600 mg BID を経口投与
800 mg QD 群：負荷用量800 mg BID を2日間経口投与後、維持用量800 mg QD を経口投与
P00041試験
入院被験者には、入院中はポサコナゾール経口懸濁液200 mg QID、退院後は400 mg BID、
外来被験者には、ポサコナゾール経口懸濁液400 mg BID を経口投与

血液生化学検査項目（ALT、AST、総ビリルビン、ALP 及びクレアチニン）のベースライン時からの変化量（中央値）は、概して小さかった[付録 2.7.4-107]。

血液生化学検査項目を程度別でみると、ベースライン値が Grade 0又は1であった被験者の大多数は、試験期間中の最も重い Grade も Grade 0又は1であった[付録 2.7.4-106]。血液生化学検査項目のベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を[表 2.7.4-117]に示す。

血液生化学検査パラメータの変動が認められた被験者の割合は、非造血幹細胞移植患者よりも造血幹細胞移植患者でわずかに高く、ALP の項目で顕著であった。なお、被験者のほとんどは合併症に対する併用薬を使用していたことから、これらが肝機能関連の検査値上昇につながった可能性がある。このため、これらの要因とポサコナゾール経口懸濁液の影響を見分けることは困難であるものの、定量的な観察として、臨床的に重要な変動の発現割合が全体に比較的低かった（2%～6%）ことからは、ポサコナゾール経口懸濁液による影響は示唆されなかった。

表 2.7.4-117　血液生化学検査項目のベースライン値が CTC Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

Laboratory Parameter	Number (%) of Subjects		
	BMT (n = 124)	Non-BMT (n = 304)	Overall rIFI Pool (n = 428)
Alanine Aminotransferase (ALT / SGPT)	9/102 (9)	12/262 (5)	21/364 (6)
Aspartate Aminotransferase (AST / SGOT)	6/ 79 (8)	9/233 (4)	15/312 (5)
Total Bilirubin	7/108 (6)	9/258 (3)	16/366 (4)
Alkaline Phosphatase	11/107 (10)	5/255 (2)	16/362 (4)
Creatinine	3/114 (3)	5/270 (2)	8/384 (2)

CTC：共通毒性基準、rIFI：難治性侵襲性真菌症
注：　データは X/Y (%)として示す。X は定義を満たす被験者数、Y はベースライン後の1時点以上で該当する検査値が得られた被験者数を示す。
ALT：アラニンアミノトランスフェラーゼ（SGPT と同じ）、AST：アスパラギン酸アミノトランスフェラーゼ（SGOT と同じ）
BMT：　造血幹細胞移植［P00041試験の治験総括報告書[資料5.3.5.2.1: P00041]では、治験薬投与前の病歴から侵襲性真菌症の発症リスクが存在する被験者集団を特定するための用語の一つとして「骨髄移植：Bone marrow transplant（BMT）」の表現が用いられたが、より適切な表現は造血幹細胞移植であったため、P01893及び P00041試験の併合解析では、BMT を造血幹細胞移植として示す。］
治験薬の用法・用量（QID：1日4回、BID：1日2回、QD：1日1回）
P01893試験
400 mg BID 群：負荷用量200 mg QID を2日間経口投与後、維持用量400 mg BID を経口投与
600 mg BID 群：負荷用量400 mg QID を2日間経口投与後、維持用量600 mg BID を経口投与
800 mg QD 群：負荷用量800 mg BID を2日間経口投与後、維持用量800 mg QD を経口投与
P00041試験
入院被験者には、入院中はポサコナゾール経口懸濁液200 mg QID、退院後は400 mg BID、
外来被験者には、ポサコナゾール経口懸濁液400 mg BID を経口投与

2.7.4.3.3.2　　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）では、血液学的検査及び血液生化学検査をベースライン時、治験薬投与中及びフォローアップ時に実施した。臨床検査値の程度分類はCTCAEを用いた。

肝機能関連の臨床検査値

肝機能毒性を評価する目的でAST、ALT、ALP及び血中ビリルビンを評価した。

これらの臨床検査項目のベースライン値のGradeから試験期間中の最も重いGradeへの変動を、投与群別に[付録2.7.4-108]（ポサコナゾール群）及び[付録2.7.4-109]（ボリコナゾール群）に示す。すべての項目で、両投与群とも、80%以上の被験者はベースライン値のGradeが0で、試験期間中の最も重いGradeも0又は1であった。

ベースライン値がGrade 0、1又は2で、試験期間中のいずれかの時点でGrade 3又は4に変動した被験者数を、[表 2.7.4-118]に示す。ポサコナゾール群では、ベースライン値がGrade 0で、試験期間中のいずれかの時点でGrade 3に変動したALTの被験者が最も多かった。ボリコナゾール群では、ベースライン値がGrade 0、1又は2で、試験期間中のいずれかの時点でGrade 3又は4に変動した項目は認められなかった。また、いずれの投与群でも、Grade 4に変動した項目は認められなかった。

「ALT又はASTがULNの3倍以上かつALPがULNの2倍以下、総ビリルビンがULNの2倍以上、胆管閉塞のエビデンスがない」の基準に合致した被験者は、いずれの投与群でも認められなかった。

代謝機能関連の臨床検査値

代謝機能毒性を評価する目的で高カリウム血症、低カリウム血症、高ナトリウム血症及び低ナトリウム血症を評価した。

これらの臨床検査項目のベースライン値のGradeから試験期間中の最も重いGradeへの変動を、投与群別に[付録2.7.4-110]（ポサコナゾール群）及び[付録2.7.4-111]（ボリコナゾール群）に示す。低ナトリウム血症以外の項目では、両投与群とも、80%以上の被験者はベースライン値のGradeが0で、試験期間中の最も重いGradeも0又は1であった。低ナトリウム血症では、両投与群とも、60%以上の被験者はベースライン値のGradeが0で、試験期間中の最も重いGradeも0又は1であり、30%以上の被験者はベースライン値のGradeが1で、試験期間中の最も重いGradeも1であった。

ベースライン値がGrade 0、1又は2で、試験期間中のいずれかの時点でGrade 3又は4に変動した被験者数を、[表 2.7.4-118]に示す。ポサコナゾール群では、ベースライン値がGrade 0で、試験期間中のいずれかの時点でGrade 3に変動した低カリウム血症の被験者が最も多かった。また、低カリウム血症については、ポサコナゾール群で、Grade 0からGrade 4に変動した被験者が2例、Grade 1からGrade 4に変動した被験者が2例認められた。ボリコナゾール群では、ベースライン値がGrade 0で、試験期間中のいずれかの時点でGrade 3に変動した高カリウム血症及び低カリウム血症がいずれも1例ずつ認められた。

腎機能関連の臨床検査値

腎機能毒性を評価する目的でクレアチニンを評価した。

クレアチニンのベースライン値の Grade から試験期間中の最も重い Grade への変動を投与群別に[付録 2.7.4-112]（ポサコナゾール群）及び[付録 2.7.4-113]（ボリコナゾール群）に示す。

ベースライン値が Grade 0、1又は2で、試験期間中のいずれかの時点で Grade 3又は4に変動した被験者数を、[表 2.7.4-118]に示す。いずれの投与群でも、Grade 3又は4への変動は認められなかった。

表 2.7.4-118　ベースライン値が CTCAE Grade 0、1 又は 2 で、試験期間中のいずれかの時点で Grade 3 又は 4 に変動した被験者数 ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects			
		ポサコナゾール群（N=77）		ボリコナゾール群（N=38）	
		Grade 3	Grade 4	Grade 3	Grade 4
肝機能関連の臨床検査値					
Aspartate aminotransferase increased (IU/L)	0	2 (2.6)	0	0	0
	1	0	0	0	0
	2	0	0	0	0
Alanine aminotransferase increased (IU/L)	0	4 (5.2)	0	0	0
	1	0	0	0	0
	2	1 (1.3)	0	0	0
Alkaline phosphatase increased (IU/L)	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
Blood bilirubin increased (mg/dL)	0	1 (1.3)	0	0	0
	1	0	0	0	0
	2	0	0	0	0
代謝機能関連の臨床検査値					
Hyperkalemia (mmol/L)	0	0	0	1 (2.6)	0
	1	0	0	0	0
	2	0	0	0	0
Hypokalemia (mmol/L)	0	6 (7.8)	2 (2.6)	1 (2.6)	0
	1	1 (1.3)	2 (2.6)	0	0
	2	0	0	0	0
Hypernatremia (mmol/L)	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
Hyponatremia (mmol/L)	0	0	0	0	0
	1	1 (1.3)	0	0	0
	2	0	0	0	0
腎機能関連の臨床検査値					
Creatinine increased (mg/dL)	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで300 mg を QD にて投与
ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

2.7.4.4　　バイタルサイン、身体的所見及び安全性に関連する他の観察項目

本項では、バイタルサイン及び心電図の評価を要約する。

2.7.4.4.1　　バイタルサイン

健康被験者を対象とした試験結果の要約を[2.7.4.4.1.1項]に、患者を対象とした予防投与試験及び治療試験の結果を[2.7.4.4.1.2項]及び[2.7.4.4.1.3項]にそれぞれ示す。

2.7.4.4.1.1　　健康被験者を対象とした試験結果の要約

2.7.4.4.1.1.1　　経口懸濁液（旧錠剤又は旧カプセルを含む）を投与した第Ⅰ相試験（計20試験）（非日本人）

ポサコナゾール経口懸濁液の血圧への影響を評価するため、5試験（P02489、P02810、P02811、P02812及びP02862試験）に含まれる経口懸濁液の、海外における治療目的の臨床推奨用量である400 mgをBIDで、7日間以上投与した被験者のデータを解析した。

ベースライン時及び投与後に測定した血圧の平均値、変動の最小値及び最大値を[付録2.7.4-114]に要約する。これらの5試験は、血圧の変化を特異的に評価するようデザインされていなかったため、測定時点は試験間で様々であった。そのため、定常状態に達していると想定した投与後5日目以降の測定値のみを投与後の値の評価対象とした。全体として、スクリーニング値と比較して投与後の収縮期又は拡張期血圧の平均値に臨床的に問題となる上昇は認められなかった[資料5.3.3.4.10: P02489] [資料5.3.3.3.1: P02810] [資料5.3.3.3.2: P02811] [資料5.3.1.1.2: P02812] [資料5.3.3.4.6: P02862]。

また、他のポサコナゾール経口懸濁液（旧錠剤又は旧カプセルを含む）を投与した第Ⅰ相試験を含め、血圧、心拍数及び体温をバイタルサインとして評価したものの、それらの変動は臨床的に意義のある変動ではなかった[資料5.3.3.1.12: C96_104] [資料5.3.3.1.13: P02418] [資料5.3.3.3.1: P02810] [資料5.3.3.3.2: P02811] [資料5.3.1.1.2: P02812] [資料5.3.3.1.5: I95_098] [資料5.3.1.2.1: I95_099] [資料5.3.3.1.6: I96_089] [資料5.3.1.2.2: I96_099] [資料5.3.3.1.10: P04547] [資料5.3.3.1.11: P05270] [資料5.3.3.3.5: I97_195] [資料5.3.3.3.4: P01940] [資料5.3.3.4.10: P02489] [資料5.3.3.4.6: P02862] [資料5.3.3.4.12: C96_120] [資料5.3.3.4.2: C96_173] [資料5.3.3.4.4: C96_201] [資料5.3.3.4.3: I96_207] [資料5.3.3.4.1: I97_016]。

2.7.4.4.1.1.2　　新錠剤を投与した第Ⅰ相試験（計5試験）（非日本人）

健康被験者を対象としたポサコナゾール新錠剤100～400 mgを単回若しくは反復投与した第Ⅰ相試験では、血圧、心拍数及び体温をベースライン時及び投与後に測定した。それらの変動は臨床的に意義のある変動ではなかった[資料5.3.1.2.3: P04975] [資料5.3.1.2.4: P07691] [資料5.3.3.4.13: P07764] [資料5.3.1.1.1: P07783] [資料5.3.3.1.7: P05637]。

2.7.4.4.1.1.3　　静注用溶液を投与した第Ⅰ相試験（計3試験）（非日本人）

健康被験者を対象としたポサコナゾール静注用溶液50～300 mgを単回若しくは反復投与した第Ⅰ相試験では、血圧、心拍数及び体温をベースライン時及び投与後に測定した。それらの変動は臨床的に意義のある変動ではなかった[資料5.3.3.1.8: P04985] [資料5.3.1.1.1: P07783] [資料5.3.3.1.9: P06356]。

2.7.4.4.1.1.4　　新錠剤及び静注用溶液を投与した第Ⅰ相試験（P067試験）（日本人）

日本人の健康被験者を対象としたポサコナゾール新錠剤及び静注用溶液の第Ⅰ相試験（P067試験）では、血圧、心拍数、体温及び呼吸数を測定した。単回及び反復投与いずれのパートでも、臨床的に意義のある変動は認められなかった[資料5.3.3.1.4: P067]。

2.7.4.4.1.2　　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.4.1.2.1　　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及びP01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験のC/I98-316試験では、血圧、心拍数、体温及び呼吸数を、P01899試験では血圧、心拍数及び体温を測定した。それぞれの試験のポサコナゾール群及び対照群（フルコナゾール群及びイトラコナゾール群）で、臨床的に意義のある変動は認められなかった[資料5.3.5.1.2: CI98_316] [資料5.3.5.1.1: P01899]。

2.7.4.4.1.2.2　　新錠剤を投与した後期第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

ポサコナゾール新錠剤の予防投与試験（P05615試験）では、血圧、心拍数及び体温を測定した。200 mgコホート及び300 mgコホートいずれにおいても、臨床的に意義のある変動は認められなかった[資料5.3.3.2.2: P05615]。

2.7.4.4.1.2.3　　静注用溶液を投与した後期第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）では、血圧、心拍数及び体温を測定した。コホート1（ポサコナゾール静注用溶液200 mg反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID経口投与）並びにコホート2（ポサコナゾール静注用溶液300 mg反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID 経口投与）及びコホート3（ポサコナゾール静注用溶液300 mg反復静脈内投与+ポサコナゾール経口懸濁液200 mg TID又は400 mg BID経口投与）併合のいずれにおいても、臨床的に意義のある変動は認められなかった[資料5.3.3.2.3: P05520]。

2.7.4.4.1.3　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.4.1.3.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及びP00041試験）では、血圧、心拍数、体温及び呼吸数を測定した。これらの項目に臨床的に意義のある変動は認められなかった[資料5.3.5.1.4: P01893] [資料5.3.5.2.1: P00041]。

2.7.4.4.1.3.2　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）では、血圧、心拍数及び体温を測定した。ベースラインからの平均変化量（上昇）は、収縮期血圧において、ボリコナゾール群に比べてポサコナゾール群で高かったものの[付録 2.7.4-117]、拡張期血圧は両群間で大きな差はなく[付録 2.7.4-116]、事前に規定した収縮期血圧及び拡張期血圧の変動範囲の基準に合致した被験者数は、両投与群で大きく異ならなかった[付録 2.7.4-121]。一方、体温のベースラインからの平均変化量は、両投与群で小さかったものの[付録 2.7.4-119]、事前に規定した体温の変動範囲の基準に合致した被験者数は、ボリコナゾール群に比べてポサコナゾール群で多かった[付録2.7.4-121]。なお、ポサコナゾール群では発熱の有害事象が32.5%（25/77例報告されたが[2.7.4.2.2.1.2.2.2 項]、このうち重度以上と判定された被験者は2例[付録2.7.4-26]、重篤な有害事象と判定された被験者は2例[2.7.4.2.2.3.2.2 項]、投与中止に至った被験者は5例であった[2.7.4.2.2.4.2.2 項]。

その他の項目では、臨床的に意義のある変動は認められなかった[付録2.7.4-115] [付録2.7.4-116] [付録 2.7.4-118] [付録 2.7.4-120] [付録 2.7.4-121]。

2.7.4.4.2　　心電図検査

心拍数で補正した心電図 QT 間隔（QTc 間隔）の延長は、重篤な心室性不整脈や死亡に至る可能性があるため、アゾール系抗真菌薬の使用時の臨床的な懸念事項となっている。そこで、ポサコナゾールが心電図の記録に及ぼす影響を慎重に評価した。

健康被験者を対象とした試験結果の要約を[2.7.4.4.2.1 項]に示す。患者を対象とした予防投与試験及び治療試験の結果の要約を[2.7.4.4.2.2 項]及び[2.7.4.4.2.3 項]にそれぞれ示す。

2.7.4.4.2.1　　健康被験者を対象とした試験

2.7.4.4.2.1.1　　経口懸濁液を投与した第Ⅰ相試験（非日本人）

健康被験者にポサコナゾール経口懸濁液を投与したときの QT 間隔延長の影響を評価するため、5つの第Ⅰ相試験（P02489、P02810、P02811、P02812及び P02862試験）の189例を対象に、同一時刻で複数時点の心電図を記録した。ポサコナゾール経口懸濁液の T_{max} の中央値が約5時間であるため、すべての試験において、ポサコナゾール経口懸濁液又はプラセボ反復投与の-1日目（ベースライン）、最終投与日又はその前日の同一の時点（朝投与直前、2、4、5、6及び12時間後）で心電図を記録した（一部の試験では、これ以外の時点でも心電図を記録）。

5試験のうち1試験（P02810試験）では、プラセボ群（n＝16）を設定していた。すべての心電図のデータは盲検化され、外部の第三者が中央で読影し、試験ごとに個別に評価した。各試験で QT 間隔の絶対値、QTc 間隔（Fridericia 及び Bazett）、PR、QRS 及び心拍数を記述統計量で示した。また、主要な評価にはベースラインからの QTc 間隔の変化量を用いた。

QTc 間隔の各解析では Bazett（QTcB 間隔）及び Fridericia（QTcF 間隔）の両補正法を用いたが、Bazett 補正法は心拍数が高いと過大な補正になり、心拍数が60 bpm 未満では過小な補正になることが知られているため（本解析の対象となった被験者には心拍数が60 bpm 未満の被験者も含まれた）、本項では QTcF 間隔のみを示す。

ポサコナゾール経口懸濁液投与による QTc 間隔の延長を評価するために中心傾向の解析及びカテゴリカル解析を用いた。中心傾向の解析では、以下に示したように、12時間までの同一時刻での QTc 間隔の平均変化量を算出した。

1) 12時間に計6つの時点で記録した心電図データを用いて、投与前（-1日目）から投与7～8日目の同一時刻での QTcF 間隔の変化量を被験者ごとに算出した［例：（8日目の投与4時間後の QTcF 間隔）－（-1日目の4時間後の QTcF 間隔）］。
2) 6つの時点のそれぞれの QTcF 間隔の変化量（上記1)に基づく）の平均を被験者ごとに求めた。
3) 被験者ごとの QTcF 間隔の平均変化量（上記2)に基づく）について、ポサコナゾール群及びプラセボ群の要約統計量（平均値、中央値、最大値、最小値）を算出した。

これらの QTc 間隔評価の表及び図は、[付録 2.7.4-122]～[付録 2.7.4-137]に示す。

プラセボ対照試験の結果

P02810試験では、健康成人をポサコナゾール経口懸濁液400 mg BID 又はプラセボに3:1の割合で割り付け、計8日間投与し、64例が投与を完了した（ポサコナゾール群：48例、プラセボ群：16例）。なお、本試験では投与24時間後にも心電図を記録した。記録ポイントごとの QTcF 間隔の変化量の要約統計量（平均値、最小値、最大値）には、臨床的に重要な変化は認められなかった[表 2.7.4-119]。

表 2.7.4-119　QTcF 間隔のベースラインからの平均変化量
健康被験者へのポサコナゾール経口懸濁液投与試験（P02810 試験）（Study Completed Subjects）

ECG Evaluation	Change from Baseline in QTc (Fridericia) Interval (msec)					
	Posaconazole (n = 48)			Placebo (n = 16)		
Time (hr)	Mean	Min	Max	Mean	Min	Max
Pre-dose	-7.00	-38	45	-3.63	-42	83
2	-5.94	-45	41	2.19	-45	38
4	-10.0	-80	29	-9.75	-35	15
5	-3.63	-49	50	-6.75	-43	35
6	-2.94	-43	57	-0.06	-23	25
12	-11.3	-120	35	-1.19	-24	33
24	-5.75	-50	35	-3.25	-41	15

治験薬の用法・用量（BID：1日2回）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与又はプラセボ BID 経口投与を8日間

全体として、投与2時間後から24時間後までの QTcF 間隔の平均変化量は、ポサコナゾール群で-6.59 msec［95%信頼区間（CI）：-10.1～-3.05 msec］、プラセボ群で-3.14 msec（95% CI：-7.79～1.52 msec）であった。同一時刻での QTcF 間隔の平均変化量は、年齢又は性別を問わずポサコナゾール群のすべての被験者で30 msec 以下であった[付録 2.7.4-122]。QTcF 間隔のベースラインからの変化量（増加）の最大値は、ポサコナゾール群で57 msec（18から45歳の若年男性被験者）、プラセボ群で83 msec（65歳以上の高齢女性被験者）であり、QTcF 間隔の変化量（減少）の最大値は、ポサコナゾール群で-120 msec（65歳以上の高齢女性被験者）、プラセボ群で-45 msec（65歳以上の高齢男性被験者）であった[付録 2.7.4-125]。

QTcF 間隔の最大変化量は、ポサコナゾール群の被験者の過半数（48例中29例、60%）で0～30 msec 未満、4例（8%）で30～60 msec 未満であり、60 msec 以上の被験者はいなかった[表 2.7.4-120]。ポサコナゾール群と同様、プラセボ群でも被験者の大多数（11例、69%）で QTcF 間隔の最大変化量が0～30 msec 未満であり、1例（6%）で30～60 msec 未満であった。しかし、ポサコナゾール群と異なり、プラセボ群の1例（6%）で QTcF 間隔の最大変化量が60 msec 以上であった。

これらの試験結果は、QTc 間隔の変動が被験者固有のものであることを示している。プラセボ群でのベースラインからの変化量は、ポサコナゾール群で認められた変化量と同程度であり、プラセボとの比較において、ポサコナゾール経口懸濁液投与が QTcF 間隔の延長を誘発しないこと

が示された[資料5.3.3.3.1: P02810]。

表 2.7.4-120　QTcF 間隔のベースラインからの最大変化量の被験者分布

健康被験者へのポサコナゾール経口懸濁液投与試験（P02810 試験）（Study Completed Subjects）

Baseline†	n	QTcF Interval Change from Baseline (msec)	n	%
Posaconazole				
Normal	47	-30 to <0	14	29.79
		0 to <30	29	61.70
		30 to <60	4	8.51
		≥ 60	0	0.00
Borderline	1	-30 to <0	1	100.00
		0 to <30	0	0.00
		30 to <60	0	0.00
		≥ 60	0	0.00
Placebo‡				
Normal	16	-30 to <0	3	18.75
		0 to <30	11	68.75
		30 to <60	1	6.25
		≥ 60	1	6.25

† ベースラインとは、0～12時間における QTcF 間隔の平均値とする。
‡ プラセボ群では、QTcF 間隔のベースライン値が境界域の被験者がいなかった。
正常：成人男性430 msec 以下、成人女性450 msec 以下
境界域：成人男性431～450 msec、成人女性451～470 msec
治験薬の用法・用量（BID：1日2回）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与又はプラセボ BID 経口投与を8日間

5試験の併合解析の結果

上述のプラセボ対照試験（P02810試験）に加えて、プラセボ対照を設定しない4試験（P02489、P02811、P02812及び P02862試験）を実施した。これらの試験は P02810試験と同様の方法により複数時点で心電図を記録した。これら5試験の心電図データを併合し評価した。

その結果、合計189例（ポサコナゾール群：173例、プラセボ群：16例）の被験者が含まれた。性別及び年齢が QT 間隔の延長に関連することが知られているが、ポサコナゾール群には女性（38%）及び高齢被験者（14%）が含まれていた。5試験でポサコナゾール経口懸濁液又はプラセボが投与されたすべての被験者での、投与後12時間の QTcF 間隔のベースラインからの変化量の要約統計量を[表 2.7.4-121]に試験別に示す。

表 2.7.4-121　QTcF 間隔のベースラインからの平均変化量（投与後 0～12 時間）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）

Protocol	n	Change from Baseline in QTc (Fridericia) Interval (msec)				
		Median	Mean	STD	Min	Max
P02810-Placebo	16	-2.75	-3.20	14.70	-23.83	33.00
ALL-posaconazole	173	-4.67	-5.59	10.86	-50.50	25.33
P02489-posaconazole	12	-2.33	-5.32	13.66	-43.67	8.00
P02810-posaconazole	48	-8.08	-6.80	12.66	-29.50	25.33
P02811-posaconazole	56	-4.58	-4.12	10.43	-50.50	17.17
P02812-posaconazole	22	-3.50	-3.89	9.79	-23.00	13.00
P02862-posaconazole	35	-5.33	-7.46	8.25	-24.33	5.50

治験薬の用法・用量（BID：1日2回）
P02489試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を10日間（その間、グリピジドを2回単回投与）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与又はプラセボ BID 経口投与を8日間
P02811試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02812試験
ポサコナゾール経口懸濁液400 mg を単回、その後400 mg BID 経口投与を8日間
P02862試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間（その間、タクロリムスを2回単回投与）

投与後12時間の QTcF 間隔の平均変化量の要約統計量（平均値、中央値、最小値、最大値）では、いずれの試験でも、ポサコナゾール経口懸濁液投与後に臨床的に重要な変化は認められず、プラセボ対照試験（P02810試験）の結果が裏付けられた。

全体として、QTcF 間隔の平均変化量を解析した結果、ポサコナゾール群では平均値及び中央値が約-5 msec の QTcF 間隔の変化が認められた。同一時刻での QTcF 間隔の平均変化量の最大値は、ポサコナゾール群の全被験者（25 msec）に比べてプラセボ群の16例（33 msec）で大きかった[表 2.7.4-121]。

併合解析の結果から、ポサコナゾール経口懸濁液は健康被験者において QTc 間隔延長を誘発せず、認められた変化は QTc 間隔の正常な変動の範囲内であることが示唆された。

併合データのカテゴリカル解析では、ベースライン値を正常及び境界域のカテゴリーに分け、各被験者の投与後の QTcF 間隔の最大変化量をベースラインからの変化量に基づいて各カテゴリーに分類した。男性被験者の2例でベースライン値が正常範囲よりわずかに高かった（437 msec 及び434 msec）ものの、それらを除くすべての被験者でベースライン時の QTcF 間隔は正常範囲内であった。すべての被験者における投与後のカテゴリー別 QTcF 間隔のベースラインからの最大変化量を[表 2.7.4-122]に示す。

表 2.7.4-122　QTcF 間隔のベースラインからの最大変化量の被験者分布
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

Baseline†	n	QTcF Interval Change from Baseline (msec)	n	%
Normal	171	-30 to <0 0 to <30 30 to <60 ≥ 60	38 127 6 0	22.22 74.27 3.51 0.00
Borderline	2‡	-30 to <0 0 to <30 30 to <60 ≥ 60	1 1 0 0	50.00 50.00 0.00 0.00

† ベースラインとは、0～12時間における QTcF 間隔の平均値とする。
　正常：成人男性430 msec 以下、成人女性450 msec 以下
　境界域：成人男性431～450 msec、成人女性451～470 msec
‡ 男性被験者で437 msec 及び434 msec であった
治験薬の用法・用量（BID：1日2回）
P02489試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を10日間（その間、グリピジドを2回単回投与）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02811試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02812試験
ポサコナゾール経口懸濁液400 mg を単回、その後400 mg BID 経口投与を8日間
P02862試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間（その間、タクロリムスを2回単回投与）

QTcF 間隔のベースラインからの最大変化量の比較において、被験者の大多数（74%）は QTcF 間隔の最大変化量が0～30 msec 未満であり、最大変化量が60 msec 以上の被験者はいなかった[表 2.7.4-122]。また、ベースライン値に対する QTcF 間隔の平均変化量の比較では、すべての被験者でポサコナゾール経口懸濁液投与後の変化量が30 msec 未満であった[付録 2.7.4-128]。

QTcF 間隔のベースラインからの変化量とポサコナゾールの血漿中濃度との相関を検討するため、各被験者の T_{max} における QTcF 間隔の変化量の要約統計量を算出した。全体及び試験ごとの T_{max} における QTcF 間隔のベースラインからの変化量を[表 2.7.4-123]に示す。

各試験を併合したとき、T_{max} における QTcF 間隔の変化量の平均値及び中央値（約-4 msec）は、全体の平均変化量（約-5 msec、[表 2.7.4-121]）と同程度であった。そのため、QTcF 間隔の変化量はポサコナゾール曝露量の増加と相関していないものと考えられた。

表 2.7.4-123　T_{max}における QTcF 間隔のベースラインからの変化量
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

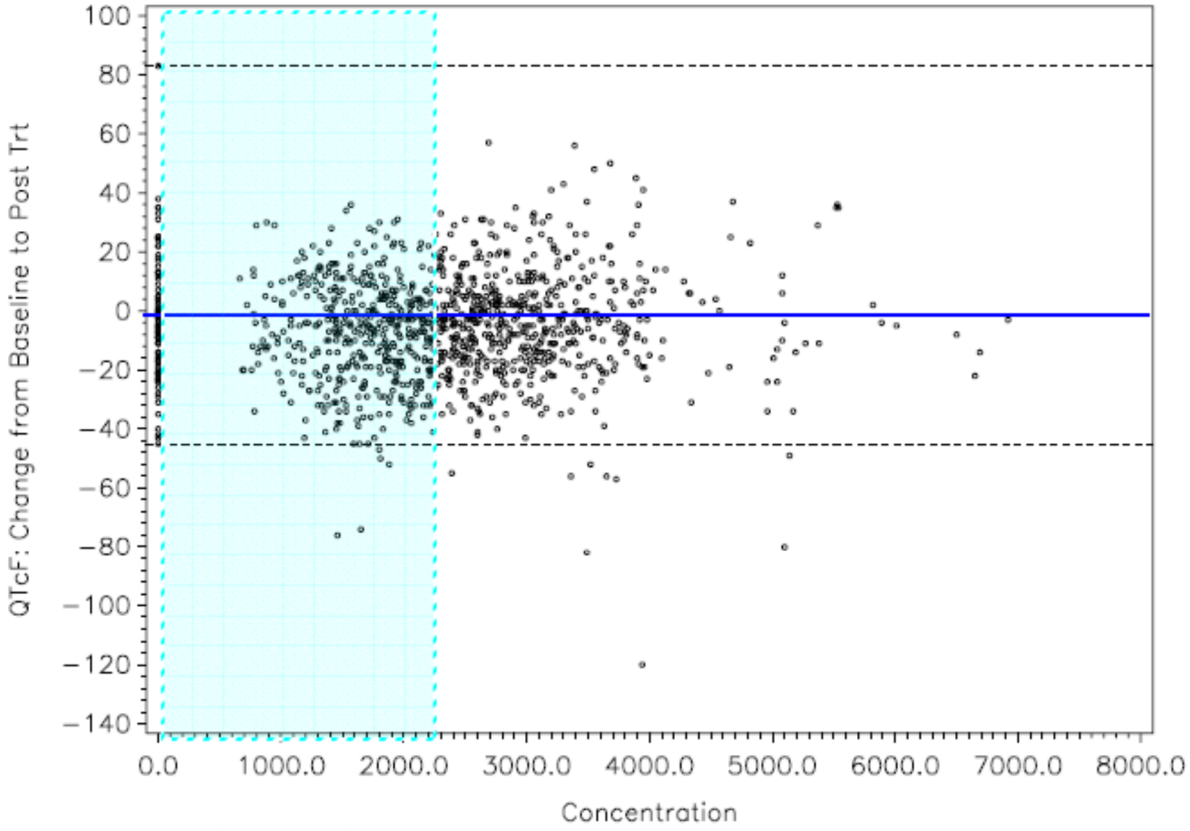
Protocol	N	QTc (Fridericia) Interval (msec)				
		Median	Mean	STD	Min	Max
ALL-posaconazole	173	-4.00	-4.42	20.95	-120.00	57.00
P02489-posaconazole	12	-9.00	-10.25	19.73	-57.00	17.00
P02810-posaconazole	48	-11.00	-7.25	28.37	-120.00	57.00
P02811-posaconazole	56	-1.50	-2.13	18.09	-50.00	41.00
P02812-posaconazole	22	-3.00	-3.36	15.16	-34.00	20.00
P02862-posaconazole	35	-4.00	-2.86	16.60	-33.00	48.00

治験薬の用法・用量（BID：1日2回）
P02489試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を10日間（その間、グリピジドを2回単回投与）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02811試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02812試験
ポサコナゾール経口懸濁液400 mg を単回、その後400 mg BID 経口投与を8日間
P02862試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間（その間、タクロリムスを2回単回投与）

投与後の心電図記録時点で、それぞれ血漿検体を採取したため、対応する心電図上の QTcF 間隔のベースラインからの変化量に対してそれぞれのポサコナゾールの血漿中濃度をプロットした。[図 2.7.4-1]の各点は、血漿中濃度の記録結果ごとの心電図上の QTcF 間隔の変化量を表す（被験者1例あたり約6点）。破線はプラセボ群における QTcF 間隔の最大変化量（増加及び減少）を表し、実線はゼロを表す。色付けされた枠は、健康被験者を対象とした試験で評価した用量であるポサコナゾール経口懸濁液400 mg BID が投与された P01893試験の被験者で、定常状態にて認められた血漿中濃度の範囲を示す。

それぞれの血漿中濃度と QTcF 間隔のベースラインからの変化量との間に相関関係はなかった。また、個々の AUC 値とベースラインからの変化量との間（線形回帰の傾き=0.000085）、並びに個々の C_{max} 値と T_{max} における時間を一致させたベースラインからの変化量との間（線形回帰の傾き=0.00115）にも相関関係はなかった[付録 2.7.4-136] [付録 2.7.4-134] [資料5.3.3.4.10: P02489] [資料5.3.3.3.1: P02810] [資料5.3.3.3.2: P02811] [資料5.3.1.1.2: P02812] [資料5.3.3.4.6: P02862]。

図 2.7.4-1　　ポサコナゾールの血漿中濃度に対する QTcF 間隔のベースラインからの変化図
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）



治験薬の用法・用量（BID：1日2回）
P02489試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を10日間（その間、グリピジドを2回単回投与）
P02810試験
ポサコナゾール経口懸濁液400 mg BID 経口投与又はプラセボ BID 経口投与を8日間
P02811試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間
P02812試験
ポサコナゾール経口懸濁液400 mg を単回、その後400 mg BID 経口投与を8日間
P02862試験
ポサコナゾール経口懸濁液400 mg BID 経口投与を8日間（その間、タクロリムスを2回単回投与）

2.7.4.4.2.1.2　　新錠剤を投与した第Ⅰ相試験（計5試験）（非日本人）

1)　単回投与試験（P04975、P07691、P07764試験及び P07783試験パート1）

健康被験者を対象としたポサコナゾール新錠剤100～400 mg を単回投与した第Ⅰ相試験では、単回投与後8日目、あるいは3日目及び8日目に QTc 間隔の評価を実施した。このため、ベースラインからの QTc 間隔変動の解析の重要性は低いと考え評価しなかった。

2)　反復投与試験（P05637試験及び P07783試験パート2）

健康被験者を対象としたポサコナゾール新錠剤（200 mg、300 mg 及び400 mg）を反復投与した際の QTc 間隔（QTcB 間隔及び QTcF 間隔）の異常値及びベースラインからの変化量の要約を[表 2.7.4-124]に示す。また、QTc 間隔のベースラインからの変化量が0 msec 未満、0 msec 超30 msec 以下、30 msec 超60 msec 以下及び60 msec 超に区分した結果を含む要約を[付録 2.7.4-138]に示す。

QTc 間隔がベースラインから60 msec を超えて増加した被験者は認められなかった。また、全体で QTc 間隔が500 msec を超えた被験者はおらず、男性で450 msec 以上又は女性で470 msec 以上の被験者もいなかった[資料5.3.3.1.7: P05637] [資料5.3.1.1.1: P07783]。

表 2.7.4-124　QTc 間隔の異常値及びベースラインからの変化量の要約
健康被験者へのポサコナゾール新錠剤反復投与試験（P05637 及び P07783 試験パート 2）
n/全被験者数（%）

		Any QTc	Bazett QTc	Fridericia QTc
200 mg MD P05637 (n = 10)	Change from Baseline >60 msec†	0 / 10	0 / 10	0 / 10
	Treatment Phase Value >500 msec‡	0 / 10	0 / 10	0 / 10
	Males - Treatment Phase Value ≥450 msec‡	0 / 5	0 / 5	0 / 5
	Males - Change from Baseline ≥60 msec to ≥450 msec†	0 / 5	0 / 5	0 / 5
	Females - Treatment Phase Value ≥470 msec‡	0 / 5	0 / 5	0 / 5
	Females - Change from Baseline ≥60 msec to ≥470 msec†	0 / 5	0 / 5	0 / 5
300 mg MD P07783 (n = 12)	Change from Baseline >60 msec†	0 / 12	0 / 12	0 / 12
	Treatment Phase Value >500 msec‡	0 / 12	0 / 12	0 / 12
	Males - Treatment Phase Value ≥450 msec‡	0 / 6	0 / 6	0 / 6
	Males - Change from Baseline ≥60 msec to ≥450 msec†	0 / 6	0 / 6	0 / 6
	Females - Treatment Phase Value ≥470 msec‡	0 / 6	0 / 6	0 / 6
	Females - Change from Baseline ≥60 msec to ≥470 msec†	0 / 6	0 / 6	0 / 6
400 mg MD P05637 (n = 9)	Change from Baseline >60 msec†	0 / 9	0 / 9	0 / 9
	Treatment Phase Value >500 msec‡	0 / 9	0 / 9	0 / 9
	Males - Treatment Phase Value ≥450 msec‡	0 / 6	0 / 6	0 / 6
	Males - Change from Baseline ≥60 msec to ≥450 msec†	0 / 6	0 / 6	0 / 6
	Females - Treatment Phase Value ≥470 msec‡	0 / 3	0 / 3	0 / 3
	Females - Change from Baseline ≥60 msec to ≥470 msec†	0 / 3	0 / 3	0 / 3

† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
MD：反復投与
治験薬の用法・用量（BID：1日2回、QD：1日1回）
P05637試験
200 mg MD（コホート1）：　ポサコナゾール新錠剤を1日目に200 mg 単回、6日目に200 mg BID、7-14日目に200 mg QD、15-22日目に200 mg BID 経口投与
400 mg MD（コホート2）：　ポサコナゾール新錠剤を1日目に400 mg 単回、6日目に400 mg BID、7-14日目に400 mg QD 経口投与
P07783試験
300 mg MD（パート2）：ポサコナゾール新錠剤を1日目に300 mg BID、2-8日目に300 mg QD 経口投与

2.7.4.4.2.1.3　　静注用溶液を投与した第 I 相試験（P06356試験）（非日本人）

健康被験者を対象としたポサコナゾール静注用溶液の第 I 相試験のうち、P06356試験でのみ心電図及び心エコー検査を1日目の C_{max} 付近で実施した。そのため、本項では P06356試験を用いて評価する。QTc 間隔（QTcB 間隔及び QTcF 間隔）の異常値及びベースラインからの変化量の要約を[付録 2.7.4-139]に示す。

心電図データ

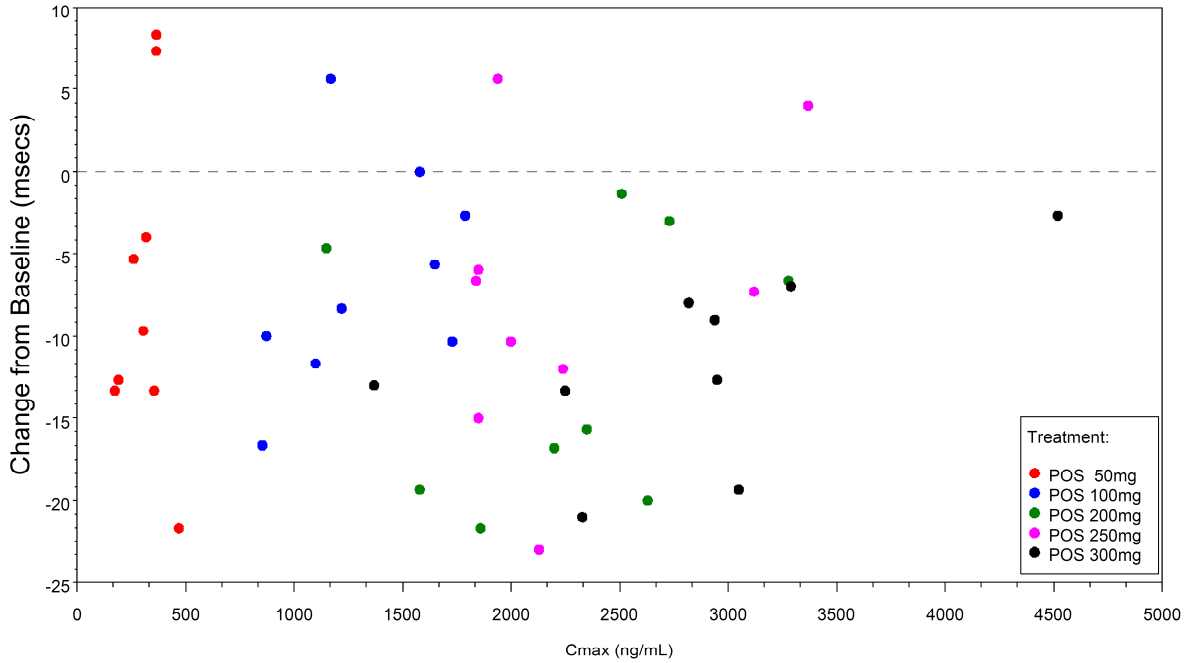
ポサコナゾール静注用溶液（50 mg、100 mg、200 mg、250 mg 及び300 mg）を単回投与した際、QTc 間隔がベースラインから60 msec を超えて増加した被験者は認められなかった。また、全体で QTc 間隔が500 msec を超えた被験者はおらず、男性で450 msec 以上又は女性で470 msec 以上の被験者もいなかった[付録 2.7.4-139]。

また、投与後30分の時点（T_{max}）における QTcF 間隔のベースラインからの個々の変化量を、C_{max} 別に[図 2.7.4-2]に示す。この図から、ほとんどの変化量が QTcF 間隔の短縮であり、ベースライン

から臨床的に意義のある QTcF 間隔の延長はないことが確認された。また、ポサコナゾール経口懸濁液と同様に[2.7.4.4.2.1.1 項]、C_{max} の増加に伴い QTcF 間隔がより大きく変化する傾向がないことも示唆された。

以上より、健康被験者を対象にポサコナゾール静注用溶液を投与した際の心電図データにおいて、臨床的に注目すべき所見はなかった。

図 2.7.4-2　　T_{max} における C_{max} 別の QTcF 間隔のベースラインからの変化図
健康被験者へのポサコナゾール静注用溶液投与試験（P06356 試験）
（単回投与の実薬群のみ）



治験薬の用法・用量
P06356試験
- 単回投与（パート1）：ポサコナゾール静注用溶液50 mg、100 mg、200 mg、250 mg、300 mg を単回末梢静脈内投与

心エコーデータ

P06356試験では、リアルタイムの左室駆出率（LVEF）測定値に基づき心室機能を評価した。LVEF を評価するための心エコーは、1日目の投与（ポサコナゾール静注用溶液の単回投与）後30分及び2時間の時点で実施した。

その結果、以下の定義に合致した被験者はいなかった。

- ベースライン時に LVEF が50.00%以上55.00%未満の場合、投与後に測定した LVEF が5ポイント以上の低下を示し、いずれかの時点で50.00%未満

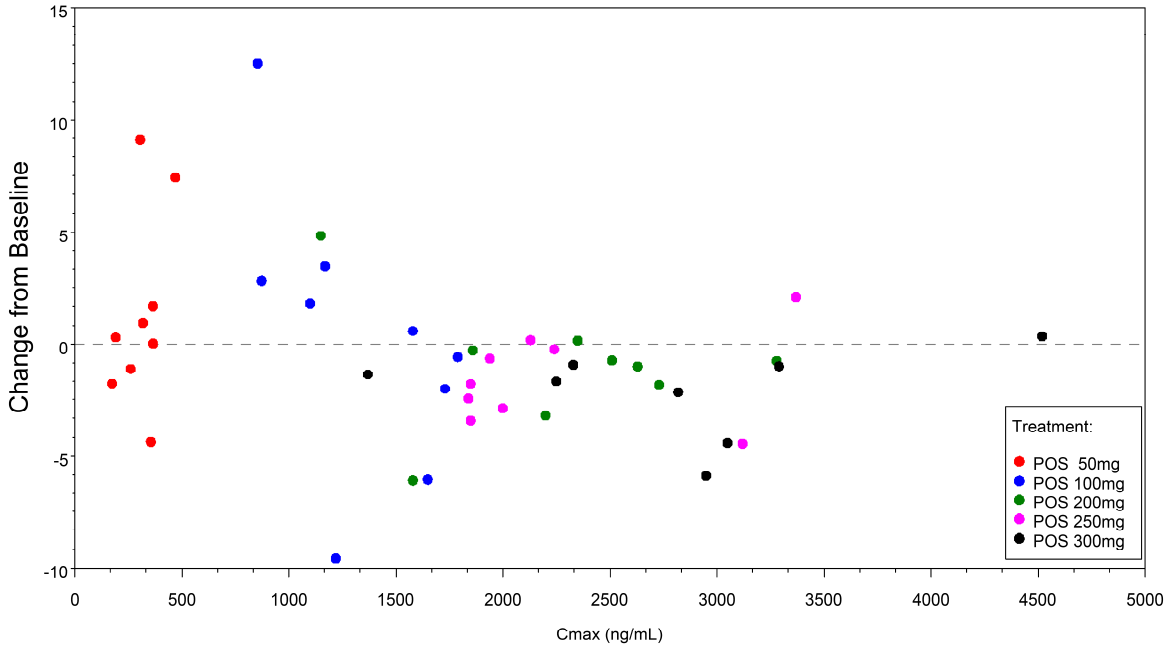
- ベースライン時に LVEF が55.00%以上であった場合、投与後に測定した LVEF が10ポイント以上の低下を示し、いずれかの時点で50.00%未満

P06356試験でポサコナゾール静注用溶液300 mg を単回投与した9例において、LVEF の平均値はベースライン時の57.6%から1日目の投与後30分の時点で54.6%に低下した。投与後2時間の時点で再度評価した際、この群の LVEF 平均値は55.9%であった。ポサコナゾール静注用溶液をより低い用量（50～250 mg）で単回投与したとき、1日目の投与後30分及び2時間の時点での LVEF 平均値は55%を超えており、ほぼベースライン値で維持された。ポサコナゾール静注用溶液投与後の個々の LVEF 測定値はすべて50%を超えていた。

投与後30分の時点（T_{max}）における LVEF のベースラインからの個々の変化量を、C_{max} 別に[図2.7.4-3]に示す。この図から、LVEF の変化量はわずかで臨床的な意義はないが、C_{max} の増加に伴い LVEF が低下する被験者が多くなる可能性が若干あることが示された。

Confidential

図 2.7.4-3　　T_{max}における C_{max}別の左室駆出率（%）のベースラインからの変化図
健康被験者へのポサコナゾール静注用溶液投与試験（P06356 試験）
（単回投与の実薬群のみ）



治験薬の用法・用量
P06356試験
・　単回投与（パート1）：ポサコナゾール静注用溶液50 mg、100 mg、200 mg、250 mg、300 mg を単回末梢静脈内投与

2.7.4.4.2.1.4　新錠剤及び静注用溶液を投与した第 I 相試験（P067試験）（日本人）

日本人の健康被験者を対象としたポサコナゾール新錠剤及び静注用溶液を単回又は反復投与した第 I 相試験（P067試験）では、心電図の結果に臨床的に意義のある変動はみられなかった[資料5.3.3.1.4: P067]。

2.7.4.4.2.2　　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.4.2.2.1　　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及び P01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）におけるポサコナゾール群（605例）、フルコナゾール群（539例）、イトラコナゾール群（58例）の心電図データを併合し、解析した[表 2.7.4-125]。C/I98-316試験ではベースライン、投与1ヵ月（4週）後及び4ヵ月（16週）後に、P01899試験ではベースライン、投与開始日及び投与終了日（無作為割付から治験薬の最終投与7日後まで）に心電図を記録した。

Bazett 及び Fridericia 式補正による心拍数補正法を用いて、中央評価者による QTc 間隔の読取り値を評価した。以下には Fridericia 法で補正した QTc 間隔（QTcF 間隔）のみを示す。

ベースライン時の QTcF 間隔の平均値及び中央値はポサコナゾール群とフルコナゾール群で類似していた（平均値約403 msec、中央値約406 msec）。C/I98-316試験は投与開始から16週間、P01899試験は無作為割付から最長12週間の最終測定時点で、QTcF 間隔のベースラインからの変化量の平均値はポサコナゾール群-1.8 msec、フルコナゾール群-6.3 msec であり、中央値は各群の平均値と同様であった[表 2.7.4-125]。

表 2.7.4-125　QTcF 間隔のベースライン値及びベースラインからの変化量の要約統計量
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

		QTcF (msec)				
Variable	n	Mean	SD	Median	Minimum	Maximum
Posaconazole (N = 605)						
Baseline Value	500	402.5	37.7	405	47	579
Change from Baseline at Endpoint	500	-1.8	41.3	-1	-419	426
Maximum Value - Change from Baseline During the Treatment Phase	500	7.7	36.9	9	-234	426
Fluconazole (N = 539)						
Baseline Value	430	403.5	38.5	407	40	589
Change from Baseline at Endpoint	430	-6.3	41.2	-5	-217	322
Maximum Value - Change from Baseline During the Treatment Phase	430	3.7	38.2	5	-217	322
Itraconazole (N = 58)						
Baseline Value	54	415.7	24.4	419	360	479
Change from Baseline at Endpoint	54	8.0	30.5	7	-67	78
Maximum Value - Change from Baseline During the Treatment Phase	54	19.6	29.4	19	-51	81

治験薬の用法・用量（TID：1日3回、QD：1日1回、BID：1日2回）
C/I98-316試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾールカプセル剤400 mg を QD 経口投与
P01899試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾール経口懸濁液400 mg を QD 経口投与
イトラコナゾール群：イトラコナゾール内用液200 mg を BID 経口投与

さらに、予防投与併合集団での中心傾向の解析に加えて、QTc 間隔の延長疑いがある重要な QTc 間隔又は QTc 間隔のベースラインからの変化量を次のように定義し、いずれかの基準に合致した被験者の割合を評価した。

1) QTcF 間隔のベースラインからの変化量が60 msec 以上
2) ベースライン値を問わず、投与後の QTcF 間隔が500 msec 以上
3) 男性被験者で、投与後の QTcF 間隔が450 msec 以上（全症例又はベースラインから60 msec 以上延長した症例）
4) 女性被験者で、投与後の QTcF 間隔が470 msec 以上（全症例又はベースラインから60 msec 以上延長した症例）

予防投与併合集団で、上記いずれかの QTc 間隔の延長疑いの基準に合致した被験者の要約を[付録 2.7.4-140]に示す。

ポサコナゾール群の10%（51/515例）及びフルコナゾール群の10%（43/440例）の被験者に QTcF 間隔の延長疑いが認められた[表 2.7.4-126]。6例（ポサコナゾール群3例、フルコナゾール群2例、イトラコナゾール群1例）で、QTcF 間隔が投与期間中の1時点以上で500 msec 以上となった。これらの6例は治験薬の投与前に QTc 間隔延長の既往歴があったほか、低カリウム血症や低マグネシウム血症等の電解質失調が認められていたか、心毒性のある化学療法を受けていた。

表 2.7.4-126　投与後の QTc 間隔及びベースラインからの変化量の要約
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

Values and Changes in Values	Number (%) of Subjects		
	Any QTc Correction	Bazett Correction	Fridericia Correction
Posaconazole			
All Posaconazole Subjects			
Any Increase From Baseline ≥60 msec†	26/500 (5)	22/500 (4)	15/500 (3)
Any Value ≥500 msec During Treatment Phase‡	8/515 (2)	7/515 (1)	3/515 (1)
Male			
Any Value ≥450 msec During Treatment Phase‡	80/304 (26)	76/304 (25)	37/304 (12)
Any Increase From Baseline ≥60 msec to a Value ≥450 msec During Treatment Phase†	11/296 (4)	9/296 (3)	3/296 (1)
Female			
Any Value ≥470 msec During Treatment Phase‡	13/211 (6)	12/211 (6)	6/211 (3)
Any Increase From Baseline ≥60 msec to a Value ≥470 msec During Treatment Phase†	5/204 (2)	5/204 (2)	4/204 (2)
Any Condition Met‡	**101/515 (20)**	**96/515 (19)**	**51/515 (10)**
Fluconazole			
All Fluconazole Subjects			
Any Increase From Baseline ≥60 msec†	25/430 (6)	24/430 (6)	17/430 (4)
Any Value ≥500 msec During Treatment Phase‡	5/440 (1)	4/440 (1)	2/440 (<1)
Male			
Any Value ≥450 msec During Treatment Phase‡	73/260 (28)	73/260 (28)	27/260 (10)
Any Increase From Baseline ≥60 msec to a Value ≥450 msec During Treatment Phase†	10/251 (4)	10/251 (4)	4/251 (2)
Female			
Any Value ≥470 msec During Treatment Phase‡	11/180 (6)	10/180 (6)	3/180 (2)
Any Increase From Baseline ≥60 msec to a Value ≥470 msec During Treatment Phase†	3/179 (2)	3/179 (2)	0/179
Any Condition Met‡	**96/440 (22)**	**94/440 (21)**	**43/440 (10)**
Itraconazole			
All Itraconazole Subjects			
Any Increase From Baseline ≥60 msec†	6/54 (11)	1/54 (2)	6/54 (11)
Any Value ≥500 msec During Treatment Phase‡	1/54 (2)	0/54	1/54 (2)
Male			
Any Value ≥450 msec During Treatment Phase‡	18/29 (62)	17/29 (59)	10/29 (34)
Any Increase From Baseline ≥60 msec to a Value ≥450 msec During Treatment Phase†	3/29 (10)	1/29 (3)	3/29 (10)
Female			
Any Value ≥470 msec During Treatment Phase‡	4/25 (16)	4/25 (16)	2/25 (8)
Any Increase From Baseline ≥60 msec to a Value ≥470 msec During Treatment Phase†	2/25 (8)	0/25	2/25 (8)
Any Condition Met‡	**22/54 (41)**	**21/54 (39)**	**13/54 (24)**

† 上記のデータは X/Y として示す。X は上記の定義を満たす被験者数、Y はベースライン値が得られ、かつ投与期間中の1時点以上で検査値が得られた被験者数を示す。
‡ 上記のデータは X/Y として示す。X は上記の定義を満たす被験者数、Y は投与期間中の1時点以上で検査値が得られた被験者数を示す。
治験薬の用法・用量（TID：1日3回、QD：1日1回、BID：1日2回）
C/I98-316試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾールカプセル剤400 mg を QD 経口投与
P01899試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾール経口懸濁液400 mg を QD 経口投与
イトラコナゾール群：イトラコナゾール内用液200 mg を BID 経口投与

予防投与併合集団で、治験担当医師により有害事象と判定された心電図 QT 延長を認めた被験者の割合はポサコナゾール群4.0%とフルコナゾール群3.5%で同程度であった[付録 2.7.4-19]。このうち、治験担当医師により副作用と判定されたものは、ポサコナゾール群2.3%及びフルコナゾール群1.1%であった[付録 2.7.4-20]。

ポサコナゾール群1例及びフルコナゾール群2例で、重篤な有害事象として心電図 QT 延長が報告された[付録 2.7.4-32]。ポサコナゾール群8例及びフルコナゾール群4例が、心電図 QT 延長の有害事象により治験薬の投与を中止した[付録 2.7.4-36]。

予防投与併合集団でトルサード ド ポアントが2例報告された。これらの被験者の簡潔な叙述を以下に示す。これらの被験者の詳細な叙述は[資料5.3.5.1.1: P01899] 14.3.3 項に示す。

- 被験者番号[redacted]：当該被験者は[redacted]歳の[redacted]人[redacted]性で、AML に対してイダルビシン及びシタラビンの投与を受けた後、P01899試験のポサコナゾール群に無作為に割り付けられた。この被験者には、動悸、低カリウム血症及び低マグネシウム血症の既往歴があった。また、低カリウム血症に伴う QTc 間隔延長の既往歴もあった。ベースライン時に QTc 間隔は 430 msec で、低カリウム血症に該当する T 波異常が認められた。無作為割付から21日目に動悸に続いて失神が起こり、遠隔記録でトルサード ド ポアントが認められた。無作為割付から22日目の QTc 間隔は566 msec であった。また、低マグネシウム血症及び低カルシウム血症が認められ、リドカイン、マグネシウム及びカリウムの投与後に症状は回復した。ポサコナゾールは投与中止となり、その後の発現は報告されなかった。治験担当医師は失神、QT/QTc 延長及びトルサード ド ポアントの事象と治験薬（ポサコナゾール）との因果関係をどちらともいえないと判定した。また、治験依頼者は治験薬との因果関係をどちらともいえないと判定する一方、アントラサイクリンの催不整脈性が低カリウム血症、低マグネシウム血症及び潜在的な遅発性心毒性に寄与していると判断した。
- 被験者番号[redacted]：当該被験者は[redacted]歳の[redacted]系[redacted]性で、AML に対してシタラビン及びイダルビシンの投与を受けた後、真菌症の予防投与のため P01899試験のフルコナゾール群に無作為に割り付けられた。被験者には低カルシウム血症の既往歴があり、ベースライン時の心電図で QTc 間隔は453 msec であった。投与17日目にアスペルギルス肺炎によりフルコナゾールは中止された。フルコナゾールの最終投与から22日後に重度の呼吸不全が認められ、人工呼吸が必要となった。翌日、血液量減少性ショック及び血胸が報告され、2日後にトルサード ド ポアントが認められた。被験者は1週間後（最終投与から33日後）に真菌性肺炎の進行により死亡した。トルサード ド ポアントとフルコナゾールとの因果関係は考えにくいと判定された。

以上より、免疫不全被験者に対して重篤な真菌症の予防にポサコナゾール経口懸濁液を使用した場合、フルコナゾールと同様に、QT 間隔延長が誘発される可能性は低いと考えられる。一方で、他のアゾール系抗真菌薬で認められているようにポサコナゾールは強いチトクロム P450（CYP）

3A4阻害作用を有しているため、この経路を介して代謝され、QT 間隔延長を引き起こすことが知られている他の薬剤は慎重に併用投与する必要があると考えられる。

2.7.4.4.2.2.2　　新錠剤を投与した後期第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

ポサコナゾール新錠剤の予防投与試験（P05615試験）の心電図データを解析した。心電図検査はベースライン、投与1日目（投与開始前）、3日目、8日目、28日目（又は投与終了時）に実施した。

200 mg コホートには、パート1A（ポサコナゾール新錠剤200 mg を投与1日目に BID、2日目以降は QD 経口投与）の被験者のデータを含めた。300 mg コホートには、パート1B 及びパート2（ポサコナゾール新錠剤300 mg を投与1日目に BID、2日目以降は QD 経口投与）の被験者のデータを含めた。

1)　200 mg コホート

ポサコナゾール新錠剤200 mg を投与した被験者では、治験実施計画書に事前に規定した有意な QT 間隔への作用（QTc 間隔：500 msec を超える）の基準に合致した被験者はいなかった[表 2.7.4-127]。

表 2.7.4-127　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（200 mg コホート）（All Treated Subjects）

	Count/Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 200 mg		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >60 msec†	0/20	0/20	0/20
Treatment Phase Value >500 msec‡	0/20	0/20	0/20
Males - Treatment Phase Value ≥450 msec‡	1/12 (8)	1/12 (8)	0/12
Males - Change from Baseline ≥60 msec to ≥450 msec†	0/12	0/12	0/12
Females - Treatment Phase Value ≥470 msec‡	1/8 (13)	1/8 (13)	1/8 (13)
Females - Change from Baseline ≥60 msec to ≥470 msec†	0/8	0/8	0/8

n：被験者数、POS：ポサコナゾール
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
200 mg コホート：ポサコナゾール新錠剤200 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

2)　300 mg コホート

ポサコナゾール新錠剤300 mg を投与した被験者のうち、QTcF 間隔が投与期間中の1時点以上で500 msec を超えた被験者は1例（被験者番号[redacted]）であった[表 2.7.4-128]。治験実施計画書に

事前に規定した有意な QT 間隔への作用（QTc 間隔：500 msec を超える）の基準に合致したこの被験者の簡潔な叙述は以下に、詳細な叙述は[資料5.3.3.2.2: P05615] 14.8.4 項に示す。

- 被験者番号[redacted]：当該被験者は、高血圧、左脚ブロック及び初発 AML の既往歴がある[redacted]歳の[redacted]性であった。AML に対して化学療法を受け、重度の好中球減少症に対する抗真菌薬予防投与として治験薬（ポサコナゾール 300 mg QD）を投与された。投与前（1日目）の心電図で、心拍数77（左脚ブロックなし）、QT 間隔:369 msec、QTcB 間隔:418 msec、QTcF 間隔:401 msec であった。治験薬投与3日目の心電図で、心拍数109（左脚ブロックあり）、QT 間隔:363 msec、QTcB 間隔:490 msec、QTcF 間隔:443 msec であった。8日目の心電図で、心拍数102（左脚ブロックあり）、QT 間隔:420 msec、QTcB 間隔:549 msec、QTcF 間隔:502 msec であった。16日目の心電図で、心拍数111（左脚ブロックあり）、QT 間隔:364 msec、QTcB 間隔:494 msec、QTcF 間隔:446 msec であった。治験薬投与は中止されず、被験者は29日間の投与を完了した。治験薬の最終投与日（29日目）の心電図で、心拍数111（左脚ブロックあり）、QT 間隔:367 msec、QTcB 間隔:500 msec、QTcF 間隔:451 msec であった。被験者に症状はなかった。ポサコナゾールの血漿中トラフ濃度の最大値は14日目の2070 ng/mL であった。

表 2.7.4-128　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール新錠剤の予防投与試験（P05615 試験）
（300 mg コホート）（All Treated Subjects）

	Count/Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >60 msec†	14/208 (7)	9/208 (4)	11/208 (5)
Treatment Phase Value >500 msec‡	3/208 (1)	3/208 (1)	1/208
Males - Treatment Phase Value ≥450 msec‡	41/130 (32)	41/130 (32)	24/130 (18)
Males - Change from Baseline ≥60 msec to ≥450 msec†	7/130 (5)	5/130 (4)	5/130 (4)
Females - Treatment Phase Value ≥470 msec‡	11/78 (14)	11/78 (14)	6/78 (8)
Females - Change from Baseline ≥60 msec to ≥470 msec†	3/78 (4)	1/78 (1)	3/78 (4)

n：被験者数、POS：ポサコナゾール
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
300 mg コホート：ポサコナゾール新錠剤300 mg を治験薬投与1日目は BID、2日目以降は QD 経口投与

2.7.4.4.2.2.3　　静注用溶液を投与した後期第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）の心電図データを解析した。心電図検査は、コホート1及び2でベースライン、投与1日目、3日目、7日目及び14日目（又は投与終了時）に実施し、コホート3でベースライン、投与1日目、5日目及び10日目に実施した。心電図検査はすべてポサコナゾールの注入終了時に行った。

1)　200 mg反復静脈内投与（コホート1）

コホート1（ポサコナゾール静注用溶液200 mg 反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID 経口投与）では、治験実施計画書に事前に規定した有意な QT 間隔延長（QTc 間隔：500 msec を超える）の基準に合致した被験者はいなかった。被験者ごとの心電図結果の一覧を[資料5.3.3.2.3: P05520] 14.5.9.1 項に、QTc 間隔の異常値及びベースラインからの変化量の要約を[表 2.7.4-129]に示す。

表 2.7.4-129　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（200 mg 反復静脈内投与：コホート 1）（All Treated Subjects）

	Count/Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects Cohort 1 POS IV 200 mg + Oral suspension 400 mg BID		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline ≥60 msec†	1 / 21 (5)	0 / 21	1 / 21 (5)
Treatment Phase Value ≥500 msec‡	0 / 21	0 / 21	0 / 21
Males - Treatment Phase Value ≥450 msec‡	5 / 13 (38)	4 / 13 (31)	3 / 13 (23)
Males - Change from Baseline ≥60 msec to ≥450 msec†	1 / 13 (8)	0 / 13	1 / 13 (8)
Females - Treatment Phase Value ≥470 msec‡	0 / 8	0 / 8	0 / 8
Females - Change from Baseline ≥60 msec to ≥470 msec†	0 / 8	0 / 8	0 / 8

n：被験者数、POS：ポサコナゾール
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート1：　ポサコナゾール静注用溶液200 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

2)　300 mg反復静脈内投与（コホート2及び3併合）

コホート2（ポサコナゾール静注用溶液300 mg 反復静脈内投与+ポサコナゾール経口懸濁液400 mg BID 経口投与）及びコホート3（ポサコナゾール静注用溶液300 mg 反復静脈内投与+ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID 経口投与）併合の被験者ごとの心電図結果の一覧を[資料5.3.3.2.3: P05520] 14.5.9.1 項に、QTc 間隔の異常値及びベースラインからの変化量の要約を[表 2.7.4-130]及び[表 2.7.4-131]に示す。

表 2.7.4-130　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 2）（All Treated Subjects）

	Count/Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects Cohort 2 POS IV 300 mg + Oral suspension 400 mg BID		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline ≥60 msec†	1 / 24 (4)	0 / 24	1 / 24 (4)
Treatment Phase Value ≥500 msec‡	0 / 24	0 / 24	0 / 24
Males - Treatment Phase Value ≥450 msec‡	4 / 13 (31)	4 / 13 (31)	2 / 13 (15)
Males - Change from Baseline ≥60 msec to ≥450 msec†	1 / 13 (8)	0 / 13	1 / 13 (8)
Females - Treatment Phase Value ≥470 msec‡	3 / 11 (27)	3 / 11 (27)	2 / 11 (18)
Females - Change from Baseline ≥60 msec to ≥470 msec†	0 / 11	0 / 11	0 / 11

n：被験者数、POS：ポサコナゾール
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QD：1日1回）
コホート2：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～14日目は QD にて中心静脈内投与、治験薬投与15日目以降は、ポサコナゾール経口懸濁液400 mg を BID にて14日間経口投与

表 2.7.4-131　QTc 間隔のベースラインからの変化量及び異常値が認められた被験者の要約
ポサコナゾール静注用溶液の予防投与試験（P05520 試験）
（300 mg 反復静脈内投与：コホート 3）（All Treated Subjects）

	Count/Number of Subjects/Number of Subjects Evaluable (n/N,%) All Treated Subjects Cohort 3 POS IV 300 mg + Oral suspension 200 mg TID or Oral suspension 400 mg BID		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline ≥60 msec†	5 / 203 (2)	4 / 203 (2)	3 / 203 (1)
Treatment Phase Value ≥500 msec‡	2 / 208 (1)	2 / 208 (1)	2 / 208 (1)
Males - Treatment Phase Value ≥450 msec‡	23 / 113 (20)	23 / 113 (20)	13 / 113 (12)
Males - Change from Baseline ≥60 msec to ≥450 msec†	3 / 109 (3)	2 / 109 (2)	3 / 109 (3)
Females - Treatment Phase Value ≥470 msec‡	14 / 95 (15)	14 / 95 (15)	3 / 95 (3)
Females - Change from Baseline ≥60 msec to ≥470 msec†	1 / 94 (1)	1 / 94 (1)	0 / 94

n：被験者数、POS：ポサコナゾール
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QD：1日1回、TID：1日3回）
コホート3：　ポサコナゾール静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2～5日目（薬物動態評価期間の延長例では10日目まで）は QD にて中心静脈内投与（同一の末梢静脈カテーテルからの投与は1回のみ可とした）、治験薬投与6日目（又は11日目）以降、切替え可能な場合は、ポサコナゾール経口懸濁液200 mg TID 又は400 mg BID にて最長23日間経口投与

コホート2及び3では、投与期間中の1時点以上で QTc 間隔が500 msec 以上となった被験者は2例であった。1例（被験者番号[redacted]）は投与1日目の QTcF が500 msec であり、もう1例（被験者

番号[redacted]）は投与5日目の QTcF が542 msec であった。被験者番号[redacted]の簡潔な叙述は以下に、詳細な叙述は[資料5.3.3.2.3: P05520] 14.6.2 項に示す。

- 被験者番号[redacted]：当該被験者は[redacted]歳の[redacted]人[redacted]性で、造血幹細胞移植（HSCT）後に試験に参加した。被験者には、大動脈拡張［20[redacted]年（安定）］、心房細動［20[redacted]年（回復）］、心嚢液貯留［20[redacted]年（安定）］及び洞性徐脈［20[redacted]年（安定）］の心疾患関連の既往歴があった。ベースライン時の QTc 間隔は500 msec 未満（456 msec、未補正）であったが、5日目に QTc 間隔が500 msec 以上となった。治験薬の投与は中止され、治験担当医師は心電図 QTc 間隔延長とポサコナゾールとの因果関係をどちらともいえないと判断した。3日目のポサコナゾールの C_{min} は1,050 ng/mL であった。

2.7.4.4.2.3　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.4.2.3.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及びP00041試験）（rIFI併合集団）でQT間隔に対するポサコナゾールの潜在的な作用を検討するため、P01893試験で収集した心電図データを用いてrIFI併合集団における中心傾向の解析を行った。この試験では、ベースライン時及びポサコナゾール投与後の規定の時点で、心拍数、RR間隔、PR間隔、QRS間隔、Bazett補正式によるQT間隔（QTcB間隔）、Fridericia補正式によるQT間隔（QTcF間隔）を記録する標準的な12誘導心電図を用いて測定した。すべての心電図データを収集後、中央検査室に転送した。ベースライン時のQTcF間隔の平均値及び中央値は約401 msecであった。発熱性好中球減少症被験者は最長42日、rIFI被験者は最長6ヵ月の最終測定時点で、QTcF間隔のベースラインからの変化量の平均値は-2.3 msec、中央値は-1 msecであった[表2.7.4-132]。P00041試験でも同様の数値が認められ、QTcF間隔のベースラインからの変化量の中央値は1ヵ月目が0 msec（n＝161）、最終測定時点が-3.7 msec（n＝186）であった。

表2.7.4-132　QTcF間隔のベースライン値及びベースラインからの変化量の要約統計量
ポサコナゾール経口懸濁液の治療試験（P01893試験）（All Randomized Subjects）

Variable	n	QTcF (msec)				
		Mean	Std	Median	Minimum	Maximum
Baseline Value	98	401.9	25.9	401	350	463
Change from Baseline at Endpoint	79	-2.3	26.3	-1	-66	85
Maximum Change from Baseline During the Treatment Phase	79	5.1	25.6	4	-61	85

Treatment Phase：治験薬投与開始から最終投与7日後まで
治験薬の用法・用量（BID：1日2回、QID：1日4回、QD：1日1回）
P01893試験
400 mg BID群：負荷用量200 mg QIDを2日間経口投与後、維持用量400 mg BIDを経口投与
600 mg BID群：負荷用量400 mg QIDを2日間経口投与後、維持用量600 mg BIDを経口投与
800 mg QD群：負荷用量800 mg BIDを2日間経口投与後、維持用量800 mg QDを経口投与

さらに、rIFI併合集団での中心傾向の解析に加えて、QTc間隔に対する潜在的作用の疑いがある重要なQTc間隔又はQTc間隔のベースラインからの変化量を次のように定義し、いずれかの基準に合致した被験者の割合を評価した。

1) QTc間隔のベースラインからの変化量が60 msec以上
2) ベースライン値を問わず、投与後のQTc間隔が500 msec以上
3) 男性被験者で、ベースライン値を問わず、投与後のQTc間隔が450 msec以上（全症例又はベースラインから60 msec以上延長した症例）
4) 女性被験者で、ベースライン値を問わず、投与後のQTc間隔が470 msec以上（全症例又はベースラインから60 msec以上延長した症例）

rIFI 併合集団で、上記いずれかの QTc 間隔に対する潜在的作用の基準に合致した被験者の要約を[付録 2.7.4-141]に示す。この要約は、補正法（Bazett、Fridericia 又は機器読取り）に加えて、すべての QTc 間隔の異常値を対象とする。心電図パラメータに対するポサコナゾールの有害作用を示唆する一貫性のあるパターンは認められなかった。

ベースライン時及び投与期間中の1時点以上で心電図を記録した rIFI 併合集団の被験者のうち、6%で QTcF 間隔のベースラインからの変化量が60 msec 以上であり、1%で投与期間中の QTcF 間隔が500 msec 以上であった[表 2.7.4-133]。

表 2.7.4-133　QTcF 間隔のベースラインからの変化量及び異常値が認められた被験者の要約
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

All Subjects rIFI Pool (n = 428)	
Change from baseline QTc interval ≥60 msec†	17 / 265　(6)
Treatment Phase QTc interval ≥500 msec‡	2 / 288　(1)

Treatment Phase：治験薬投与開始から最終投与7日後まで
上記のデータは X/Y（%）として示す。
X は定義を満たす被験者数、Y は投与期間中の1時点以上で該当する検査値が記録された被験者数を示す。
† ベースライン時及び投与期間中の1時点以上で検査値がある被験者を分母とする。
‡ 投与期間中の1時点以上で検査値がある被験者を分母とする。
治験薬の用法・用量（BID：1日2回、QID：1日4回、QD：1日1回）
P01893試験
400 mg BID 群：負荷用量200 mg QID を2日間経口投与後、維持用量400 mg BID を経口投与
600 mg BID 群：負荷用量400 mg QID を2日間経口投与後、維持用量600 mg BID を経口投与
800 mg QD 群：負荷用量800 mg BID を2日間経口投与後、維持用量800 mg QD を経口投与
P00041試験
入院被験者には、入院中はポサコナゾール経口懸濁液200 mg QID、退院後は400 mg BID、
外来被験者には、ポサコナゾール経口懸濁液400 mg BID を経口投与

rIFI 併合集団の1%（2/288例）で、投与期間中の QTcF 間隔が500 msec 以上であった。これらの被験者の簡潔な叙述を以下に示す。なお、いずれも P00041試験の被験者であった。

- 被験者番号[redacted]：当該被験者は、電解質失調、貧血及び血小板減少症の既往歴がある[redacted]歳[redacted]性で、165日目に自己免疫性溶血性貧血と診断された。171日目に QTcF 間隔がベースラインから117 msec 増加して515 msec となり、このとき、発熱、低血圧及び黄疸も認められた。被験者は試験を継続し、223日目に試験を完了した。
- 被験者番号[redacted]：当該被験者は腎不全に罹患した[redacted]歳[redacted]性で、2日目の心電図（この被験者で記録した唯一の心電図）で QTcF 間隔が542 msec となった。被験者はアレルギー反応により9日目に試験を中止した。

別の16例で QTcF 間隔のベースラインからの変化量が60 msec 以上であった。これらの被験者には不整脈の既往歴、心疾患、末期臓器不全等の複数の寄与因子があり、大多数に電解質失調及び血液疾患、一部に敗血症が認められた。

2.7.4.4.2.3.2　　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）では、心拍数、RR 間隔、PR 間隔、QRS 間隔、Bazett 補正式による QT 間隔（QTcB 間隔）、Fridericia 補正式による QT 間隔（QTcF 間隔）を記録する12誘導心電図を用いて測定した。心電図はベースライン、投与1、3、8、42、84日目及び最終投与の14日後、製剤を切り替えた被験者では製剤切替時に、それぞれ血漿中薬物濃度が最高値付近となるであろう測定推奨時間帯（ポサコナゾール静注用溶液：投与終了直後、ポサコナゾール新錠剤：投与後3～5時間、注射用ボリコナゾール：投与終了直後、ボリコナゾール錠：投与後1～2時間）に記録した。

ポサコナゾール群のベースライン時の QTcF 間隔の平均値及び中央値は約410 msec であった。投与期間中の QTcF 間隔のベースラインからの最大変化量の平均値は13.0 msec、中央値は10.0 msec であり[表 2.7.4-134]、ボリコナゾール群も同様の結果であった[表 2.7.4-135]。また、本試験において QT 延長とポサコナゾールの曝露量（C_{avg}）との関連性を評価した結果、QT 延長の有害事象及び副作用の発現並びに当該事象発現患者での投与中止に関して、概して曝露量との関連性は認められなかった[2.7.2.1.4.3.2 項]。

表 2.7.4-134　QTcF 間隔のベースラインからの変化量の要約
ポサコナゾール新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101 試験）
（コホート 1 及び 2 併合）ポサコナゾール群（ASaT）
Summary Statistics for Baseline and Change from Baseline in QTc Intervals, Based on the Fridericia Calculation
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	N	QTc Interval Fridericia (msec)				
		Mean	SD	Median	Min	Max
Baseline Value	77	412.2	19.4	409.0	370.0	448.0
Maximum Change From Baseline During the Treatment Phase	76	13.0	16.9	10.0	-37.0	65.0

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase.
SD=Standard deviation, Min=Minimum, Max=Maximum

Source: [P101MK5592: adam-adeg]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで 300 mg を QD にて投与

表 2.7.4-135　QTcF 間隔のベースラインからの変化量の要約
ポサコナゾール新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101 試験）
（コホート 1 及び 2 併合）ボリコナゾール群（ASaT）
Summary Statistics for Baseline and Change from Baseline in QTc Intervals, Based on the Fridericia Calculation
in Voriconazole Treatment Group
Cohort 1 and 2 (ASaT)

	N	QTc Interval Fridericia (msec)				
		Mean	SD	Median	Min	Max
Baseline Value	38	409.8	17.2	411.0	369.0	443.0
Maximum Change From Baseline During the Treatment Phase	38	10.6	10.1	10.0	-7.0	41.0
Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. SD=Standard deviation, Min=Minimum, Max=Maximum						

Source: [P101MK5592: adam-adeg]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

QTc 間隔に対する潜在的作用の疑いがある重要な QTc 間隔又は QTc 間隔のベースラインからの変化量を次のように定義し、いずれかの基準に合致した被験者の割合を評価した。

1)　QTcF 間隔のベースラインからの変化量が60 msec 超
2)　ベースライン値を問わず、投与後の QTcF 間隔が500 msec 以上

上記 QTc 間隔に対する潜在的作用のいずれかの基準に合致した被験者の要約を[表 2.7.4-136]に示す。

ポサコナゾール群及びボリコナゾール群（以下同順）の7.8%（6/77例）及び2.6%（1/38例）で QTcF 間隔のベースラインからの変化量が60 msec 超であり、5.2%（4/77例）及び0.0%（0/38例）で投与後の QTcF 間隔が500 msec 以上であった。

表 2.7.4-136　QTcF 間隔のベースラインからの変化量及び異常値が認められた被験者の要約
ポサコナゾール新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Subjects With ECG Findings That Met Predetermined Criteria
Cohort 1 and 2 (ASaT)

Test Name (Unit)	Criterion	MK-5592		Voriconazole	
		n/m	(%)	n/m	(%)
Subjects in population		77		38	
QTc Interval Fridericia (msec)	Prolongation compared to baseline ≥ 30 to ≤ 60 msec	14/77	(18.2)	3/38	(7.9)
	Prolongation compared to baseline > 60 msec	6/77	(7.8)	1/38	(2.6)
	Post-baseline value ≥ 500 msec	4/77	(5.2)	0/38	(0.0)
n / m = Number of subjects in the population with valid predose and postdose values of the given parameter meeting the predefined limit criteria / Number of subjects in the population with valid predose and postdose values of the given parameter.					

Source: [MK5592PN101: adam-adeg]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで 300 mg を QD にて投与
ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで 4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

投与期間中の QTcF 間隔が500 msec 以上であった4例の簡潔な叙述を以下に示す。

- 被験者番号[redacted]：当該被験者は、慢性肺アスペルギルス症と診断された[redacted]歳[redacted]性で、ポサコナゾール群に割り付けられた。ポサコナゾール新錠剤の投与12日目に重篤な間質性肺疾患のため治験薬を投与中止した。投与中止3日後の QTcF 間隔はベースラインの398 msec より増加して514 msec となり、治験担当医師は、心電図 QT 延長の副作用と判定した。翌日の QTcF 間隔は502 msec であった。
- 被験者番号[redacted]：当該被験者は、慢性肺アスペルギルス症と診断された[redacted]歳[redacted]性で、ポサコナゾール群に割り付けられた。ポサコナゾール新錠剤の投与14日目に重篤な発熱のため治験薬を休薬した。休薬3日後に重篤な慢性閉塞性肺疾患が発現し、同日 QTcF 間隔はベースラインの410 msec より増加して523 msec となり、治験担当医師は、心電図 QT 延長の副作用と判定した。休薬15日後の QTcF 間隔は408 msec に回復した。
- 被験者番号[redacted]：当該被験者は、慢性肺アスペルギルス症と診断された[redacted]歳[redacted]性で、ポサコナゾール群に割り付けられた。ポサコナゾール新錠剤の投与29日目に発熱の副作用が発現したため、31日目で治験薬を投与中止した。投与中止5日後の QTcF 間隔はベースラインの400 msec より増加して527 msec となり、同日の別の記録は392 msec であり、投与中止14日後の QTcF 間隔も395 msec に回復した。

- 被験者番号[redacted]：当該被験者は、[redacted]歳[redacted]性でポサコナゾール群に割り付けられたが、臨床判定委員会により治験対象である慢性肺アスペルギルス症、侵襲性アスペルギルス症、フサリウム症、ムーコル症のいずれにも該当しないと判定された。ポサコナゾール新錠剤の投与43日目の QTcF 間隔はベースラインの435 msec より増加して540 msec となり、治験担当医師は心電図 QT 延長を副作用と判定して治験薬を投与中止した。同日、上室性期外収縮の副作用も認められた。投与中止14日後の QTcF 間隔は432 msec に回復した。

2.7.4.4.3　安全性に関連する他の観察項目及び評価

2.7.4.4.3.1　副腎皮質刺激ホルモン

ステロイド生成へのポサコナゾールの影響を評価するため、血中コルチゾール及びアルドステロンの測定、並びに ACTH 負荷後の血中コルチゾール及びアルドステロンへの影響を評価した。

2.7.4.4.3.1.1　健康被験者を対象とした試験結果

####### 2.7.4.4.3.1.1.1　経口懸濁液（旧錠剤又は旧カプセルを含む）を投与した第Ⅰ相試験（非日本人）

健康被験者を対象としたポサコナゾール経口懸濁液の投与試験（I95-098及び I96-089試験）では、ステロイド生成へのポサコナゾールの影響を評価するため、血中テストステロン及びコルチゾール濃度を測定した。その結果、コルチゾール濃度に変化はなかったものの、一部の被験者でテストステロン濃度の減少が認められた。大部分のテストステロン濃度は基準範囲（14～35.0 nmol/L）から大きく外れるものではなかった[資料5.3.3.1.5: I95_098] [資料5.3.3.1.6: I96_089]。

####### 2.7.4.4.3.1.1.2　新錠剤を投与した第Ⅰ相試験（非日本人）

健康被験者を対象としたポサコナゾール新錠剤を反復投与した P05637試験では、ポサコナゾール新錠剤投与が血中アルドステロンに及ぼす影響、並びに ACTH 負荷後のアルドステロン及びコルチゾールに及ぼす影響を評価した。

血中アルドステロンへの影響

ポサコナゾール200 mg 群では、血中アルドステロン濃度はベースライン時の177.5 pmol/L から1日目に86.0 pmol/L、11日目に61.0 pmol/L に減少した。24日目には128.3 pmol/L となり、部分的にベースライン値まで回復した[表 2.7.4-137]。

ポサコナゾール400 mg 群では、血中アルドステロン濃度はベースライン時に197.3 pmol/L であり、1日目に67.8 pmol/L、11日目に72.8 pmol/L に減少した。16日目は166.4 pmol/L であり、部分的にベースライン値に回復した[表 2.7.4-138]。

なお、プラセボ群でも、血中アルドステロン濃度がベースライン時の249.7 pmol/L から1日目に152.6 pmol/L に減少したが、11日目に221.9 pmol/L まで回復した。16日目には628.8 pmol/L に増加し、24日目には554.8 pmol/L であった[資料5.3.3.1.7: P05637]。

以上より、ポサコナゾール200 mg 及び400 mg を QD/BID 投与したとき、血中アルドステロン濃度が減少するものの、経時的にベースライン値に回復する傾向が認められ、この傾向はプラセボ群でも認められた。また、アルドステロン濃度に対するポサコナゾールの影響と用量との間に相関性はないと思われた。

表 2.7.4-137　血中アルドステロン濃度（pmol/L）の時間区分別要約統計量
健康被験者へのポサコナゾール新錠剤投与試験（P05637 試験）
（ポサコナゾール新錠剤 200 mg QD/BID 投与群：コホート 1）

POS 200 mg QD/BID							
Lab Test	Relative Time	n	Mean	SD	Median	Minimum	Maximum
Aldosterone	Baseline	10	177.5	103.1	152.6	83	416
	Day 1	10	86.0	51.4	55.5	55	194
	Day 11	10	61.0	17.5	55.5	55	111
	Day 24	8	128.3	86.4	83.2	55	250

検出限界は55 pmol/L であり、検出限界未満の結果は55 pmo/L として計算した
POS：ポサコナゾール、QD：1日1回、BID：1日2回、n：被験者数、SD：標準偏差
治験薬の用法・用量
P05637試験
200 mg QD/BID（コホート1）：ポサコナゾール新錠剤を1日目に200 mg 単回、6日目に200 mg BID、7-14日目に200 mg QD、15-22日目に200 mg BID 経口投与

表 2.7.4-138　血中アルドステロン濃度（pmol/L）の時間区分別の要約統計量
健康被験者へのポサコナゾール新錠剤投与試験（P05637 試験）
（ポサコナゾール新錠剤 400 mg QD/BID 投与群：コホート 2）

POS 400 mg QD/BID							
Lab Test	Relative Time	n	Mean	SD	Median	Minimum	Maximum
Aldosterone	Baseline	9	197.3	124.4	166.4	55	416
	Day 1	9	67.8	37.0	55.5	55	166
	Day 11	8	72.8	49.0	55.5	55	194
	Day 16	8	166.4	281.7	55.5	55	860

検出限界は55 pmol/L であり、検出限界未満の結果は55 pmo/L として計算した
POS：ポサコナゾール、QD：1日1回、BID：1日2回、n：被験者数、SD：標準偏差
治験薬の用法・用量
P05637試験
400 mg QD/BID（コホート2）：ポサコナゾール新錠剤を1日目に400 mg 単回、6日目に400 mg BID、7-14日目に400 mg QD 経口投与

ACTH 負荷後の血中アルドステロン及びコルチゾールへの影響

ポサコナゾール新錠剤200 mg 又はプラセボを QD/BID 投与したコホート（コホート1）では-1日目、10日目及び23日目、ポサコナゾール新錠剤400 mg 又はプラセボを QD/BID 投与したコホート（コホート2）では-1日目、10日目及び15日目に ACTH（cosyntropin）250 μg を午前7時に静脈内投与した。ACTH の負荷前及び負荷60分後に、血中アルドステロン及び血中コルチゾールの濃度測定用の血液検体を採取した。

コホート1の被験者では、ACTH の負荷により、血中アルドステロン濃度が-1日目に177.5 pmol/L（0分）から663.0 pmol/L（60分後）、10日目に355.1 pmol/L（0分）から610.3 pmol/L（60分後）、23日目に72.8 pmol/L（0分）から131.8 pmol/L（60分後）に増加した。また、血中コルチゾール濃度は、-1日目に369.5 nmol/L（0分）から783.2 nmol/L（60分後）、10日目に440.1 nmol/L（0分）から800.9 nmol/L（60分後）、23日目に459.7 nmol/L（0分）から722.9 nmol/L（60分後）に増加した[表2.7.4-139]。

表 2.7.4-139　ACTH 負荷投与試験後の
血中アルドステロン濃度（pmol/L）及びコルチゾール濃度（nmol/L）の時間区分別の要約統計量
健康被験者へのポサコナゾール新錠剤投与試験（P05637 試験）
（ポサコナゾール新錠剤 200 mg QD/BID 投与群：コホート 1）

POS 200 mg QD/BID							
Lab Test	Relative Time	n	Mean	SD	Median	Minimum	Maximum
Aldosterone	Day -1 - 0 min	10	177.5	103.1	152.6	83	416
	Day -1 - 60 min	10	663.0	284.8	610.3	361	1304
	Day 10 - 0 min	10	355.1	200.8	332.9	83	804
	Day 10 - 60 min	10	610.3	289.2	596.4	139	1110
	Day 23 - 0 min	8	72.8	20.6	69.4	55	111
	Day 23 - 60 min	8	131.8	100.3	97.1	55	361
Cortisol	Day -1 - 0 min	10	369.5	120.8	368.6	211	555
	Day -1 - 60 min	10	783.2	94.9	790.7	606	954
	Day 10 - 0 min	10	440.1	121.5	412.5	270	687
	Day 10 - 60 min	10	800.9	94.4	772.5	693	955
	Day 23 - 0 min	8	459.7	125.6	442.8	295	709
	Day 23 - 60 min	8	722.9	67.0	714.6	601	830

ACTH：副腎皮質刺激ホルモン、QD：1日1回、BID：1日2回、POS：ポサコナゾール、Lab：臨床検査、n：被験者数、SD：標準偏差
治験薬の用法・用量
P05637試験
200 mg QD/BID（コホート1）：ポサコナゾール新錠剤を1日目に200 mg単回、6日目に200 mg BID、7-14日目に200 mg QD、15-22日目に200 mg BID経口投与

コホート2の被験者では、ACTH の負荷により、血中アルドステロン濃度が-1日目に197.3 pmol/L（0分）から795.2 pmol/L（60分後）、10日目に74.0 pmol/L（0分）から194.2 pmol/L（60分後）、15日目に111.0 pmol/L（0分）から163.0 pmol/L（60分）に増加した。また、血中コルチゾール濃度は、-1日目に417.8 nmol/L（0分）から807.8 nmol/L（60分後）、10日目に455.8 nmol/L（0分）から764.9 nmol/L（60分後）、15日目に449.7 nmol/L（0分）から719.1 nmol/L（60分後）に増加した[表 2.7.4-140]。

表 2.7.4-140　ACTH 負荷投与試験後の
血中アルドステロン濃度（pmol/L）及びコルチゾール濃度（nmol/L）の時間区分別の要約統計量
健康被験者へのポサコナゾール新錠剤投与試験（P05637 試験）
（ポサコナゾール新錠剤 400 mg QD/BID 投与群：コホート 2）

POS 400 mg QD/BID							
Lab Test	Relative Time	n	Mean	SD	Median	Minimum	Maximum
Aldosterone	Day -1 - 0 min	9	197.3	124.4	166.4	55	416
	Day -1 - 60 min	9	795.2	458.3	499.3	388	1553
	Day 10 - 0 min	9	74.0	39.2	55.5	55	166
	Day 10 - 60 min	9	194.2	135.9	138.7	83	444
	Day 15 - 0 min	8	111.0	126.7	55.5	55	416
	Day 15 - 60 min	8	163.0	194.7	55.5	55	583
Cortisol	Day -1 - 0 min	9	417.8	126.9	427.6	141	618
	Day -1 - 60 min	9	807.8	80.6	819.4	695	960
	Day 10 - 0 min	9	455.8	88.3	422.1	348	588
	Day 10 - 60 min	9	764.9	85.1	794.6	643	888
	Day 15 - 0 min	8	449.7	85.9	462.1	328	596
	Day 15 - 60 min	8	719.1	94.8	717.3	555	855

ACTH：副腎皮質刺激ホルモン、QD：1日1回、BID：1日2回、POS：ポサコナゾール、Lab：臨床検査、n：被験者数、SD：標準偏差
治験薬の用法・用量
P05637試験
400 mg QD/BID（コホート2）：ポサコナゾール新錠剤を1日目に400 mg 単回、6日目に400 mg BID、7-14日目に400 mg QD 経口投与

以上より、ポサコナゾール新錠剤200 mg 群及び400 mg 群では、ポサコナゾール新錠剤投与-1、10及び15日目又は23日目の ACTH 負荷投与60分後に血中アルドステロン及び血中コルチゾールの濃度が上昇していることから、ポサコナゾール新錠剤が副腎機能を阻害しないことが示された。またポサコナゾール新錠剤200 mg 群、400 mg 群及びプラセボ群では ACTH 負荷反応に大きな差はなかった。([資料5.3.3.1.7: P05637] 11.4.1.2.2 項)。

2.7.4.4.3.1.1.3　新錠剤及び静注用溶液を投与した第 I 相試験（P067試験）（パート2）（日本人）

日本人の健康被験者を対象とした新錠剤及び静注用溶液の第 I 相試験（P067試験）の反復経口投与群（パート2）では、-1から1日目（投与前）及び10から11日目に24時間蓄尿した尿中アルドステロン濃度を測定し、10日目に血中アルドステロン濃度を測定した。また、Prestudy（投与前4週間以内）及び11日目に ACTH 250 µg を午前7時に静脈内投与した。ACTH の負荷前及び負荷60分後に、血中アルドステロン及び血中コルチゾールの濃度測定用の血液検体を採取した。

ACTH 負荷投与試験の結果、ACTH 負荷後の血中コルチゾールの濃度が18.0 µg/mL 未満の被験者はおらず、ACTH 負荷後の血中コルチゾール及び血中アルドステロンの濃度は、いずれも上昇していた。また、尿中アルドステロンの濃度もいずれも正常範囲内であった[資料5.3.3.1.4: P067]。

2.7.4.4.3.1.2　　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.4.3.1.2.1　　静注用溶液を投与した後期第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）のコホート1（200 mg 反復静脈内投与）及びコホート2（300 mg 反復静脈内投与）の被験者で、ACTH 負荷投与前後の血中アルドステロン及び血中コルチゾールを治験薬投与前及び治験薬投与中に測定した。

1)　200 mg 反復静脈内投与（コホート1）

ベースライン時の ACTH 負荷前及び負荷60分後の血中アルドステロン濃度は、それぞれ117.6 pmol/L 及び358.5 pmol/L であった。13日目の負荷前及び負荷60分後の血中アルドステロン濃度は、それぞれ117.4 pmol/L 及び162.4 pmol/L に減少した。28日目の負荷前及び負荷60分後の血中アルドステロン濃度は、それぞれ114.4 pmol/L 及び226.6 pmol/L であった。

ベースライン時の ACTH 負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ363.2 pmol/L 及び784.9 pmol/L であった。13日目の負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ681.7 pmol/L 及び1380.2 pmol/L、28日目の負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ373.3 pmol/L 及び862.9 pmol/L であった。試験中の血中コルチゾール値に経時的な副腎機能の低下を示唆する傾向は認められなかった。

副腎機能の変化に起因するカリウム又はナトリウム濃度の電解質の不均衡は認められなかった。

コホート1の被験者における ACTH 負荷後の血中アルドステロン及びコルチゾール濃度の結果を、[資料5.3.3.2.3: P05520] 14.5.8.3 項に示す。

2)　300 mg 反復静脈内投与（コホート2及び3併合）

ベースライン時の ACTH 負荷前及び負荷60分後の血中アルドステロン濃度は、それぞれ119.8 pmol/L 及び316.2 pmol/L であった。13日目の負荷前及び負荷後（60分後）の血中アルドステロン濃度は、それぞれ91.0 pmol/L 及び106.5 pmol/L に減少した。その後、これらの値は28日目までにベースライン時の値を超えるか、近い値にまで増加した（それぞれ153.9 pmol/L 及び258.3 pmol/L）。

ベースライン時の ACTH 負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ339.7 pmol/L 及び743.4 pmol/L であった。13日目の負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ410.8 pmol/L 及び725.9 pmol/L で、28日目の負荷前及び負荷60分後の血中コルチゾール濃度は、それぞれ467.1 pmol/L 及び855.3 pmol/L であった。試験中の血中コルチゾール値に経時的な副腎機能の低下を示唆する傾向は認められなかった。

副腎機能の変化に起因するカリウム又はナトリウム濃度の電解質の不均衡は認められなかった。

コホート2の被験者における ACTH 負荷後の血中アルドステロン及びコルチゾール濃度の結果を、[資料5.3.3.2.3: P05520] 14.5.8.3 項に示す。

2.7.4.4.3.2　　カルシウム恒常性

カルシウムの恒常性への影響を評価するため、ポサコナゾール経口懸濁液を用いた第Ⅱ相試験及び第Ⅲ相試験において、以下の事象（WHO-ART の基本語）をカルシウム恒常性に関連する有害事象として評価した：圧迫骨折（compression fracture）、骨折（bone fracture）、低カルシウム血症（hypocalcemia）、骨折（fracture）、骨減少症（osteopenia）、骨粗鬆症（osteoporosis）、腎結石（renal calculus）、腎結石増悪（renal calculus aggravated）。また、予防投与試験では病的骨折（fracture pathological）も評価に含めた。その結果、ポサコナゾールのカルシウム恒常性への影響は認められなかった。

2.7.4.4.3.2.1　　経口懸濁液を予防投与した第Ⅲ相試験（C/I98-316及び P01899試験）で報告されたカルシウム恒常性に関連する事象

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）で認められたカルシウム恒常性に関連する有害事象の発現割合はポサコナゾール群とフルコナゾール群で類似しており、その大部分が軽度又は中等度であった[表 2.7.4-141]。最もよくみられた有害事象は低カルシウム血症であった。この低カルシウム血症のうち、重度／生命を脅かす事象は、ポサコナゾール群とフルコナゾール群で1%（ポサコナゾール群：8/605例、フルコナゾール群：3/539例）認められたが、ポサコナゾール群の1例のみが重篤な有害事象と判断された。

圧迫骨折のうち、生命を脅かす事象は、ポサコナゾール群の1例で認められ、重篤な有害事象と判断された。骨折（bone fracture）のうち、重度／生命を脅かす事象は、ポサコナゾール群の4例及びフルコナゾール群の1例で認められ、いずれも重篤な有害事象と判断された。病的骨折は、フルコナゾール群の1例で認められ、重篤な有害事象と判断された。

腎結石の1例を除き、すべての事象が治験担当医師により治験薬との因果関係はなしと判断された。腎結石の1例は、ポサコナゾールとの因果関係はどちらともいえないと判断されたが軽度であった。

表 2.7.4-141　カルシウム恒常性に関連する有害事象の発現例数（%）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

	Posaconazole n=605				Fluconazole n=539				Itraconazole n=58			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
Subjects Reporting any Adverse Event	67	(11)	13	(2)	59	(11)	5	(1)	5	(9)	1	(2)
傷害及び中毒	7	(1)	5	(1)	2	(<1)	1	(<1)	0		0	
圧迫骨折	1	(<1)	1	(<1)	0		0		0		0	
骨折（bone fracture）	6	(1)	4	(1)	2	(<1)	1	(<1)	0		0	
代謝・栄養障害	56	(9)	8	(1)	55	(10)	3	(1)	5	(9)	1	(2)
低カルシウム血症	56	(9)	8	(1)	55	(10)	3	(1)	5	(9)	1	(2)
筋・骨格系障害	2	(<1)	0		3	(1)	1	(<1)	0		0	
病的骨折	0		0		1	(<1)	1	(<1)	0		0	
骨減少症	2	(<1)	0		0		0		0		0	
骨粗鬆症	0		0		2	(<1)	0		0		0	
腎および尿路障害	4	(1)	0		0		0		0		0	
腎結石	4	(1)	0		0		0		0		0	

注 : C/I98-316試験の有害事象は、治験薬投与開始から最終投与30日後までに発現又は悪化した事象を、P01899試験の有害事象は、無作為割付けから治験薬最終投与30日後までに発現又は悪化した事象を集計した。
注：有害事象名は WHO-ART を用いた。
治験薬の用法・用量（TID：1日3回、QD：1日1回、BID：1日2回）
C/I98-316試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾールカプセル剤400 mg を QD 経口投与
P01899試験
ポサコナゾール群：ポサコナゾール経口懸濁液200 mg を TID 経口投与
フルコナゾール群：フルコナゾール経口懸濁液400 mg を QD 経口投与
イトラコナゾール群：イトラコナゾール内用液200 mg を BID 経口投与

2.7.4.4.3.2.2　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）で報告されたカルシウム恒常性に関連する事象

侵襲性真菌症患者を対象としたポサコナゾール経口懸濁液の治療試験（P01893及び P00041試験）（rIFI 併合集団）では、カルシウム恒常性に関連する有害事象のうち、骨折（bone fracture）、低カルシウム血症及び腎結石が報告された[表 2.7.4-142]。いずれの事象もポサコナゾールとの因果関係はなしと判定され、ほとんどが軽度又は中等度であった。

最もよくみられた有害事象は低カルシウム血症で、このうち、造血幹細胞移植患者群の1例が生命を脅かす事象として報告され、非造血幹細胞移植患者群の1例が重篤な有害事象と判断された。骨折（bone fracture）のうち、非造血幹細胞移植患者群の2例が重篤な有害事象と判断され、このうち1例が投与中止に至った。2例の腎結石（いずれも重度）のうち1件が重篤な有害事象と判断された。

骨折（bone fracture）及び低カルシウム血症を発現した被験者のうち、重篤な有害事象又は重度／生命を脅かす事象が認められた上記の被験者は、初発 AML、急性リンパ性白血病又は非ホジキンリンパ腫に罹患していた。この患者集団で認められたカルシウム減少は、化学療法によるカルシウム及びマグネシウム喪失との因果関係が疑われ、また可能性はより低いものの、栄養状態不良によるアルブミン減少とも因果関係が疑われた。また、がん患者でみられるような長期的なステロイド投与も骨脱灰及び骨折に至る可能性が考えられる。

表 2.7.4-142　カルシウム恒常性に関連する有害事象の発現例数（%）
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

有害事象†	Number (%) of Subjects: POS All Doses (n=428)			
	Any Grade	Grade 3	Grade 4	副作用 (Any Grade)
Subjects Reporting any Adverse Event‡	**34 (8)**	**5 (1)**	**1 (<1)**	**0**
骨折（bone fracture）	4 (1)	2 (<1)	0	0
低カリウム血症	28 (7)	1 (<1)	1 (<1)	0
腎結石	2 (<1)	2 (<1)	0	0

POS：ポサコナゾール
注：有害事象は、治験薬投与開始から最終投与30日後までに発現又は悪化した事象を集計した。
† 有害事象名は WHO-ART を用いた
‡ 試験期間中に特定事象が報告された被験者の例数であり、同一被験者で複数事象が報告されることもある
治験薬の用法・用量（BID：1日2回、QID：1日4回、QD：1日1回）
P01893試験
400 mg BID 群：負荷用量200 mg QID を2日間経口投与後、維持用量400 mg BID を経口投与
600 mg BID 群：負荷用量400 mg QID を2日間経口投与後、維持用量600 mg BID を経口投与
800 mg QD 群：負荷用量800 mg BID を2日間経口投与後、維持用量800 mg QD を経口投与
P00041試験
入院被験者には、入院中はポサコナゾール経口懸濁液200 mg QID、退院後は400 mg BID、
外来被験者には、ポサコナゾール経口懸濁液400 mg BID を経口投与

2.7.4.4.3.3　　日本人患者及び非日本人患者における安全性プロファイルの比較

国内試験（P101試験）では、試験の早期中止の割合がボリコナゾール群よりポサコナゾール群で高く、その原因は有害事象による投与中止の割合にあった[2.7.3.2.2.5 項]。そこで、P101試験のポサコナゾール群での有害事象による投与中止の割合の高さは、国内外の安全性の差異によるものかを評価した。

国内外の試験ではそれぞれ異なる投与期間が設定されていることから[表 2.7.4-143]、国内外の安全性の比較では、比較可能であった投与開始1ヵ月間での安全性プロファイルを国内外で比較した。各集団での有害事象の要約を[表 2.7.4-144]に、個々の有害事象の発現割合をそれぞれの項に示す[表 2.7.4-143]。なお、ポサコナゾール新錠剤の予防投与試験（P05615試験）及びポサコナゾール静注用溶液の予防投与試験（P05520試験）では、投与期間が約28日に設定されていたため、再解析は行わず試験結果をそのまま用いた。

その結果、投与開始1ヵ月間での投与中止に至った有害事象の発現割合に、国内外で大きな差はなかった。さらに、投与開始1ヵ月間での有害事象、重篤な有害事象及び重篤な副作用の発現割合も、国内外で大きな差はなかった。一方、副作用の発現割合及び投与中止に至った副作用の発現割合は、海外試験の解析集団と比べ国内試験で高かった[表 2.7.4-144]。しかしながら、国内試験でみられた副作用のうち、相対的に発現割合が高かった発熱、肝機能異常、食欲減退及び高血圧のほとんどは軽度又は中等度で、重篤なものは少なく、日本人特有に発現しているものではなかった。また、国内試験で投与中止に至った副作用のうち、最も多かった事象は発熱の5例であったが、いずれも軽度又は中等度で、それ以外の事象はすべて2例以下の発現であった。以上より、副作用の発現割合及び投与中止に至った副作用の発現割合は、海外試験と比べ国内試験で高かったものの、国内試験と海外試験で安全性プロファイルに大きな差はないと考えられた。

詳細を以下に記載する。

投与開始1ヵ月間での投与中止に至った有害事象の発現割合は、国内試験（P101試験）（27.3%）及び海外試験［C/I98-316及び P01899試験（予防投与併合集団）、P05615試験（300 mg コホート）、P05520試験（300 mg 反復静脈内投与：コホート2及び3併合）、P01893及び P00041試験（rIFI 併合集団）］（15.4%～23.5%）で大きな差はなかった[表 2.7.4-144]。なお、国内試験で相対的に発現割合が高かった投与中止に至った有害事象は、発熱6.5%（5/77例）及び肺炎3.9%（3/77例）であり[付録 2.7.4-158]、いずれの事象も海外試験で認められている。また、投与開始1ヵ月間に発現した有害事象、重篤な有害事象、重篤な副作用も、国内試験及び海外試験で大きな差はなかった。

投与開始1ヵ月間に発現した副作用の発現割合は、海外試験（27.2%～40%）と比べ国内試験（66.2%）で高値を示した[表 2.7.4-144]。国内試験でよくみられた副作用は、発熱22.1%（17/77例）、肝機能異常11.7%（9/77例）、食欲減退11.7%（9/77例）及び高血圧10.4%（8/77例）あった[付録 2.7.4-155]。発熱は、いずれも軽度又は中等度であった[資料5.3.7.3.6: P101_ae]。1例は、重篤な副作用と判定され、投与中止に至った。このほかに4例が投与中止に至ったが、いずれも重篤と判定されなかった。肝機能異常は、重度の1例を除き、いずれも軽度又は中等度であった[資料5.3.7.3.6: P101_ae]。中等度の2例が投与中止に至ったが、このほかに投与中止に至った肝機能異常は認めら

れず、いずれも重篤な副作用ではなかった。食欲減退は、重度の4例を除き、いずれも軽度又は中等度であった[資料5.3.7.3.6: P101_ae]。重度の4例のうち、1例は投与中止に至ったが、このほかに投与中止に至った食欲減退は認められず、いずれも重篤な副作用ではなかった[資料5.3.7.3.6: P101_ae]。高血圧は、重度が4例、中等度が4例であった。重篤又は投与中止に至った高血圧は認められなかった[資料5.3.7.3.6: P101_ae]。これらの事象は、国内試験で高頻度に認められたものの、いずれの事象も、海外試験でも認められており、日本人特有の事象ではなかった。

投与開始1ヵ月間に発現した投与中止に至った副作用は、海外試験（3.3%～7.3%）と比べ国内試験（18.2%）で高値を示した。国内試験でよくみられた事象は発熱（5例）で、発熱以外の事象は、いずれも2例以下であった[付録 2.7.4-159]。投与中止に至った副作用の発熱は、いずれも軽度又は中等度であった[資料5.3.7.6.6: P101_discon]。

表 2.7.4-143　試験別の投与期間及び投与開始 1 ヵ月間に発現した個々の有害事象

試験番号	P101	C/I98-316	P01899	P05615 （300 mg コホート）	P05520 （300 mg 反復静脈内投与）‡	P01893	P00041
対象	日本人	非日本人					
試験目的	治療	予防投与		予防投与	予防投与	治療	
剤形	新錠剤及び静注用溶液	経口懸濁液		新錠剤	静注用溶液§	経口懸濁液	
併合解析集団	-	予防投与併合集団		-	-	rIFI 併合集団	
投与期間	84日間	16週間又は侵襲性真菌症の発症まで	最長84日間（12週間）	最長28日間	約28日間	最長6ヵ月又は42日間‖	最長365日
投与開始1ヵ月間に発現した個々の有害事象†の発現割合	[付録 2.7.4-154] [付録 2.7.4-155] [付録 2.7.4-156] [付録 2.7.4-157] [付録 2.7.4-158] [付録 2.7.4-159]	[付録 2.7.4-142] [付録 2.7.4-143] [付録 2.7.4-144] [付録 2.7.4-145] [付録 2.7.4-146] [付録 2.7.4-147]		[2.7.4.2.2.1.1.2 項] [2.7.4.2.2.3.1.2 項] [2.7.4.2.2.4.1.2 項]	[2.7.4.2.2.1.1.3 項] [2.7.4.2.2.3.1.3 項] [2.7.4.2.2.4.1.3 項]	[付録 2.7.4-148] [付録 2.7.4-149] [付録 2.7.4-150] [付録 2.7.4-151] [付録 2.7.4-152] [付録 2.7.4-153]	

† 有害事象、副作用、重篤な有害事象、重篤な副作用、投与中止に至った有害事象、投与中止に至った副作用
‡ コホート2及び3併合
§ 静注用溶液を静脈内投与後、経口懸濁液を経口投与
‖ 難治性侵襲性真菌症患者：最長6ヵ月間、発熱性好中球減少症患者：最長42日間

表 2.7.4-144　投与開始 1 ヵ月間に発現した有害事象の要約（ポサコナゾール群）

試験番号	P101	C/I98-316	P01899	P05615 （300 mg コホート）	P05520 （300 mg 反復 静脈内投与）†	P01893	P00041
対象	日本人	非日本人					
試験目的	治療	予防投与		予防投与	予防投与	治療	
剤形	新錠剤及び 静注用溶液	経口懸濁液		新錠剤	静注用溶液‡	経口懸濁液	
併合解析集団	-	予防投与併合集団		-	-	rIFI 併合集団	
症例数	77例	588例		210例	237例	428例	
有害事象	98.7%（76例）	95.6%（562例）		99%（207例）	99%（235例）	89.0%（381例）	
副作用	66.2%（51例）	27.2%（160例）		40%（84例）	38%（90例）	28.7%（123例）	
重篤な有害事象	29.9%（23例）	41.2%（242例）		33%（69例）	30%（71例）	39.7%（170例）	
重篤な副作用	6.5%（5例）	7.3%（43例）		3%（6例）	1%（3例）	4.7%（20例）	
投与中止に至った有害事象	27.3%（21例）	23.5%（138例）		18%（38例）	19%（45例）	15.4%（66例）	
投与中止に至った副作用	18.2%（14例）	7.3%（43例）		5%（11例）	5%（13例）	3.3%（14例）	

† コホート2及び3併合
‡ 静注用溶液を静脈内投与後、経口懸濁液を経口投与
P101試験：All Subjects as Treated
C/I98-316及び P01899試験：All Treated Subjects
P05615試験：All Treated Subjects（300 mg コホート）
P05520試験：All Treated Subjects［300 mg 反復静脈内投与（コホート2及び3併合）］
P01893及び P00041試験：All Randomized Subjects（rIFI Pool All Doses）

2.7.4.5　特別な患者集団及び状況下における安全性

2.7.4.5.1　内因性要因

本項では、試験ごとに検討した内因性要因別の安全性を示す。以下に検討した項目を示す。

- 経口懸濁液を投与した試験（非日本人）：年齢別、性別、人種別
- 新錠剤及び静注用溶液を投与した試験（非日本人）：年齢別、性別、体重別及び基礎疾患別
- 新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）：年齢別、性別及び体重別

上記に加えて、日本人と非日本人の低体重高齢者の安全性プロファイルを評価した。

なお、ポサコナゾール新錠剤を投与したP05615試験の200 mgコホート（20例）及びポサコナゾール静注用溶液を投与したP05520試験の200 mg反復静脈内投与（コホート1）（21例）は例数が限られるため、P05615試験では300 mgコホート（210例）、P05520試験では主に300 mg反復静脈内投与（コホート2及び3併合）（237例）のデータを示す。

また、アジア人での参考データとして、中国人被験者を対象とした試験における安全性の結果を要約する。さらに、腎機能障害者、肝機能障害者及び好中球減少患者を対象とした臨床薬理試験における安全性の結果を要約する。

2.7.4.5.1.1　年齢

2.7.4.5.1.1.1　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.5.1.1.1.1　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及びP01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）での年齢別の有害事象の発現割合を[付録 2.7.4-160]に、重度／生命を脅かす有害事象の発現割合を[付録 2.7.4-161]に示す。

ポサコナゾール群（605例）では、13歳以上18歳未満12例、18歳以上65歳未満530例、65歳以上63例であった。フルコナゾール群（539例）では、13歳以上18歳未満16例、18歳以上65歳未満460例、65歳以上63例であった。ポサコナゾール群の年齢別の有害事象の発現割合は、13歳以上18歳未満100.0%（12/12例）、18歳以上65歳未満98.3%（521/530例）、65歳以上98.4%（62/63例）であり、同程度であった。フルコナゾール群の年齢別の有害事象の発現割合は、13歳以上18歳未満100.0%（16/16例）、18歳以上65歳未満98.3%（452/460例）、65歳以上100.0%（63/63例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。ポサコナゾール群の年齢別の重度／生命を脅かす有害事象の発現割合は、13歳以上18歳未満58.3%（7/12例）、18歳以上65歳未満73.6%（390/530例）、65歳以上81.0%（51/63例）であり、高齢者での発現割合が数値上高かった。フルコナゾール群の年齢別の重度／生命を脅かす有害事象の発現割合は、13歳以上18歳未満62.5%（10/16例）、18歳以上65歳未満70.9%（326/460例）、65歳以上71.4%（45/63例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。また、有害事象プロファイルは年齢間で概して類似していた。

2.7.4.5.1.1.1.2　新錠剤を投与した第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

300 mg コホート

ポサコナゾール新錠剤の予防投与試験（P05615試験）でポサコナゾール新錠剤300 mg を投与した被験者における年齢別の有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び投与中止に至った有害事象の発現割合を[資料5.3.3.2.2: P05615] 14.7.1.27 項に示す。

300 mg コホート（210例）では、65歳未満175例、65歳以上35例であった。なお、本試験の対象患者は18歳以上であった。年齢別の有害事象の発現割合は、65歳未満98%（172/175例）、65歳以上100%（35/35例）で同程度であった。副作用の発現割合は、65歳未満38%（66/175例）、65歳以上51%（18/35例）で、65歳以上の被験者で数値上高かった。死亡に至った有害事象の発現割合は、65歳未満9%（15/175例）、65歳以上9%（3/35例）、重篤な有害事象の発現割合は、65歳未満33%（57/175例）、65歳以上34%（12/35例）であり、年齢間で同程度であった。投与中止に至った有害事象の発現割合は、65歳未満16%（28/175例）、65歳以上29%（10/35例）であり、65歳以上の被験者で数値上高かった。また、有害事象プロファイルは年齢間で概して類似していた（[資料5.3.3.2.2: P05615] 14.7.1.27.1 項）。

2.7.4.5.1.1.1.3　静注用溶液を投与した第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

300 mg 反復静脈内投与（コホート2及び3併合）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）でポサコナゾール静注用溶液300 mg を投与した被験者における年齢別の有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び投与中止に至った有害事象の発現割合を[資料5.3.3.2.3: P05520] 14.4.1.25 項に示す。

300 mg 反復静脈内投与（コホート2及び3併合）（237例）では、65歳未満195例、65歳以上42例であった。なお、本試験の対象患者は18歳以上であった。年齢別の静脈内投与期の有害事象の発現割合は、65歳未満93%（181/195例）、65歳以上93%（39/42例）で同程度であった。静脈内投与期の副作用の発現割合も65歳未満29%（57/195例）、65歳以上36%（15/42例）で同程度であった。静脈内投与期の死亡に至った有害事象の発現割合は、65歳未満4%（7/195例）、65歳以上7%（3/42例）で同程度であった。静脈内投与期の重篤な有害事象の発現割合は、65歳未満10%（20/195例）、65歳以上17%（7/42例）であり、65歳以上の被験者で数値上高かった。静脈内投与期の投与中止に至った有害事象の発現割合は、65歳未満12%（23/195例）、65歳以上14%（6/42例）で同程度であった。また、有害事象プロファイルは年齢間で概して類似していた（[資料5.3.3.2.3: P05520] 14.4.1.25.1 項）。

2.7.4.5.1.1.2　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.5.1.1.2.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及び P00041試験）（rIFI 併合集団）での年齢別の有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-162]及び[付録 2.7.4-163]に示す。

rIFI 併合集団（428例）では、18歳未満16例、18歳以上65歳未満364例、65歳以上48例であった。年齢別の有害事象の発現割合は、18歳未満100.0%（16/16例）、18歳以上65歳未満97.0%（353/364例）、65歳以上89.6%（43/48例）であり、同程度であった。年齢別の副作用の発現割合は、18歳未満37.5%（6/16例）、18歳以上65歳未満38.2%（139/364例）、65歳以上39.6%（19/48例）であり、同程度であった。また、有害事象プロファイルは年齢間で概して類似していた。

2.7.4.5.1.1.2.2　　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）での年齢別の有害事象の要約を[表 2.7.4-145]に示す。また、年齢別の有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-164]及び[付録 2.7.4-165]に示す。

本試験では、65歳以上の被験者が多かったため、65歳未満、65歳以上70歳未満、70歳以上の部分集団で比較した。ポサコナゾール群での副作用の発現割合は、65歳未満63.3%（19/30例）、65歳以上70歳未満68.8%（11/16例）及び70歳以上83.9%（26/31例）であり、70歳以上の発現割合が高かった。また、ポサコナゾール群での投与中止に至った有害事象の発現割合は、65歳未満20.0%（6/30例）、65歳以上70歳未満25.0%（4/16例）及び70歳以上48.4%（15/31例）であり、70歳以上の発現割合が高かった。しかしながら、有害事象、死亡に至った有害事象、重篤な有害事象、重篤な副作用及び投与中止に至った副作用の発現割合に大きな差はなかった。また、個々の有害事象についても、重篤な有害事象や重度の有害事象が、特定の部分集団に偏って発現していることはなかった。

さらにポサコナゾール群での被験者数が同程度の65歳未満（30例）と70歳以上（31例）の部分集団間で15%以上（5例以上）の差があった事象は、有害事象で末梢性浮腫［65歳未満：3.3%（1/30例）、70歳以上：19.4%（6/31例）］及び食欲減退［65歳未満：13.3%（4/30例）、70歳以上：29.0%（9/31例）］であったものの、これらの事象は、いずれも非重篤で、ほとんどが軽度又は中等度であり、投与中又は投与中止により回復した。

以上より、例数が限られていることから解釈には注意が必要であるものの、有害事象プロファイルは年齢間で概して類似していた。

表 2.7.4-145　年齢別の有害事象の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Adverse Event Summary by Age (Years)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	30		16		31		19		7		12	
with one or more adverse events	30	(100.0)	16	(100.0)	31	(100.0)	19	(100.0)	6	(85.7)	12	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
with drug-related† adverse events	19	(63.3)	11	(68.8)	26	(83.9)	18	(94.7)	6	(85.7)	10	(83.3)
with serious adverse events	11	(36.7)	7	(43.8)	12	(38.7)	2	(10.5)	0	(0.0)	3	(25.0)
with serious drug-related adverse events	1	(3.3)	3	(18.8)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
who died	3	(10.0)	0	(0.0)	3	(9.7)	0	(0.0)	0	(0.0)	1	(8.3)
discontinued‡ due to an adverse event	6	(20.0)	4	(25.0)	15	(48.4)	1	(5.3)	2	(28.6)	0	(0.0)
discontinued due to a drug-related adverse event	4	(13.3)	4	(25.0)	10	(32.3)	1	(5.3)	2	(28.6)	0	(0.0)
discontinued due to a serious adverse event	3	(10.0)	3	(18.8)	5	(16.1)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	1	(3.3)	3	(18.8)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで300 mg を QD にて投与
ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

2.7.4.5.1.2　　性別

2.7.4.5.1.2.1　　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.5.1.2.1.1　　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及び P01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）での性別ごとの有害事象の発現割合を[付録 2.7.4-166]に、重度／生命を脅かす有害事象の発現割合を[付録 2.7.4-167]に示す。

ポサコナゾール群（605例）では、男性361例、女性244例であった。フルコナゾール群（539例）では、男性315例、女性224例であった。ポサコナゾール群の性別ごとの有害事象の発現割合は、男性98.3%（355/361例）、女性98.4%（240/244例）で同程度であった。フルコナゾール群の性別ごとの有害事象の発現割合は、男性98.1%（309/315例）、女性99.1%（222/224例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。ポサコナゾール群の性別ごとの重度／生命を脅かす有害事象の発現割合は、男性73.7%（266/361例）、女性74.6%（182/244例）で同程度であった。フルコナゾール群の性別ごとの重度／生命を脅かす有害事象の発現割合は、男性68.6%（216/315例）、女性73.7%（165/224例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。また、有害事象プロファイルは性別間で概して類似していた。

2.7.4.5.1.2.1.2　　新錠剤を投与した第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

300 mg コホート

ポサコナゾール新錠剤の予防投与試験（P05615試験）でポサコナゾール新錠剤300 mg を投与した被験者における性別ごとの有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び投与中止に至った有害事象の発現割合を[資料5.3.3.2.2: P05615] 14.7.1.28 項に示す。

300 mg コホート（210例）では、男性131例、女性79例であった。性別ごとの有害事象の発現割合は、男性100%（131/131例）、女性96%（76/79例）で同程度であった。副作用の発現割合も男性40%（52/131例）、女性41%（32/79例）で同程度であった。死亡に至った有害事象の発現割合は、男性11%（14/131例）、女性5%（4/79例）、重篤な有害事象の発現割合は、男性37%（48/131例）、女性27%（21/79例）、投与中止に至った有害事象の発現割合は、男性17%（22/131例）、女性20%（16/79例）であり、大きな差はなかった。また、有害事象プロファイルは性別間で概して類似していた（[資料5.3.3.2.2: P05615] 14.7.1.28.1 項）。

2.7.4.5.1.2.1.3　　静注用溶液を投与した第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

300 mg 反復静脈内投与（コホート2及び3併合）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）でポサコナゾール静注用溶液300 mg を投与した被験者における性別ごとの有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び投与中止に至った有害事象の発現割合を[資料5.3.3.2.3: P05520] 14.4.1.26 項に示す。

300 mg 反復静脈内投与（コホート2及び3併合）（237例）では、男性130例、女性107例であった。性別ごとの静脈内投与期の有害事象の発現割合は、男性91%（118/130例）、女性95%（102/107例）

で同程度であった。静脈内投与期の副作用の発現割合も男性31%（40/130例）、女性30%（32/107例）で同程度であった。静脈内投与期の死亡に至った有害事象の発現割合は、男性2%（3/130例）、女性7%（7/107例）、重篤な有害事象の発現割合は、男性9%（12/130例）、女性14%（15/107例）、投与中止に至った有害事象の発現割合は、男性10%（13/130例）、女性15%（16/107例）であり、女性被験者で数値上高かった。また、有害事象プロファイルは性別間で概して類似していた（[資料5.3.3.2.3: P05520] 14.4.1.26.1 項）。

2.7.4.5.1.2.2　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.5.1.2.2.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及びP00041試験）（rIFI併合集団）での性別の有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-168]及び[付録 2.7.4-169]に示す。

rIFI併合集団（428例）では、男性277例、女性151例であった。性別ごとの有害事象の発現割合は、男性96.8%（268/277例）、女性95.4%（144/151例）で同程度であった。性別ごとの副作用の発現割合は、男性37.5%（104/277例）、女性39.7%（60/151例）で同程度であった。また、有害事象プロファイルは性別間で概して類似していた。

2.7.4.5.1.2.2.2　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）での性別ごとの有害事象の要約を[表 2.7.4-146]に示す。また、性別ごとの有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-170]及び[付録 2.7.4-171]に示す。

本試験に組み入れられた被験者のうち、ポサコナゾール群の男性は71例、女性は6例で男女間の被験者数に偏りがあり、女性の例数が限られるため、性別間で比較することは困難であった。

表 2.7.4-146　性別ごとの有害事象の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Adverse Event Summary by Gender
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	71		6		33		5	
with one or more adverse events	71	(100.0)	6	(100.0)	33	(100.0)	4	(80.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
with drug-related† adverse events	52	(73.2)	4	(66.7)	31	(93.9)	3	(60.0)
with serious adverse events	30	(42.3)	0	(0.0)	5	(15.2)	0	(0.0)
with serious drug-related adverse events	5	(7.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	6	(8.5)	0	(0.0)	1	(3.0)	0	(0.0)
discontinued‡ due to an adverse event	24	(33.8)	1	(16.7)	2	(6.1)	1	(20.0)
discontinued due to a drug-related adverse event	18	(25.4)	0	(0.0)	2	(6.1)	1	(20.0)
discontinued due to a serious adverse event	11	(15.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	5	(7.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

治験薬の用法・用量（BID：1日2回、QD：1日1回）
ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで300 mg を QD にて投与
ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

2.7.4.5.1.3　人種

2.7.4.5.1.3.1　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.5.1.3.1.1　経口懸濁液を投与した第Ⅲ相試験（C/I98-316及び P01899試験）（非日本人）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316及び P01899試験）（予防投与併合集団）での人種別の有害事象の発現割合を[付録 2.7.4-172]に、重度／生命を脅かす有害事象の発現割合を[付録 2.7.4-173]に示す。

ポサコナゾール群（605例）では、白人479例、非白人126例であった。フルコナゾール群（539例）では、白人428例、非白人111例であった。ポサコナゾール群の人種別の有害事象の発現割合は、白人98.3%（471/479例）、非白人98.4%（124/126例）で同程度であった。フルコナゾール群の人種別の有害事象の発現割合は、白人98.4%（421/428例）、非白人99.1%（110/111例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。ポサコナゾール群の人種別の重度／生命を脅かす有害事象の発現割合は、白人74.1%（355/479例）、非白人73.8%（93/126例）で同程度であった。フルコナゾール群の人種別の重度／生命を脅かす有害事象の発現割合は、白人71.5%（306/428例）、非白人67.6%（75/111例）であり、ポサコナゾール群とフルコナゾール群で同程度であった。また、有害事象プロファイルは人種間で概して類似していた。

2.7.4.5.1.3.2　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.5.1.3.2.1　経口懸濁液を投与した第Ⅱ相試験（P01893試験）及び第Ⅲ相試験（P00041試験）（非日本人）

ポサコナゾール経口懸濁液の治療試験（P01893及び P00041試験）（rIFI 併合集団）での人種別の有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-174]及び[付録 2.7.4-175]に示す。

rIFI 併合集団（428例）では、白人289例、黒人27例、アジア人27例、ヒスパニック系84例、その他1例であった。その他1例を除く人種ごとの有害事象の発現割合は、白人96.2%（278/289例）、黒人92.6%（25/27例）、アジア人96.3%（26/27例）、ヒスパニック系97.6%（82/84例）で同程度であった。その他1例を除く人種別の副作用の発現割合は、白人33.6%（97/289例）、黒人48.1%（13/27例）、アジア人63.0%（17/27例）、ヒスパニック系44.0%（37/84例）であった。また、有害事象プロファイルは人種間で概して類似していた。

2.7.4.5.1.4　体重

2.7.4.5.1.4.1　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.5.1.4.1.1　新錠剤を投与した第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

300 mg コホート

ポサコナゾール新錠剤の予防投与試験（P05615試験）でポサコナゾール新錠剤300 mg を投与した被験者における体重別の有害事象及び副作用の発現割合を[資料5.3.3.2.2: P05615] 14.7.1.29 項に示す。

300 mg コホート（210例）では、70 kg 未満73例、70 kg 以上137例であった。体重別の有害事象の発現割合は、70 kg 未満96%（70/73例）、70 kg 以上100%（137/137例）で同程度であった。副作用の発現割合も70 kg 未満37%（27/73例）、70 kg 以上42%（57/137例）で同程度であった。また、有害事象プロファイルは体重間で概して類似していた（[資料5.3.3.2.2: P05615] 14.7.1.29.1 項）。

2.7.4.5.1.4.1.2　静注用溶液を投与した第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

300 mg反復静脈内投与（コホート2、3）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）でポサコナゾール静注用溶液300 mg を投与した被験者における体重別の有害事象及び副作用の発現割合を[資料5.3.3.2.3: P05520] 14.4.1.28 項に示す。

300 mg 反復静脈内投与（コホート2）では、70 kg 未満8例、70 kg 以上16例であった。体重別の静脈内投与期の有害事象の発現割合は、70 kg 未満100%（8/8例）、70 kg 以上94%（15/16例）で同程度であった。静脈内投与期の副作用の発現割合も70 kg 未満13%（1/8例）、70 kg 以上19%（3/16例）で同程度であった。また、有害事象プロファイルは体重間で概して類似していた（[資料5.3.3.2.3: P05520] 14.4.1.28.1 項）。

300 mg 反復静脈内投与（コホート3）では、70 kg 未満68例、70 kg 以上144例であり、このほかにベースライン時の体重が欠測していた被験者が1例いた。体重別の静脈内投与期の有害事象の発現割合は、70 kg 未満91%（62/68例）、70 kg 以上93%（134/144例）で同程度であった。静脈内投与期の副作用の発現割合は、70 kg 未満26%（18/68例）、70 kg 以上35%（50/144例）であり、70 kg 以上の被験者で数値上高かった。また、有害事象プロファイルは体重間で概して類似していた（[資料5.3.3.2.3: P05520] 14.4.1.28.1 項）。

2.7.4.5.1.4.2　侵襲性真菌症患者又は深在性真菌症患者を対象とした治療試験

2.7.4.5.1.4.2.1　新錠剤及び静注用溶液を投与した第Ⅲ相試験（P101試験）（日本人）

日本人を対象としたポサコナゾール新錠剤及び静注用溶液の治療試験（P101試験）での体重別の有害事象の要約を[表 2.7.4-147]に示す。また、体重別の有害事象及び副作用の発現割合を、それぞれ[付録 2.7.4-176]及び[付録 2.7.4-177]に示す。

ポサコナゾール群での副作用の発現割合は、50 kg 以下85.7%（24/28例）、50 kg 超60 kg 以下78.6%（22/28例）及び60 kg 超47.6%（10/21例）であり、60 kg 以下での発現割合が高かったが、有害事象、死亡に至った有害事象、重篤な有害事象、重篤な副作用、投与中止に至った有害事象及び投与中止に至った副作用の発現割合には大きな差はなかった。また、個々の有害事象についても、重篤な有害事象や重度の有害事象が、特定の部分集団に偏って発現していることはなかった。

さらに、いずれかの部分集団間で15%以上の差があった事象は、有害事象で発熱［50 kg 以下：35.7%（10/28例）、50 kg 超60 kg 以下：39.3%（11/28例）、60 kg 以上：19.0%（4/21例）］、肝機能異常［50 kg 以下：17.9%（5/28例）、50 kg 超60 kg 以下：28.6%（8/28例）、60 kg 以上：4.8%（1/21例）］、ALT 増加［50 kg 以下：21.4%（6/28例）、50 kg 超60 kg 以下：7.1%（2/28例）、60 kg 以上：4.8%（1/21

例)］、食欲減退［50 kg 以下：28.6%（8/28例)、50 kg 超60 kg 以下：10.7%（3/28例)、60 kg 以上：14.3%（3/21例)］及び低カリウム血症［50 kg 以下：28.6%（8/28例)、50 kg 超60 kg 以下：21.4%（6/28例)、60 kg 以上：9.5%（2/21例)］であった。副作用は、発熱［50 kg 以下：28.6%（8/28例)、50 kg 超60 kg 以下：32.1%（9/28例)、60 kg 以上：0.0%（0/21例)］及び低カリウム血症［50 kg 以下：21.4%（6/28例)、50 kg 超60 kg 以下：14.3%（4/28例)、60 kg 以上：0.0%（0/21例)］であった。しかしながら、これらの事象は、ほとんどが非重篤で軽度又は中等度の程度であり、投与中又は投与中止により回復した。

以上より、例数が限られていることから解釈には注意が必要であるものの、有害事象プロファイルは体重間で概して類似していた。

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表 2.7.4-147　体重別の有害事象の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Adverse Event Summary by Weight (kg)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	28		28		21		15		15		8	
with one or more adverse events	28	(100.0)	28	(100.0)	21	(100.0)	14	(93.3)	15	(100.0)	8	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
with drug-related† adverse events	24	(85.7)	22	(78.6)	10	(47.6)	13	(86.7)	13	(86.7)	8	(100.0)
with serious adverse events	9	(32.1)	12	(42.9)	9	(42.9)	3	(20.0)	1	(6.7)	1	(12.5)
with serious drug-related adverse events	2	(7.1)	1	(3.6)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died	1	(3.6)	3	(10.7)	2	(9.5)	1	(6.7)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	10	(35.7)	10	(35.7)	5	(23.8)	2	(13.3)	1	(6.7)	0	(0.0)
discontinued due to a drug-related adverse event	8	(28.6)	7	(25.0)	3	(14.3)	2	(13.3)	1	(6.7)	0	(0.0)
discontinued due to a serious adverse event	3	(10.7)	4	(14.3)	4	(19.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	2	(7.1)	1	(3.6)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Source: [P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

治験薬の用法・用量（BID：1日2回、QD：1日1回）

ポサコナゾール群：　新錠剤又は静注用溶液300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで300 mg を QD にて投与

ボリコナゾール群：　錠剤300 mg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで200 mg を BID にて投与、又は注射用液6 mg/kg を治験薬投与1日目は BID、治験薬投与2日目以降は原則84日目まで4 mg/kg を BID にて投与
ボリコナゾールの血漿中トラフ濃度に基づき適宜用量調整
コホート1については、体重40 kg 未満又は軽度から中等度の肝機能低下（Child-Pugh 分類のクラス A 又は B の肝硬変に相当）の被験者も用量調整

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2.7.4.5.1.5　基礎疾患

2.7.4.5.1.5.1　侵襲性真菌症のハイリスク患者を対象とした予防投与試験

2.7.4.5.1.5.1.1　新錠剤を投与した第Ⅰ相／第Ⅲ相試験（P05615試験）（非日本人）

300 mg コホート

ポサコナゾール新錠剤の予防投与試験（P05615試験）でポサコナゾール新錠剤300 mg を投与した被験者における基礎疾患別の有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び投与中止に至った有害事象の発現割合を[資料5.3.3.2.2: P05615] 14.7.1.30 項に示す。

300 mg コホート（210例）では、基礎疾患が AML 又は MDS の被験者を併合して AML/MDS 集団（119例）とし、造血幹細胞移植患者のみで構成された HSCT 集団（91例）と比較した。基礎疾患別の有害事象の発現割合は、AML/MDS 集団100%（119/119例）、HSCT 集団97%（88/91例）で同程度であった。副作用の発現割合は、AML/MDS 集団48%（57/119例）、HSCT 集団30%（27/91例）であり、AML/MDS 集団の方が数値上高かった。死亡に至った有害事象の発現割合は、AML/MDS 集団7%（8/119例）、HSCT 集団11%（10/91例）、重篤な有害事象の発現割合は、AML/MDS 集団30%（36/119例）、HSCT 集団36%（33/91例）、投与中止に至った有害事象の発現割合は、AML/MDS 集団21%（25/119例）、HSCT 集団14%（13/91例）であり、大きな差はなかった。

発現割合が高かった有害事象（被験者全体で発現割合20%以上）は、下痢［AML/MDS 集団：41%（49/119例）、HSCT 集団：13%（12/91例）、以下同順］、発熱［40%（48/119例）、12%（11/91例）］、悪心［29%（35/119例）、23%（21/91例）］、低カリウム血症［29%（35/119例）、12%（11/91例）］及び発熱性好中球減少症［34%（40/119例）、2%（2/91例）］であった。下痢、発熱及び発熱性好中球減少症は、集団間の発現割合の差が大きく、有害事象プロファイルが集団間で異なった（[資料5.3.3.2.2: P05615] 14.7.1.30.1 項）。

AML/MDS 集団で発現割合が高かった器官別大分類の有害事象（HSCT 集団より発現割合の差が20%以上）は、「呼吸器、胸郭および縦隔障害」［AML/MDS 集団：61%（73/119例）、HSCT 集団：23%（21/91例）、以下同順］、「一般・全身障害および投与部位の状態」［77%（92/119例）、40%（36/91例）］、「血液およびリンパ系障害」［55%（65/119例）、24%（22/91例）］、「胃腸障害」［83%（99/119例）、54%（49/91例）］、「感染症および寄生虫症」［63%（75/119例）、36%（33/91例）］、「皮膚および皮下組織障害」［59%（70/119例）、36%（33/91例）］及び「臨床検査」［45%（54/119例）、23%（21/91例）］であった（[資料5.3.3.2.2: P05615] 14.7.1.30.9 項）。重度／生命を脅かす有害事象の発現割合は、AML/MDS 集団で HSCT 集団よりも高かった［62%（74/119例）、41%（37/91例）］（[資料5.3.3.2.2: P05615] 14.7.1.30.11 項）。

AML/MDS 集団で発現割合が高かった副作用は、「胃腸障害」の器官別大分類［AML/MDS 集団：32%（38/119例）、HSCT 集団：18%（16/91例）、以下同順］に属する事象であった（[資料5.3.3.2.2: P05615] 14.7.1.30.10 項）。これらの副作用のうち、悪心は発現割合が両集団間で同程度であり［11%（13/119例）、11%（10/91例）］、下痢は AML/MDS 集団の方が HSCT 集団よりも高かった［13%（15/119例）、1%（1/91例）］。重度／生命を脅かす副作用の発現割合は、両集団間で同程度であった［11%（13/119例）、7%（6/91例）］（[資料5.3.3.2.2: P05615] 14.7.1.30.12 項）。

2.7.4.5.1.5.1.2　　静注用溶液を投与した第Ⅰ相／第Ⅲ相試験（P05520試験）（非日本人）

300 mg反復静脈内投与（コホート3）

ポサコナゾール静注用溶液の予防投与試験（P05520試験）でポサコナゾール静注用溶液300 mgを投与した被験者における基礎疾患別の有害事象及び副作用の発現割合を[資料5.3.3.2.3: P05520] 14.4.1.27 項に示す。

300 mg反復静脈内投与（コホート3）（213例）では、基礎疾患がAML又はMDSの被験者を併合してAML/MDS集団（131例）とし、造血幹細胞移植患者のみで構成されたHSCT集団（82例）と比較した。基礎疾患別の静脈内投与期の有害事象の発現割合は、AML/MDS 集団95%（125/131例）、HSCT集団88%（72/82例）であり、AML/MDS集団で数値上高かった。副作用の発現割合もAML/MDS 集団40%（52/131例）、HSCT 集団20%（16/82例）であり、AML/MDS 集団で数値上高かった。

静脈内投与期で発現割合が高かった有害事象（AML/MDS集団、HSCT集団いずれかで発現割合20%以上）は、下痢［AML/MDS集団：39%（51/131例）、HSCT集団：18%（15/82例）、以下同順］、発熱［24%（31/131例）、15%（12/82例）］、悪心［20%（26/131例）、20%（16/82例）］、低カリウム血症［27%（36/131例）、13%（11/82例）］及び発熱性好中球減少症［24%（31/131例）、7%（6/82例）］であった。下痢、低カリウム血症及び発熱性好中球減少症は、集団間の発現割合の差が大きく、有害事象プロファイルが集団間で異なった（[資料5.3.3.2.3: P05520] 14.4.1.27.1 項）。

AML/MDS集団で発現割合が高かった静脈内投与期の器官別大分類の有害事象（HSCT集団より発現割合の差が20%以上）は、「胃腸障害」［AML/MDS集団：76%（100/131例）、HSCT集団：46%（38/82例）］であった（[資料5.3.3.2.3: P05520] 14.4.1.27.1 項）。重度／生命を脅かす有害事象の発現割合は、AML/MDS集団がHSCT集団よりも高かった［36%（47/131例）、27%（22/82例）］（[資料5.3.3.2.3: P05520] 14.4.1.27.3 項）。

AML/MDS 集団で発現割合が高かった静脈内投与期の副作用は、「胃腸障害」の器官別大分類［AML/MDS集団：22%（29/131例）、HSCT集団：7%（6/82例）、以下同順］に属する事象であった（[資料5.3.3.2.3: P05520] 14.4.1.27.2 項）。これらの副作用のうち、悪心及び下痢の発現割合は、AML/MDS集団の方がHSCT集団よりも高かった［悪心：8%（10/131例）、2%（2/82例）、下痢：13%（17/131例）、1%（1/82例）］。重度／生命を脅かす副作用の発現割合は、両集団間で同程度であった［8%（10/131例）、4%（3/82例）］（[資料5.3.3.2.3: P05520] 14.4.1.27.4 項）。

2.7.4.5.1.6　　低体重高齢者における安全性プロファイルの評価

国内試験（P101試験）開始後、ポサコナゾール群15例中11例が早期中止例となったため（[資料5.3.5.1.5: P101] 16.2.1 項）、申請者の判断で組入れを中断した（コホート1）。早期中止例11例中7例は有害事象による投与中止で、このうち4例が体重45 kg未満65歳以上の低体重高齢者であった（[資料5.3.5.1.5: P101] 16.2.1 項及び16.2.4.2 項）。また、日本人治療患者（P101試験）の C_{avg} は非日本人予防患者と比べ、同程度からより高曝露な範囲に分布していた[2.7.2.1.4.3.1 項]。P101試験（コホート2）終了後に行った母集団薬物動態モデル及びシミュレーションの結果から、主に低体重と高年齢がポサコナゾールの高曝露量につながり、バイオアベイラビリティに関する病態の効果も曝露量を増加させる内因性要因の一つであることが示された[2.7.2.1.4.3.1 項]。一方、年齢又は体重のそれぞれの内因性要因では、ポサコナゾールの安全性プロファイルに大きな差は認められておらず[2.7.4.5.1項]、例数が限られていることから解釈には注意が必要であるものの、P101試験（コホート1及び2併合）及び海外試験（C/I98-316、P01899、P05615、P05520、P01893及び P00041試験）における、低体重及び高年齢（体重45 kg 未満65歳以上）被験者での安全性プロファイルを評価した。

P101試験（コホート1及び2併合）の結果、体重45 kg 未満65歳以上の被験者集団6例（被験者番号[redacted]及び[redacted]）での有害事象、副作用、重篤な有害事象、重篤な副作用及び投与中止に至った副作用の発現割合は、ほかの被験者集団（体重45 kg 以上65歳以上の被験者及び体重45 kg 以上65歳未満の被験者）と概して類似していた[表 2.7.4-148]。また、体重45 kg 未満65歳以上の被験者で2例以上に発現した有害事象は、発熱3例、並びに便秘、食欲減退及び低カリウム血症 各2例であった[付録 2.7.4-178]。これらの有害事象はポサコナゾール投与時によくみられる事象であり、いずれも非重篤で、発熱の1例以外は投与中又は投与中止後に回復した[資料5.3.7.3.6: P101_ae]。また、2例以上に発現した副作用は、発熱の3例であった[付録 2.7.4-179]。重篤な有害事象は、細菌性肺炎及び敗血症 各1例で、いずれも治験薬との因果関係はなしと判定された[資料5.3.7.5.6: P101_sae]。なお、敗血症は、フォローアップ時に発現した死亡に至った有害事象であった[資料5.3.7.4.6: P101_death]。

投与中止に至った有害事象の発現割合は、体重45 kg 未満65歳以上の被験者で66.7% (4/6例) で、ほかの被験者集団［体重45 kg 以上65歳以上の被験者36.6% (15/41例) 及び体重45 kg 以上65歳未満の被験者17.2% (5/29例)］よりも高かった[表 2.7.4-148]。しかしながら、4例の投与中止に至った有害事象は発熱、敗血症、心電図 ST 部分上昇及び低カリウム血症が各1例であり、体重45 kg 未満65歳以上の被験者集団に高頻度にみられた個別の事象はなく、敗血症以外は、いずれも非重篤で、投与中止により回復した[資料5.3.7.6.6: P101_discon]。

海外試験では、体重45 kg 未満65歳以上の被験者は、ポサコナゾール経口懸濁液の予防投与試験 (P01899試験) 及びポサコナゾール経口懸濁液の治療試験 (P00041試験) で各1例組み入れられた。P01899試験の被験者（被験者番号[redacted]）は、体重[redacted]kg、年齢[redacted]歳で、低血圧及び心停止の有害事象により死亡したが、いずれの事象も治験薬との因果関係はなしと判定された。P00041試験の被験者（被験者番号[redacted]）は、体重[redacted]kg、年齢[redacted]歳で、高血圧及び心室性頻脈により治験薬の投与が中止されたが、いずれの事象も因果関係はなしと判定された。これらの被験者で

は、重篤な有害事象を含むいくつかの有害事象が報告されているものの[資料5.3.7.3.3: P01899_ae] [資料5.3.7.3.7: P00041_ae]、特定の事象で高頻度に認められたものではなく、軽度の強心剤濃度増加（被験者番号[redacted]）以外は、いずれも治験薬との因果関係はなしと判定された。

以上より、国内試験では海外試験に比べて体重45 kg 未満65歳以上の低体重高齢者が多く、例数が限られていることから解釈には注意が必要であるものの、国内外の低体重高齢者の安全性プロファイルに、特定の傾向は認められなかった。

表 2.7.4-148　体重・年齢別の有害事象の要約
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ポサコナゾール群（ASaT）

	65歳未満				65歳以上			
	45 kg 未満		45 kg 以上		45 kg 未満		45 kg 以上	
	n	(%)	n	(%)	n	(%)	n	(%)
症例数	1		29		6		41	
有害事象	1	(100.0)	29	(100.0)	6	(100.0)	41	(100.0)
副作用†	1	(100.0)	18	(62.1)	5	(83.3)	32	(78.0)
重篤な有害事象	1	(100.0)	10	(34.5)	2	(33.3)	17	(41.5)
重篤な副作用	0	(0.0)	1	(3.4)	0	(0.0)	4	(9.8)
投与中止‡に至った有害事象	1	(100.0)	5	(17.2)	4	(66.7)	15	(36.6)
投与中止に至った副作用	1	(100.0)	3	(10.3)	2	(33.3)	12	(29.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

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2.7.4.5.1.7　　中国人被験者を対象とした臨床試験

中国人健康被験者を対象とした単回経口及び静脈内投与試験（P111試験）

本試験では、治験薬を投与した全被験者18例を安全性解析対象集団に含めた[2.7.6.2.27 項]。中国人健康被験者にポサコナゾール静注用溶液300 mg を空腹時に30分かけて単回末梢静脈内投与又は新錠剤 D（黄色）300 mg を空腹時又は高脂肪食摂取後に単回経口投与した際、安全で忍容性は良好であった。重篤な有害事象、妊娠及び死亡はなく、有害事象により中止した被験者もいなかった。被験者18例に有害事象計47件が認められた。28件の有害事象が副作用と判定された。発現割合の高かった有害事象（2例以上に認められた有害事象）は、ポサコナゾール静注用溶液300 mg を空腹時に30分かけて単回末梢静脈内投与した際の悪心（3例）、嘔吐（2例）、浮動性めまい（3例）、発疹（2例）、下腹部痛（2例）及び第一度房室ブロック（2例）、ポサコナゾール新錠剤 D（黄色）300 mg を高脂肪食摂取後に単回経口投与した際の悪心（2例）であった。注入部位の有害事象が1例で認められた。すべての有害事象は軽度で、処置なく回復した。安全性に関する臨床検査値、心電図、バイタルサイン及び身体所見に臨床的に意味のある一貫した変化はなかった。

侵襲性真菌症のハイリスク中国人患者を対象とした反復経口投与試験（P117試験）

本試験では、治験薬を投与した全被験者65例を安全性解析対象集団に含めた[2.7.6.2.24 項]。侵襲性真菌症のハイリスク中国人患者にポサコナゾール新錠剤 D（黄色）300 mg を1日1回8～28日間（1日目は12時間ごとに2回）食事の摂取にかかわらず反復経口投与した際、安全で忍容性は良好であった。重篤な有害事象が4例（呼吸不全、肛門感染、肺感染及び頭蓋内出血）に認められたが、いずれも副作用ではなかった。また、2例の被験者が、呼吸不全及び頭蓋内出血で最終投与後14日以内に死亡したが、いずれも副作用ではなかった。5例の被験者が有害事象（斑状丘疹状皮疹、全身性真菌症、腎不全、ALT 増加、AST 増加及び肺感染）により中止したが、このうち全身性真菌症の1例は8日間の投与を完了していたため完了例として扱った。妊娠した被験者はいなかった。65例中64例で有害事象が認められ、このうち23例が副作用であった。ほとんどの有害事象は処置せず回復し、軽度又は中等度だった。発現割合の高かった有害事象は発熱（35例）、低カリウム血症（25例）、下痢（22例）、咳嗽（15例）、低カルシウム血症（15例）、血中ビリルビン増加（14例）及び発疹（14例）であった。本試験の有害事象は、経口懸濁液を投与した同様の患者集団を対象とした試験で認められた有害事象と類似していた。

肝機能検査値の異常を除く臨床検査値、バイタルサイン及び身体所見に臨床的に意味のある一貫した変化はなかった。また、心電図にも臨床的に意味のある一貫した変化は認められず、治験薬投与期間中に QTc が500 msec 以上となった被験者はいなかった。

2.7.4.5.1.8　　腎機能障害者を対象とした臨床試験

非日本人腎機能障害者を対象とした単回投与試験（P01940試験）

本試験では、治験薬を投与した全被験者24例を安全性解析対象集団に含めた[2.7.6.2.28 項]。軽度［クレアチニンクリアランス（以下同様）：50～80 mL/min/1.73 m^2］、中等度（20～

49 mL/min/1.73 m^2）及び血液透析を必要とする重度腎機能障害者（< 20 mL/min/1.73 m^2）並びに健康被験者並びに正常腎機能者にポサコナゾール経口懸濁液400 mgを高脂肪食摂取後に単回経口投与した際、安全で忍容性は良好であった。妊娠及び死亡はなく、有害事象により中止した被験者もいなかった。2例の重度腎機能障害者で入院を必要とする重篤な有害事象が認められた。1例は重篤な有害事象（カテーテル留置部位関連反応、出血、動脈瘤、腹痛及び胸痛）のため入院した。もう1例は動静脈瘻血栓症を発現し、24時間未満の入院に至った。いずれの有害事象も副作用ではないと判定された。24例中13例で有害事象が認められ、その内訳は、軽度腎機能障害者で3例、中等度及び重度腎機能障害者各5例で、正常腎機能者では有害事象は認められなかった。3例の重度腎機能障害者で認められた浮動性めまいを除き、いずれの群でも2例以上で認められた有害事象はなかった。各1例の中等度腎機能障害者で認められた2件の有害事象（下痢及び傾眠）のみ副作用と判定された。有害事象の程度はいずれも軽度から中等度であった。

臨床検査、バイタルサイン及び心電図に臨床的に意味のある一貫した変化はなかった。

2.7.4.5.1.9　　肝機能障害者を対象とした臨床試験

非日本人肝機能障害者を対象とした単回投与試験（I97-195試験）

本試験では、治験薬を投与した全被験者16例を安全性解析対象集団に含めた[2.7.6.2.29 項]。軽度［Child-Pugh スコア（以下同様）：5～6］、中等度（7～9）及び重度肝機能障害者（10～15）並びに正常肝機能者にポサコナゾール経口懸濁液200 mg を高脂肪食摂取後に単回経口投与した際、安全で忍容性は良好であった。重篤な有害事象、妊娠及び死亡はなく、有害事象により中止した被験者もいなかった。16例中1例（正常肝機能者）で1件の有害事象（中等度の頭痛）が認められたが、副作用ではなかった。その他、身体所見及びバイタルサインは投与前と類似していた。事後検査時の心電図に臨床的に意味のある一貫した変動はなかった。

非日本人肝機能障害者を対象とした単回投与試験（P03742試験）

本試験では、治験薬を投与した全被験者37例を安全性解析対象集団に含めた[2.7.6.2.30 項]。軽度［Child-Pugh スコア（以下同様）：5～6］、中等度（7～9）及び重度肝機能障害者（10～15）並びに正常肝機能者にポサコナゾール経口懸濁液400 mg を高脂肪食摂取後に単回経口投与した際、安全で忍容性は良好であった。重篤な有害事象、妊娠及び死亡はなく、有害事象により中止した被験者もいなかった。37例中12例で有害事象が認められ、その内訳は、正常肝機能者で6例、肝機能障害者で合計6例（軽度で1例、中等度で1例、重度で4例）であった。発現割合の高かった有害事象は尿検査異常（3例）、下痢（2例）及び消化不良（2例）であった。副作用は3例で認められ、いずれも正常肝機能者であった。発現割合の高かった副作用は、下痢（2例）であった。

身体所見、バイタルサイン及び臨床検査値に臨床的に意味のある一貫した変動はなかった。

心電図パラメータのいずれでも、治験薬投与後の値とベースライン値の間に臨床的に意味のある変動はなかった。軽度、中等度及び重度肝機能障害者並びに正常肝機能者でベースラインからの QTcF の延長はなかった。

2.7.4.5.1.10　　好中球減少患者を対象とした臨床試験

高用量化学療法又は骨髄移植を受け好中球が減少している非日本人患者を対象とした薬物動態評価試験（C/I96-421試験）

本試験では、治験薬を投与した全被験者31例を安全性解析対象集団に含めた[2.7.6.2.21 項]。高用量化学療法又は骨髄移植を受け好中球が減少している患者にポサコナゾール経口懸濁液200 mg又は400 mg を朝食摂取後に1日1回、若しくは200 mg を食後に1日4回7～14日間反復経口投与した際、安全で忍容性は良好であった。2例の被験者で重篤な有害事象が認められた。200 mg を1日1回投与された1例の被験者で、最終投与日の12日後に敗血症、汎血球減少症、イレウス及び急性呼吸窮迫症候群の重篤な有害事象が認められ、最終投与の30日以降に死亡した。400 mg を1日1回投与した1例の被験者で、最終投与日の11日後に急性呼吸窮迫症候群、低酸素症及び頻呼吸の重篤な有害事象が認められ、最終投与日の18日後に死亡した。これらの重篤な有害事象は副作用ではないと判定された。なお、重篤な有害事象2例の情報は試験のデータベースではなく、社内の安全性管理データベースからの情報である。妊娠及び有害事象により中止した被験者はいなかった。31例全例で有害事象が認められた。発現割合の高かった有害事象は粘膜炎（22例）、下痢（15例）、発熱（13例）及び嘔気（11例）であった。ほとんどの有害事象が軽度又は中等度で、重度の有害事象は5例に認められた。また、副作用は7例に認められた。重度の副作用は悪心で、400 mg の1日1回投与を受けた1例で1件のみ認められた。

臨床検査値に認められた変動は、患者の基礎疾患による影響と考えられた。

体温上昇の有害事象が13例に認められたが、バイタルサインに臨床的に意味のある一貫した変化はなかった。

心電図について、3例の被験者に変化が認められた。1例の被験者の心電図は、ベースライン時には基準値内であったが、ポサコナゾール投与後15日目に新たに虚血性の変化が認められ、非特異性の T 波異常及び QT 間隔の延長であることが示唆された。当該被験者の QTcB は480 msec でベースラインより46 msec 延長した。また、不整脈の既往症のある別の1例では、ベースラインは基準値内であったが、投与後9日目に種々の房室ブロックを伴う心房粗動、ST 及び T 波の異常を伴う QT 間隔の延長がみられた。いずれの被験者でも、本事象と治験薬との関連性を確認するための追加の心電図は測定されなかった。さらに別の1例では、8日目に QTcB が547 msec を示したが、投与後11日目には基準値内（440 msec）に回復した。当該被験者は低カルシウム血症及び低マグネシウム血症を含む持続的な電解質失調が認められており、複数の併用薬を投与しているため治験薬との因果関係は確認できなかった。

2.7.4.5.2　　外因性要因

本項では、ポサコナゾール静注用溶液を10日間以上投与した際の安全性を評価した。

非日本人侵襲性真菌症のハイリスク患者を対象としてポサコナゾール静注用溶液を投与したP05520試験における300 mg反復静脈内投与コホート（コホート2及び3併合）（237例）のうち、連続10日間以上投与した部分集団（105例）の安全性をコホート全体と比べ以下に示す。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の有害事象の発現割合は98%（103/105例）であり、よくみられた有害事象（発現割合30%以上）は、下痢48%（50/105例）及び発熱性好中球減少症30%（31/105例）であった（[資料5.3.3.2.3: P05520] 14.4.1.29.1項）。300 mg 反復静脈内投与コホート全体における静脈内投与期の有害事象の発現割合は93%（220/237例）で、よくみられた有害事象（発現割合20%以上）は、下痢32%（75/237例）、低カリウム血症22%（51/237例）及び発熱21%（49/237例）であった[2.7.4.2.2.1.1.3.2 項]。なお、発熱性好中球減少症の発現割合は、19%（44/237例）であった。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の重度／生命を脅かす有害事象は43%（45/105例）で、よくみられた重度／生命を脅かす有害事象（発現割合5%以上）は、発熱性好中球減少症10%（11/105例）、低カリウム血症7%（7/105例）、粘膜の炎症7%（7/105例）、下痢6%（6/105例）及び血小板減少症5%（5/105例）であった（[資料5.3.3.2.3: P05520] 14.4.1.29.3 項）。300 mg反復静脈内投与コホート全体における静脈内投与期の重度／生命を脅かす有害事象の発現割合は35%（83/237例）で、最もよくみられた重度／生命を脅かす有害事象（発現割合5%以上）は、発熱性好中球減少症7%（17/237例）であった[2.7.4.2.2.1.1.3.2 項]。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の副作用の発現割合は30%（32/105例）であり、最もよくみられた副作用（発現割合10%以上）は、下痢12%（13/105例）であった（[資料5.3.3.2.3: P05520] 14.4.1.29.2 項）。300 mg反復静脈内投与コホート全体における静脈内投与期の副作用の発現割合は30%（72/237例）で、よくみられた副作用（発現割合5%以上）は、下痢8%（19/237例）、悪心5%（12/237例）及び発疹5%（11/237例）であった[2.7.4.2.2.1.1.3.3 項]。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の死亡に至った有害事象は3%（3/105例）で、死亡に至った副作用はなかった（[資料5.3.3.2.3: P05520] 14.4.1.29.7項及び14.4.1.29.8 項）。300 mg反復静脈内投与コホート全体における静脈内投与期の死亡に至った有害事象の発現割合は4%（10/237例）で、死亡に至った副作用はなかった[2.7.4.2.2.2.1.3 項]。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の重篤な有害事象の発現割合は12%（13/105例）で、重篤な副作用はなかった（[資料5.3.3.2.3: P05520] 14.4.1.29.4項）。300 mg 反復静脈内投与コホート全体における静脈内投与期の重篤な有害事象の発現割合は11%（27/237例）であった[2.7.4.2.2.3.1.3 項]。なお、300 mg反復静脈内投与コホート全体おける静脈内投与期の重篤な副作用の発現割合は、1%（2/237例）（高ビリルビン血症1例及び肺真菌症1例）であった。

ポサコナゾール静注用溶液300 mgを10日間以上投与した部分集団での静脈内投与期の投与中止に至った有害事象の発現割合は8%（8/105例）で、このうち投与中止に至った副作用は1例（肝酵

素上昇）のみであった（[資料5.3.3.2.3: P05520] 14.4.1.29.5 項及び14.4.1.29.6 項）。300 mg 反復静脈内投与コホート全体における静脈内投与期の投与中止に至った有害事象の発現割合は、12%（29/237例）であった[2.7.4.2.2.4.1.3 項]。なお、300 mg 反復静脈内投与コホート全体における静脈内投与期の投与中止に至った副作用の発現割合は3%（8/237例）で、2例以上にみられた事象は発疹（2例）のみであった。

以上より、ポサコナゾール静注用溶液300 mg を10日間以上投与した部分集団（105例）の安全性プロファイルは、有害事象、重度／生命を脅かす有害事象、副作用、死亡に至った有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合に基づき、ポサコナゾール静注用溶液300 mg 反復静脈内投与コホート全体（237例）の安全性プロファイルと類似していると考えられた。

2.7.4.5.3　　薬物相互作用

ポサコナゾールは主として UGT1A4を介して代謝され、P-gp の基質でもあり、薬物代謝酵素誘導剤として知られるリファブチン、フェニトイン、エファビレンツとの併用によるポサコナゾールの血漿中濃度の低下が確認された[2.7.2.3.4.1.1 項]。また、ポサコナゾールは強い CYP3A4阻害作用を有しており、主としてミダゾラム、シンバスタチン及びシロリムスのような CYP3A4に対して高感度な基質との併用において、併用薬の血漿中濃度を上昇させることが確認された[2.7.2.3.4.2.1 項]。ポサコナゾールの薬物相互作用試験における安全性の結果は、2.7.6 項に示す[2.7.6.2.31 項] [2.7.6.2.32 項] [2.7.6.2.33 項] [2.7.6.2.34 項] [2.7.6.2.35 項] [2.7.6.2.36 項] [2.7.6.2.37 項] [2.7.6.2.38 項] [2.7.6.2.39 項] [2.7.6.2.40 項] [2.7.6.2.41 項] [2.7.6.2.42 項] [2.7.6.2.43 項]。

2.7.4.5.4　　妊娠及び授乳時の使用

妊婦でのポサコナゾールの使用経験は十分に得られていない。

ラットにおいて、臨床曝露量（AUC）と同程度の曝露量で、分娩障害、出生児数の減少、生存率低下及び催奇形性が認められた[2.4.4.5 項] [2.6.6.6.2.1 項] [2.6.6.6.2.2 項]。ウサギでは、臨床曝露量（AUC）を上回る曝露量で、吸収胚の増加及び胎児数の減少が認められた[2.4.4.5 項] [2.6.6.6.2.3 項] [2.6.6.6.2.4 項]。ヒトでの潜在的リスクは不明である。妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与することとした。

また、ポサコナゾールはラットで乳汁中への移行が報告されている[2.6.4.6.2 項]。ヒト乳汁中への移行は検討していない。授乳婦へのポサコナゾールの投与は、治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討することとした。

2.7.4.5.5　　過量投与

臨床試験において、ポサコナゾール新錠剤及び静注用溶液での過量投与は報告されていない。

2.7.4.5.6　　薬物乱用

臨床試験において、ポサコナゾールによる薬物乱用の可能性は認められていない。

2.7.4.5.7　　離脱症状及び反跳現象

ポサコナゾールによる離脱症状及び反跳現象を評価した臨床試験は実施していない。また、臨床試験において、ポサコナゾールによる離脱症状は示唆されていない。

2.7.4.5.8　　自動車運転及び機械操作に対する影響又は精神機能の障害

自動車運転又は機械操作に及ぼすポサコナゾールの影響を評価した臨床試験は実施していない。しかしながら、ポサコナゾール経口懸濁液、新錠剤及び静注用溶液の海外試験では、浮動性めまいや傾眠等の有害事象が報告されている。国内試験（P101試験）では、浮動性めまい及び意識消失の有害事象が各1例のみ報告されている。これらの事象は自動車運転又は機械操作に影響する可能性があるため、ポサコナゾール投与後には注意する。

Confidential

2.7.4.6　　市販後データ

海外における市販後データについて、定期的安全性最新報告（PSUR）（調査単位期間：2018年8月2日から2019年2月1日）を基に記載する[資料5.3.6.1: 04W8JC]。

2.7.4.6.1　　世界における市販後の使用経験

ポサコナゾールは、海外において、経口懸濁液、新錠剤及び静注用溶液が承認及び販売されている。承認内容の詳細は国又は地域によって異なるが、好中球減少症患者又は HSCT 患者における真菌感染症の予防、他の治療法が無効又は不耐容の患者における侵襲性真菌症の治療及び口腔咽頭カンジダ症の治療などを適応としている。

経口懸濁液は2005年10月25日に EU で初めて承認され、2019年2月1日現在、73の国及び地域で承認及び販売されている。

新錠剤は、経口懸濁液の欠点（食事とともに投与する条件など）を克服するために開発された。2014年4月23日に新錠剤が EU で承認され、2019年2月1日現在、52の国及び地域で承認及び販売されている。

静注用溶液は、患者が経口剤を服用できない期間の医学的ニーズを満たす目的で開発された。2014年9月18日に EU で承認され、2019年2月1日現在、42の国及び地域で承認及び販売されている。

安全性上の理由によってポサコナゾールの製造販売承認が取り消し又は取り下げられた記録はない。

2.7.4.6.2　　推定使用患者数

ポサコナゾールが販売開始されてから2019年2月1日までの累積出荷数に基づき、推定使用患者数を剤形（経口懸濁液、新錠剤及び静注用溶液）ごとに示す。

2.7.4.6.2.1　　経口懸濁液

ポサコナゾール経口懸濁液の用法・用量は、難治性の侵襲性真菌症の治療には400 mg（10 mL）を1日2回、侵襲性真菌症の予防には200 mg（5 mL）を1日3回、食事又は栄養補給剤とともに投与する。口腔咽頭カンジダ症の治療に推奨される用法・用量は、投与初日に200 mg（5 mL）を1日1回、その後の治療期間は100 mg（2.5 mL）を1日1回投与する。

ポサコナゾール経口懸濁液の累積出荷数は3,095091本であり、経口懸濁液の1日平均投与量を800 mg（20 mL）と仮定すると、延べ投与日数（patient treatment-days）は16,249,228日と推定された。また、患者の平均投与日数を90日間と仮定すると、推定使用患者数は180,547人であった。

2.7.4.6.2.2　　錠剤

ポサコナゾール新錠剤の用法・用量は、投与初日に負荷用量として300 mg を1日2回、2日目からは維持用量として300 mg を1日1回投与する。

ポサコナゾール新錠剤の累積出荷数は53,990,253錠であり、1日平均投与量を3錠（300 mg）と仮

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定すると、延べ投与日数（patient treatment-days）は17,996,751日であった。また、患者の平均投与日数を90日間と仮定すると、推定使用患者数は199,964人であった。

2.7.4.6.2.3　　静注用溶液

ポサコナゾール静注用溶液の用法・用量は、1日目に負荷用量として300 mg を1日2回、2日目からは維持用量として300 mg 1日1回を投与する。

ポサコナゾール静注用溶液の累積出荷数は295,318単位であり、1日平均投与量を1単位（300 mg）と仮定すると、延べ投与日数（patient treatment-days）は295,318日であった。また、患者の平均投与日数を14日間（経口投与が不可能であるため静脈内投与が必要な期間）と仮定すると、推定使用患者数は21,094人であった。

2.7.4.6.3　　重篤な副作用

ポサコナゾールが販売開始されてから2019年2月1日までに自発報告された重篤な副作用は2,084件であった。器官別大分類別の重篤な副作用の発現件数を[表 2.7.4-149]に示す。個々の副作用は PSUR に記載されている[資料5.3.6.1: 04W8JC]。

これらの症例を検討した結果、ポサコナゾールの販売開始以降に新たな安全性上の懸念は認められなかった。

表 2.7.4-149　器官別大分類別の重篤な副作用一覧（販売開始から 2019 年 2 月 1 日まで）

器官別大分類	自発報告（世界の規制当局からの報告及び文献報告を含む）（件）	非介入製造販売後臨床試験及び他の非自発的な報告（件）	計
総件数	2084	1690	3774
血液およびリンパ系障害	116	70	186
心臓障害	96	46	142
先天性、家族性および遺伝性障害	2	1	3
耳および迷路障害	6	1	7
内分泌障害	13	2	15
眼障害	26	5	31
胃腸障害	157	64	221
一般・全身障害および投与部位の状態	347	752	1099
肝胆道系障害	161	55	216
免疫系障害	29	35	64
感染症および寄生虫症	266	187	453
傷害、中毒および処置合併症	22	14	36
臨床検査	167	70	237
代謝および栄養障害	98	38	136
筋骨格系および結合組織障害	52	9	61
良性､悪性および詳細不明の新生物(嚢胞およびポリープを含む)	52	78	130
神経系障害	139	63	202
妊娠、産褥および周産期の状態	2	0	2
精神障害	38	17	55
腎および尿路障害	75	32	107
生殖系および乳房障害	2	3	5
呼吸器、胸郭および縦隔障害	62	58	120
皮膚および皮下組織障害	85	18	103
社会環境	2	0	2
外科および内科処置	34	55	89
血管障害	35	17	52

2.7.4.6.4　安全性シグナル及びリスクの評価

2.7.4.6.4.1　安全性シグナル

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., N.J., U.S.A. (MSD)（米国本社）は、2012年より、調査単位期間中に検出及び評価した安全性シグナルを PSUR に記載している。2019年2月1日までに評価された安全性シグナルを[表 2.7.4-150]に示す。

表 2.7.4-150　評価された安全性シグナル（2012 年 10 月 26 日から 2019 年 2 月 1 日まで）

シグナル	検出時期	シグナル検出の経緯	シグナル評価の方法	シグナル評価の要約	結論
低カリウム血症	2012年 第3四半期	臨床試験の症例報告	臨床試験データの分析、文献レビュー	低カリウム血症の発症は、合併症や併用薬などの患者背景に強く依存していたが、ポサコナゾールとの関連性も否定できなかった。低カリウム血症はポサコナゾールの臨床試験でみられる主な有害事象であり、他のアゾール系抗真菌薬でも報告されていることから、米国本社はポサコナゾールの企業中核安全性情報（以下、CCSI）の副作用の項に低カリウム血症を追記した。	CCSI に追記
ニューロパチー	2013年 第3四半期	規制当局からの要請	臨床試験データの分析、市販後有害事象報告書の詳細なレビュー	臨床試験及び市販後の有害事象報告として得られた情報は限られており、評価に不十分であるか、又は他の要因の関与も疑われた。これらの報告からは、ポサコナゾールとニューロパチーの因果関係は示唆されなかった。	措置不要、モニタリング継続
ポサコナゾール血中濃度 3,500 ng/mL 超での安全性	2014年 第4四半期	規制当局からの要請	市販後有害事象報告書の詳細なレビュー	ポサコナゾールの血中濃度が3,500 ng/mL を超えた症例の情報は限られており、その頻度及び有害事象プロファイルを評価することはできなかった。発現した有害事象は既知の事象が多く、新たな安全性の問題は確認されなかった。	処置不要、モニタリング継続
膵炎	2017年2月	文献情報	臨床試験データの分析、文献及び市販後有害事象報告書の詳細なレビュー	臨床試験において、膵炎の発現率は低かった。しかしながら、文献情報及び市販後の有害事象報告においては、一部の症例でポサコナゾールと膵炎発症に時間的関連性があり、ポサコナゾール休薬による改善及び再投与による再発が認められた。 米国本社はポサコナゾールが膵炎の発症に関連している可能性が高いと判断し、CCSI の副作用の項に膵炎を追記した。	CCSI に追記
ジゴキシンとの薬物相互作用	2017年6月	規制当局からの要請	文献及び市販後有害事象報告書の詳細なレビュー	ポサコナゾールとジゴキシンを併用した患者に関する文献情報及び市販後の有害事象報告において、ジゴキシンの血漿中濃度が増加し、治療を要する有害事象がみられたとの報告がある。ポサコナゾールとジゴキシンの臨床薬物相互作用試験は実施されておらず、相互作用の機序を示す決定的なエビデンスはない。しかしながら、他のアゾール系抗真菌薬でジゴキシンとの薬物相互作用が特定されており、ポサコナゾールでも因果関係を明確に否定できない症例報告が存在することから、米国本社はジゴキシンとの薬物相互作用の可能性は否定できないと判断し、ポサコナゾールの CCSI にジゴキシンとの薬物相互作用の可能性を追加した。	CCSI に追記
偽アルドステロン症	2018年3月	規制当局からの要請	臨床試験データの分析、文献のレビュー、安全性データベース†における市販後有害事象報告書の詳細なレビュー	鉱質コルチコイド過剰又は偽アルドステロン症に類似した低カリウム血症患者の症例報告（一部の患者で高血圧を併発）について書かれた6報の文献が公表されている。これらの症例は、それぞれ臨床的及び生化学的特徴が著しく異なっており、単一の病理学的機序によるものではないと考えられた。文献情報に加えて、高血圧と低カリウム血症の併発に関する市販後有害事象報告が5件収集されているが、これらの報告は潜在的な機序を識別するための臨床検査データを欠いていた。しかしながら、米国本社は得られている情報に基づき、医療従事者がこのまれな臨床症状を診断し管理することをサポートする目的で、偽アルドステロン症を CCSI に追加した。	CCSI に追記

†申請者の安全性データベース及び Eudra Vigilance Data Analysis System（EVDAS）

2.7.4.6.4.2　　重要なリスク

本 PSUR の調査単位期間の開始日（2018年8月2日）時点の企業中核の医薬品リスク管理計画（Core-RMP）に特定された安全性検討事項の一覧を[表 2.7.4-151]に示す。

表 2.7.4-151　安全性検討事項の一覧（2018 年 8 月 2 日時点）

分類	安全性検討事項
重要な特定されたリスク	・肝：肝酵素増加、肝毒性、肝不全、肝炎 ・血液：血栓性血小板減少性紫斑病、溶血性尿毒症症候群 ・心臓：トルサードドポアント、QT 延長 ・一般・全身：薬物相互作用 ・一般・全身：末梢静脈ラインから投与した場合の注入部位反応（静注用溶液） ・傷害、中毒および処置合併症：投薬過誤（錠剤と経口懸濁液の異なる剤形間での代替使用） ・内分泌：副腎機能不全 ・代謝：低カリウム血症
重要な潜在的リスク	・血液：無顆粒球症、再生不良性貧血 ・心臓：心不全、心筋梗塞 ・中枢神経：痙攣、脳虚血、脳出血 ・呼吸器：肺出血 ・血管：高血圧、静脈血栓症、動脈血栓症 ・新生物：新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫） ・視覚：光視症、視覚の明るさ、視覚障害 ・一般・全身：中心静脈ラインから投与した場合の注入部位反応（静注用溶液） ・外科および内科処置：小児における静脈用溶液の適応外使用 ・腎：スルホブチルエーテルβ-シクロデキストリンナトリウムによる腎機能障害（静脈用溶液）
不足情報	・小児への投与 ・妊婦・授乳婦への投与 ・肝機能障害患者への投与

ポサコナゾールの投与に伴う主要なリスクとして、肝障害、血液障害（凝固障害及び血栓性微小血管障害）、心臓障害（トルサードドポアント及びQT延長）、並びに薬物相互作用がある。しかしながら、肝障害を除くこれらの有害事象の発現割合はわずか5%未満である。肝障害の発現割合は16%であるが、ポサコナゾールの対象患者集団では背景発生率も高いことが知られている。

以上の有害事象の多くは、ポサコナゾールの投与中止により回復し、継続しても回復する事象もあった。適切な安全性監視及び添付文書に基づくポサコナゾールの適正使用により、これらの主要なリスクの発生を最小限に抑えることが可能である。米国本社は継続的に、医薬品安全性監視活動の中でこれらの有害事象の発生を監視し、規制当局に報告していく。

2.7.4.6.5　市販後データの結論

ポサコナゾールの良好なベネフィット・リスクプロファイルは確立しており、本 PSUR の調査単位期間に収集された有効性および安全性データによって再確認された。

2.7.4.6.6　医薬品医療機器総合機構に報告した重篤な副作用一覧

治験薬副作用・感染症症例報告制度に基づき、日本人健康成人を対象としたポサコナゾールの第Ⅰ相臨床試験（旧カプセルを用いたJPC-96-361-11試験）の初回治験計画届書の提出（1996年12月9日）以降、2018年6月4日までに医薬品医療機器総合機構に報告した重篤な副作用の一覧を本申請資料の第5部に添付した[資料5.3.6.2: SUSAR]。

2.7.4.7　　付録

付録 2.7.4-1　曝露期間の分布

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764 試験及び P07783 試験パート 1）

	100 mg SD P04975 n=16	100 mg SD P07691 n=23	Total 100 mg SD n=39	300 mg SD P07783 n=13	400 mg SD P07764 n=21	Combined n=73
No.of SD received						
Received any treatment	16 (100)	23 (100)	39 (100)	13 (100)	21 (100)	73 (100)
>= 1	16 (100)	23 (100)	39 (100)	13 (100)	21 (100)	73 (100)
>= 2	16 (100)	22 (96)	38 (97)	0	20 (95)	58 (79)
>= 3	16 (100)	0	16 (41)	0	20 (95)	36 (49)
>= 4	15 (94)	0	15 (38)	0	20 (95)	35 (48)
>= 5	15 (94)	0	15 (38)	0	20 (95)	35 (48)
>= 6	15 (94)	0	15 (38)	0	0	15 (21)
Statistics (day)						
n	16	23	39	13	21	73
Mean	5.8	2	3.5	1	4.8	3.5
SD	0.8	0.2	2	0	0.9	2
Median	6	2	2	1	5	2
Min	3	1	1	1	1	1
Max	6	2	6	1	5	6

SD = Single Dose, n = number of subjects
Note: Only subjects treated with POS solid oral formulations are included

付録 2.7.4-2　曝露期間の分布

健康被験者へのポサコナゾール新錠剤

反復投与試験（P05637 試験及び P07783 試験パート 2）

	200 mg MD P05637 n=10	300 mg MD P07783 n=12	400 mg MD P05637 n=9	Total n=31
Duration (day)				
Received any treatment	10 (100)	12 (100)	9 (100)	31 (100)
≥1	10 (100)	12 (100)	9 (100)	31 (100)
≥2	10 (100)	12 (100)	9 (100)	31 (100)
≥3	10 (100)	12 (100)	9 (100)	31 (100)
≥8	10 (100)	11 (92)	9 (100)	30 (97)
≥14	8 (80)	0	8 (89)	16 (52)
≥22	8 (80)	0	0	8 (26)
Statistics (day)				
N	10	12	9	31
Mean	19.8	7.9	13.6	13.4
Standard Deviation	4.6	0.3	1.3	5.7
Median	22	8	14	14
Min	11	7	10	7
Max	22	8	14	22
MD = Multiple Dose, n = number of subjects;				

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付録 2.7.4-3　曝露期間の分布

健康被験者へのポサコナゾール静注用溶液

投与試験（P04985、P06356 及び P07783 試験）

	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
Duration (day)							
Received any treatment	9 (100)	9 (100)	18 (100)	9 (100)	22 (100)	5 (100)	72 (100)
>= 1 (Day 1)	9 (100)	9 (100)	18 (100)	9 (100)	22 (100)	5 (100)	72 (100)
>= 2 (Day 2)	0	0	0	0	0	5 (100)	5 (7)
>= 3 (Day 3)	0	0	0	0	0	3 (60)	3 (4)
>= 4 (Day 4)	0	0	0	0	0	1 (20)	1 (1)
Statistics (day)							
n	9	9	18	9	22	5	72
Mean	1	1	1	1	1	2.8	1.1
SD	0	0	0	0	0	0.8	0.5
Median	1	1	1	1	1	3	1
Min	1	1	1	1	1	2	1
Max	1	1	1	1	1	4	4
SD = Single Dose; MD = Multiple Dose							

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付録 2.7.4-4　被験者の背景因子

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764 試験及び P07783 試験パート 1）

（All Treated Subjects）

	100 mg SD P04975 n=16	100 mg SD P07691 n=23	Total 100 mg SD n=39	300 mg SD P07783 n=13	400 mg SD P07764 n=21	Total n=73
Sex (n,%)						
Female	8 (50)	13 (57)	21 (54)	4 (31)	3 (14)	28 (38)
Male	8 (50)	10 (43)	18 (46)	9 (69)	18 (86)	45 (62)
Race (n,%)						
White	10 (63)	6 (26)	16 (41)	6 (46)	7 (33)	29 (40)
Non-White	6 (38)	17 (74)	23 (59)	7 (54)	14 (67)	44 (60)
Asian	1 (6)	0	1 (3)	0	1 (5)	2 (3)
Black or African American	4 (25)	17 (74)	21 (54)	7 (54)	13 (62)	41 (56)
Multiracial	1 (6)	0	1 (3)	0	0	1 (1)
Ethnicity (n,%)						
Hispanic or Latino	4 (25)	2 (9)	6 (15)	2 (15)	0	8 (11)
Not Hispanic or Latino	12 (75)	21 (91)	33 (85)	11 (85)	21 (100)	65 (89)
Age (yrs)						
Mean (SD)	31.4 (7.1)	37.7 (9.8)	35.1 (9.2)	36.2 (12.1)	38.2 (7.3)	36.2 (9.3)
Median	31.0	35.0	34.0	36.0	38.0	36.0
Range	19 - 45	23 - 59	19 - 59	20 - 61	24 - 53	19 - 61
Weight (kg)						
Mean (SD)	74.25 (10.02)	76.75 (12.02)	75.73 (11.17)	76.97 (13.09)	79.60 (13.93)	77.06 (12.30)
Median	73.65	73.40	73.40	75.00	78.20	75.00
Range	55.1 - 93.3	55.4 - 100.0	55.1 - 100.0	57.4 - 99.8	52.5 - 105.1	52.5 - 105.1
Height (cm)						
Mean (SD)	168.80 (10.05)	172.87 (9.62)	171.20 (9.88)	175.15 (9.62)	173.48 (8.76)	172.56 (9.52)
Median	170.50	173.00	172.00	173.00	175.00	173.00
Range	144.5 - 184.0	156.0 - 189.0	144.5 - 189.0	156.0 - 190.0	158.0 - 186.5	144.5 - 190.0
BMI						
Mean (SD)	26.09 (3.00)	25.60 (2.77)	25.80 (2.84)	24.97 (2.69)	26.30 (3.23)	25.79 (2.92)
Median	25.35	25.60	25.40	24.50	25.90	25.40
Range	21.3 - 30.5	22.0 - 30.0	21.3 - 30.5	19.7 - 29.3	21.0 - 31.7	19.7 - 31.7
Elbow Breadth (cm)						
Mean (SD)	6.63 (0.35)		6.63 (0.35)		7.22 (0.56)	6.96 (0.56)
Median	6.65		6.65		7.30	6.90
Range	5.9 - 7.1		5.9 - 7.1		6.3 - 8.0	5.9 - 8.0
Missing	0	23	23	13	0	36

SD = Single Dose, n = number of subjects
Note: Only subjects treated with POS solid oral formulations are included

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付録 2.7.4-5　被験者の背景因子

健康被験者へのポサコナゾール新錠剤

反復投与試験（P05637 試験及び P07783 試験パート 2）

（All Treated Subjects）

	200 mg MD P05637 n=10	300 mg MD P07783 n=12	400 mg MD P05637 n=9	Total n=31
Sex (n,%)				
Female	5 (50)	6 (50)	3 (33)	14 (45)
Male	5 (50)	6 (50)	6 (67)	17 (55)
Race (n,%)				
White	10 (100)	5 (42)	9 (100)	24 (77)
Non-White	0	7 (58)	0	7 (23)
Black or African American	0	7 (58)	0	7 (23)
Ethnicity (n,%)				
Hispanic or Latino	10 (100)	3 (25)	9 (100)	22 (71)
Not Hispanic or Latino	0	9 (75)	0	9 (29)
Age (yrs)				
Mean (SD)	47.7 (8.2)	35.9 (12.4)	43.8 (9.9)	42.0 (11.3)
Median	46.5	34.0	40.0	43.0
Range	33 - 59	19 – 55	31 – 56	19 - 59
Weight (kg)				
Mean (SD)	74.85 (14.13)	75.21 (16.89)	72.89 (7.61)	74.42 (13.45)
Median	71.00	74.60	72.00	72.00
Range	61.0 - 100.0	53.0 - 100.8	61.0 - 86.0	53.0 - 100.8
Height (cm)				
Mean (SD)	165.60 (5.62)	172.67 (10.55)	168.78 (7.90)	169.26 (8.73)
Median	165.00	173.50	168.00	168.00
Range	156.0 - 175.0	151.0 - 185.0	155.0 - 181.0	151.0 - 185.0
MD = Multiple Dose, n = number of subjects;				

付録 2.7.4-6　被験者の背景因子

健康被験者へのポサコナゾール静注用溶液

投与試験（P04985、P06356 及び P07783 試験）

	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
Sex (n,%)							
Female	5 (56)	3 (33)	7 (39)	5 (56)	7 (32)	1 (20)	28 (39)
Male	4 (44)	6 (67)	11 (61)	4 (44)	15 (68)	4 (80)	44 (61)
Race (n,%)							
White	8 (89)	9 (100)	16 (89)	9 (100)	14 (64)	5 (100)	61 (85)
Non-White	1 (11)	0	2 (11)	0	8 (36)	0	11 (15)
Asian	0	0	1 (6)	0	0	0	1 (1)
Black or African American	1 (11)	0	0	0	8 (36)	0	9 (13)
Multiracial	0	0	1 (6)	0	0	0	1 (1)
Ethnicity (n,%)							
Hispanic or Latino	0	0	0	0	2 (9)	0	2 (3)
Not Hispanic or Latino	9 (100)	9 (100)	18 (100)	9 (100)	20 (91)	5 (100)	70 (97)
Age (yrs)							
Mean (SD)	31.3 (13.3)	32.4 (14.3)	39.8 (16.1)	42.7 (17.4)	31.5 (11.4)	40.2 (14.2)	35.7 (14.5)
Median	29.0	28.0	32.5	42.0	28.5	40.0	30.0
Range	21 - 58	21 - 64	19 - 65	19 - 64	20 - 61	19 - 57	19 - 65
Age (n,%)							
18 - <65	9 (100)	9 (100)	16 (89)	9 (100)	22 (100)	5 (100)	70 (97)
65 or Older	0	0	2 (11)	0	0	0	2 (3)
Weight (kg)							
Mean (SD)	81.59 (13.69)	70.74 (8.92)	74.87 (9.96)	74.78 (11.52)	75.12 (11.11)	85.00 (16.32)	75.96 (11.59)
Median	83.30	71.20	73.40	78.30	74.65	86.10	74.65
Range	63.6 - 108.6	57.9 - 87.0	57.5 - 98.8	57.4 - 89.0	54.3 - 99.8	65.5 - 102.4	54.3 - 108.6
Height (cm)							
Mean (SD)	178.23 (7.96)	176.82 (8.74)	176.26 (10.63)	171.89 (6.73)	176.51 (8.90)	179.74 (10.33)	176.35 (9.01)
Median	176.50	178.00	176.50	170.40	173.50	179.00	176.00
Range	166.5 - 188.7	163.0 - 187.5	160.0 - 196.0	162.5 - 184.5	156.0 - 190.0	165.4 - 193.1	156.0 - 196.0
Elbow Breadth (cm)							
Mean (SD)	6.88 (0.41)	7.26 (0.74)	6.92 (0.55)	6.77 (0.40)	6.64 (0.50)	7.24 (0.68)	6.93 (0.56)
Median	6.90	7.30	6.75	6.80	6.70	7.50	6.90
Range	6.2 - 7.5	6.3 - 8.4	6.0 - 7.8	6.1 - 7.3	5.9 - 7.2	6.3 - 8.0	5.9 - 8.4
Missing	0	0	0	0	13	0	13

SD = Single Dose; MD - Multiple Dose

付録 2.7.4-7　有害事象の発現例数（%）（いずれかの投与群で発現割合 2%以上）

健康被験者へのポサコナゾール経口懸濁液投与試験（計 20 試験）

Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Emergent Adverse Events
Number (%) of Subjects (2% in Any Treatment Group)

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Subjects Reporting Any Adverse Event	**141 (60.5)**	**14 (66.7)**	**85 (41.3)**	**60 (50.8)**	**273 (59.1)**	**30 (62.5)**
Blood And Lymphatic System Disorders	**3 (1.3)**	**0**	**0**	**8 (6.8)**	**11 (2.4)**	**0**
Leukopenia	0	0	0	5 (4.2)	5 (1.1)	0
Cardiac Disorders	**1 (0.4)**	**1 (4.8)**	**2 (1.0)**	**0**	**4 (0.9)**	**0**
Palpitations	1 (0.4)	1 (4.8)	2 (1.0)	0	4 (0.9)	0
Eye Disorders	**4 (1.7)**	**2 (9.5)**	**1 (0.5)**	**6 (5.1)**	**13 (2.8)**	**1 (2 1)**
Asthenopia	0	0	0	5 (4.2)	5 (1.1)	0
Eye Disorder	0	0	0	0	0	1 (2.1)
Mydriasis	0	1 (4.8)	0	0	1 (0.2)	0
Visual Impairment	0	1 (4.8)	0	0	1 (0.2)	0
Gastrointestinal Disorders	**66 (28.3)**	**8 (38.1)**	**27 (13.1)**	**25 (21.2)**	**120 (26.0)**	**11 (22.9)**
Abdominal Discomfort	2 (0.9)	0	2 (1.0)	5 (4.2)	9 (1.9)	0
Abdominal Pain	5 (2.1)	1 (4.8)	0	7 (5.9)	13 (2.8)	1 (2 1)
Constipation	5 (2.1)	2 (9.5)	5 (2.4)	1 (0.8)	13 (2.8)	2 (4.2)
Diarrhoea	11 (4.7)	1 (4.8)	3 (1.5)	4 (3.4)	19 (4.1)	0
Dry Mouth	25 (10.7)	3 (14.3)	1 (0.5)	1 (0.8)	30 (6.5)	1 (2.1)
Dyspepsia	6 (2.6)	0	4 (1.9)	1 (0.8)	11 (2.4)	0
Flatulence	9 (3.9)	2 (9.5)	2 (1.0)	0	13 (2.8)	3 (6.3)
Lip Dry	1 (0.4)	5 (23.8)	3 (1.5)	0	9 (1.9)	1 (2.1)
Lip Swelling	0	1 (4.8)	0	0	1 (0.2)	0
Nausea	8 (3.4)	0	5 (2.4)	10 (8.5)	23 (5.0)	4 (8 3)
Vomiting	4 (1.7)	0	2 (1.0)	1 (0.8)	7 (1.5)	1 (2 1)
General Disorders And Administration Site Conditions	**36 (15.5)**	**4 (19.0)**	**19 (9.2)**	**16 (13.6)**	**73 (15.8)**	**5 (10.4)**
Asthenia	2 (0.9)	2 (9.5)	0	0	4 (0.9)	2 (4.2)
Fatigue	6 (2.6)	1 (4.8)	16 (7.8)	0	23 (5.0)	3 (6.3)
Feeling Cold	0	0	1 (0.5)	0	1 (0.2)	1 (2 1)

Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Emergent Adverse Events
Number (%) of Subjects (2% in Any Treatment Group)

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Feeling Hot	5 (2.1)	1 (4.8)	1 (0.5)	10 (8.5)	16 (3.5)	0
Influenza Like Illness	2 (0.9)	1 (4.8)	0	0	3 (0.6)	0
Malaise	0	0	1 (0.5)	1 (0.8)	2 (0.4)	2 (4 2)
Pain	5 (2.1)	0	0	0	5 (1.1)	0
Pyrexia	3 (1.3)	0	0	4 (3.4)	7 (1.5)	0
Infections And Infestations	**7 (3.0)**	**5 (23.8)**	**17 (8.3)**	**2 (1.7)**	**31 (6.7)**	**7 (14.6)**
Conjunctivitis	1 (0.4)	0	4 (1.9)	0	5 (1.1)	1 (2.1)
Enterobiasis	0	1 (4.8)	0	0	1 (0.2)	0
Folliculitis	0	0	2 (1.0)	0	2 (0.4)	1 (2.1)
Gingivitis	1 (0.4)	1 (4.8)	0	0	2 (0.4)	0
Injection Site Pustule	0	1 (4.8)	0	0	1 (0.2)	0
Nasopharyngitis	0	0	5 (2.4)	0	5 (1.1)	2 (4 2)
Oral Herpes	1 (0.4)	0	1 (0.5)	0	2 (0.4)	1 (2.1)
Pharyngitis	0	1 (4.8)	5 (2.4)	0	6 (1.3)	1 (2.1)
Rash Pustular	0	1 (4.8)	0	0	1 (0.2)	0
Rhinitis	0	0	1 (0.5)	2 (1.7)	3 (0.6)	1 (2.1)
Injury, Poisoning And Procedural Complications	**5 (2.1)**	**0**	**2 (1.0)**	**0**	**7 (1.5)**	**1 (2 1)**
Laceration	0	0	0	0	0	1 (2.1)
Investigations	**13 (5.6)**	**0**	**2 (1.0)**	**0**	**15 (3.2)**	**1 (2 1)**
Body Temperature Increased	4 (1.7)	0	0	0	4 (0.9)	1 (2 1)
Musculoskeletal And Connective Tissue Disorders	**24 (10.3)**	**3 (14.3)**	**10 (4.9)**	**20 (16.9)**	**54 (11.7)**	**3 (6 3)**
Arthralgia	8 (3.4)	0	1 (0.5)	1 (0.8)	10 (2.2)	0
Back Pain	3 (1.3)	0	6 (2.9)	15 (12.7)	23 (5.0)	0
Musculoskeletal Chest Pain	1 (0.4)	0	0	0	1 (0.2)	1 (2.1)
Musculoskeletal Stiffness	1 (0.4)	1 (4.8)	0	0	2 (0.4)	0
Myalgia	5 (2.1)	1 (4.8)	3 (1.5)	2 (1.7)	11 (2.4)	2 (4.2)
Neck Pain	3 (1.3)	1 (4.8)	0	0	4 (0.9)	0
Pain In Extremity	1 (0.4)	2 (9.5)	0	0	3 (0.6)	0
Nervous System Disorders	**47 (20.2)**	**14 (66.7)**	**48 (23.3)**	**46 (39.0)**	**148 (32.0)**	**17 (35.4)**

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Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Emergent Adverse Events
Number (%) of Subjects (2% in Any Treatment Group)

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Burning Sensation	0	0	0	20 (16.9)	20 (4.3)	0
Disturbance In Attention	0	1 (4.8)	1 (0.5)	0	2 (0.4)	0
Dizziness	5 (2.1)	3 (14.3)	10 (4.9)	14 (11.9)	32 (6.9)	2 (4 2)
Dysgeusia	2 (0.9)	0	2 (1.0)	4 (3.4)	8 (1.7)	0
Headache	35 (15.0)	6 (28.6)	31 (15.0)	28 (23.7)	98 (21.2)	10 (20.8)
Lethargy	4 (1.7)	0	0	7 (5.9)	9 (1.9)	0
Paraesthesia	1 (0.4)	1 (4.8)	1 (0.5)	1 (0.8)	4 (0.9)	0
Sinus Headache	1 (0.4)	0	0	0	1 (0.2)	1 (2 1)
Somnolence	1 (0.4)	5 (23.8)	13 (6.3)	1 (0.8)	20 (4.3)	5 (10.4)
Speech Disorder	0	2 (9.5)	0	0	2 (0.4)	0
Syncope	1 (0.4)	0	1 (0.5)	0	2 (0.4)	2 (4.2)
Tremor	0	2 (9.5)	1 (0.5)	2 (1.7)	5 (1.1)	0
Psychiatric Disorders	**11 (4.7)**	**0**	**2 (1.0)**	**3 (2.5)**	**16 (3.5)**	**1 (2 1)**
Insomnia	8 (3.4)	0	1 (0.5)	1 (0.8)	10 (2.2)	1 (2 1)
Renal And Urinary Disorders	**11 (4.7)**	**1 (4.8)**	**3 (1.5)**	**5 (4.2)**	**20 (4.3)**	**1 (2 1)**
Dysuria	0	0	0	3 (2.5)	3 (0.6)	0
Pollakiuria	11 (4.7)	1 (4.8)	3 (1.5)	1 (0.8)	16 (3.5)	1 (2.1)
Respiratory, Thoracic And Mediastinal Disorders	**27 (11.6)**	**4 (19.0)**	**15 (7.3)**	**6 (5.1)**	**52 (11.3)**	**4 (8 3)**
Cough	3 (1.3)	1 (4.8)	5 (2.4)	0	9 (1.9)	1 (2 1)
Epistaxis	3 (1.3)	3 (14.3)	2 (1.0)	0	8 (1.7)	2 (4.2)
Nasal Dryness	0	1 (4.8)	0	0	1 (0.2)	1 (2 1)
Oropharyngeal Pain	11 (4.7)	0	4 (1.9)	3 (2.5)	18 (3.9)	1 (2 1)
Productive Cough	1 (0.4)	0	0	0	1 (0.2)	1 (2 1)
Respiratory Tract Congestion	1 (0.4)	0	0	0	1 (0.2)	1 (2 1)
Skin And Subcutaneous Tissue Disorders	**23 (9.9)**	**5 (23.8)**	**10 (4.9)**	**4 (3.4)**	**42 (9.1)**	**5 (10.4)**
Acne	3 (1.3)	1 (4.8)	0	0	4 (0.9)	0
Blood Blister	0	1 (4.8)	0	0	1 (0.2)	0
Dry Skin	13 (5.6)	1 (4.8)	6 (2.9)	1 (0.8)	21 (4.5)	0
Eczema	0	1 (4.8)	0	0	1 (0.2)	0
Pain Of Skin	0	0	0	0	0	1 (2.1)

Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Emergent Adverse Events
Number (%) of Subjects (2% in Any Treatment Group)

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Pityriasis Rosea	0	1 (4.8)	0	0	1 (0.2)	0
Rash	2 (0.9)	0	1 (0.5)	0	3 (0.6)	1 (2.1)
Skin Discolouration	0	1 (4.8)	0	0	1 (0.2)	0
Skin Disorder	0	0	0	0	0	1 (2.1)
Skin Exfoliation	0	1 (4.8)	0	0	1 (0.2)	1 (2.1)
Skin Irritation	0	0	0	0	0	1 (2.1)
Vascular Disorders	**3 (1.3)**	**0**	**2 (1.0)**	**8 (6.8)**	**13 (2.8)**	**0**
Flushing	0	0	0	7 (5.9)	7 (1.5)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-8　副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール経口懸濁液投与試験（計 20 試験）

Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Related Treatment Emergent Adverse Events
Number (%) of Subjects

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Subjects Reporting Any Adverse Event	**105 (45.1)**	**12 (57.1)**	**54 (26.2)**	**54 (45.8)**	**203 (43.9)**	**16 (33.3)**
Blood And Lymphatic System Disorders	**2 (0.9)**	**0**	**0**	**6 (5.1)**	**8 (1.7)**	**0**
Anaemia	1 (0.4)	0	0	0	1 (0.2)	0
Leukopenia	0	0	0	3 (2.5)	3 (0.6)	0
Lymph Node Pain	1 (0.4)	0	0	1 (0.8)	2 (0.4)	0
Lymphadenopathy	0	0	0	1 (0.8)	1 (0.2)	0
Neutropenia	0	0	0	1 (0.8)	1 (0.2)	0
Ear And Labyrinth Disorders	**1 (0.4)**	**0**	**0**	**2 (1.7)**	**3 (0.6)**	**0**
Ear Pain	1 (0.4)	0	0	2 (1.7)	3 (0.6)	0
Eye Disorders	**3 (1.3)**	**1 (4.8)**	**1 (0.5)**	**4 (3.4)**	**9 (1.9)**	**0**
Asthenopia	0	0	0	4 (3.4)	4 (0.9)	0
Dry Eye	0	0	1 (0.5)	0	1 (0.2)	0
Eye Swelling	2 (0.9)	0	0	0	2 (0.4)	0
Eyelid Oedema	1 (0.4)	0	0	0	1 (0.2)	0
Vision Blurred	0	0	0	1 (0.8)	1 (0.2)	0
Visual Impairment	0	1 (4.8)	0	0	1 (0.2)	0
Gastrointestinal Disorders	**58 (24.9)**	**6 (28.6)**	**6 (2.9)**	**21 (17.8)**	**85 (18.4)**	**1 (2 1)**
Abdominal Discomfort	1 (0.4)	0	1 (0.5)	3 (2.5)	5 (1.1)	0
Abdominal Distension	2 (0.9)	0	0	0	2 (0.4)	0
Abdominal Pain	4 (1.7)	0	0	6 (5.1)	10 (2.2)	0
Abdominal Pain Lower	1 (0.4)	0	0	1 (0.8)	2 (0.4)	0
Abdominal Pain Upper	1 (0.4)	0	0	2 (1.7)	3 (0.6)	0
Anorectal Discomfort	0	0	0	2 (1.7)	2 (0.4)	0
Constipation	4 (1.7)	0	0	1 (0.8)	5 (1.1)	1 (2.1)
Diarrhoea	11 (4.7)	0	1 (0.5)	4 (3.4)	16 (3.5)	0
Dry Mouth	25 (10.7)	3 (14.3)	1 (0.5)	1 (0.8)	30 (6.5)	0
Dyspepsia	5 (2.1)	0	0	1 (0.8)	6 (1.3)	0
Faeces Hard	1 (0.4)	0	0	0	1 (0.2)	0
Faeces Pale	3 (1.3)	0	0	0	3 (0.6)	0

Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Related Treatment Emergent Adverse Events
Number (%) of Subjects

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Faeces Soft	1 (0.4)	0	0	0	1 (0.2)	0
Flatulence	7 (3.0)	0	0	0	7 (1.5)	1 (2 1)
Frequent Bowel Movements	1 (0.4)	0	0	0	1 (0.2)	0
Haematochezia	1 (0.4)	0	0	0	1 (0.2)	0
Lip Dry	0	4 (19.0)	2 (1.0)	0	6 (1.3)	0
Nausea	8 (3.4)	0	1 (0.5)	9 (7.6)	18 (3.9)	0
Paraesthesia Oral	0	0	0	1 (0.8)	1 (0.2)	0
Rectal Tenesmus	0	0	0	1 (0.8)	1 (0.2)	0
Swollen Tongue	1 (0.4)	0	0	0	1 (0.2)	0
Vomiting	4 (1.7)	0	1 (0.5)	1 (0.8)	6 (1.3)	0
General Disorders And Administration Site Conditions	**23 (9.9)**	**1 (4.8)**	**8 (3.9)**	**15 (12.7)**	**45 (9.7)**	**3 (6 3)**
Asthenia	1 (0.4)	0	0	0	1 (0.2)	0
Chest Discomfort	1 (0.4)	0	0	0	1 (0.2)	0
Chest Pain	1 (0.4)	0	0	0	1 (0.2)	0
Chills	2 (0.9)	0	0	0	2 (0.4)	0
Fatigue	6 (2.6)	1 (4.8)	7 (3.4)	0	14 (3.0)	3 (6.3)
Feeling Hot	5 (2.1)	0	0	10 (8.5)	14 (3.0)	0
Influenza Like Illness	1 (0.4)	0	0	0	1 (0.2)	0
Malaise	0	0	0	1 (0.8)	1 (0.2)	1 (2 1)
Mucosal Dryness	0	0	1 (0.5)	0	1 (0.2)	0
Oedema Peripheral	1 (0.4)	0	0	0	1 (0.2)	0
Pain	5 (2.1)	0	0	0	5 (1.1)	0
Pyrexia	1 (0.4)	0	0	3 (2.5)	4 (0.9)	0
Thirst	4 (1.7)	0	0	2 (1.7)	6 (1.3)	0
Infections And Infestations	**4 (1.7)**	**0**	**5 (2.4)**	**0**	**9 (1.9)**	**2 (4 2)**
Conjunctivitis	0	0	3 (1.5)	0	3 (0.6)	1 (2.1)
Folliculitis	0	0	2 (1.0)	0	2 (0.4)	1 (2.1)
Gingivitis	1 (0.4)	0	0	0	1 (0.2)	0
Oral Herpes	1 (0.4)	0	0	0	1 (0.2)	0
Sinusitis	2 (0.9)	0	0	0	2 (0.4)	0
Investigations	**9 (3.9)**	**0**	**2 (1.0)**	**0**	**11 (2.4)**	**1 (2 1)**

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Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Related Treatment Emergent Adverse Events
Number (%) of Subjects

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Alanine Aminotransferase Increased	2 (0.9)	0	1 (0.5)	0	3 (0.6)	0
Aspartate Aminotransferase Increased	1 (0.4)	0	1 (0.5)	0	2 (0.4)	0
Body Temperature Increased	2 (0.9)	0	0	0	2 (0.4)	1 (2 1)
Electrocardiogram T Wave Amplitude Decreased	0	0	1 (0.5)	0	1 (0.2)	0
Gamma-Glutamyltransferase Increased	3 (1.3)	0	1 (0.5)	0	4 (0.9)	0
Haematocrit Decreased	1 (0.4)	0	0	0	1 (0.2)	0
Haemoglobin Decreased	1 (0.4)	0	0	0	1 (0.2)	0
Hepatic Enzyme Increased	1 (0.4)	0	0	0	1 (0.2)	0
Liver Function Test Abnormal	1 (0.4)	0	0	0	1 (0.2)	0
Liver Function Test Increased	1 (0.4)	0	0	0	1 (0.2)	0
Red Blood Cell Count Decreased	1 (0.4)	0	0	0	1 (0.2)	0
Metabolism And Nutrition Disorders	**1 (0.4)**	**0**	**0**	**0**	**1 (0.2)**	**0**
Decreased Appetite	1 (0.4)	0	0	0	1 (0.2)	0
Musculoskeletal And Connective Tissue Disorders	**12 (5.2)**	**1 (4.8)**	**3 (1.5)**	**20 (16.9)**	**33 (7.1)**	**0**
Arthralgia	4 (1.7)	0	0	1 (0.8)	5 (1.1)	0
Back Pain	3 (1.3)	0	2 (1.0)	15 (12.7)	19 (4.1)	0
Limb Discomfort	0	0	0	1 (0.8)	1 (0.2)	0
Muscular Weakness	0	0	0	1 (0.8)	1 (0.2)	0
Musculoskeletal Discomfort	0	0	0	1 (0.8)	1 (0.2)	0
Musculoskeletal Pain	1 (0.4)	0	0	1 (0.8)	2 (0.4)	0
Myalgia	4 (1.7)	0	1 (0.5)	2 (1.7)	7 (1.5)	0
Neck Pain	1 (0.4)	1 (4.8)	0	0	2 (0.4)	0
Nervous System Disorders	**34 (14.6)**	**12 (57.1)**	**36 (17.5)**	**43 (36.4)**	**118 (25.5)**	**9 (18.8)**
Burning Sensation	0	0	0	20 (16.9)	20 (4.3)	0
Disturbance In Attention	0	1 (4.8)	1 (0.5)	0	2 (0.4)	0
Dizziness	4 (1.7)	2 (9.5)	7 (3.4)	14 (11.9)	27 (5.8)	1 (2 1)
Dizziness Postural	1 (0.4)	0	1 (0.5)	0	2 (0.4)	0

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Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Related Treatment Emergent Adverse Events
Number (%) of Subjects

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Dysgeusia	2 (0.9)	0	2 (1.0)	4 (3.4)	8 (1.7)	0
Headache	25 (10.7)	4 (19.0)	20 (9.7)	26 (22.0)	73 (15.8)	6 (12.5)
Lethargy	4 (1.7)	0	0	7 (5.9)	9 (1.9)	0
Paraesthesia	0	0	0	1 (0.8)	1 (0.2)	0
Sciatica	1 (0.4)	0	0	0	1 (0.2)	0
Somnolence	1 (0.4)	4 (19.0)	11 (5.3)	1 (0.8)	17 (3.7)	4 (8 3)
Tremor	0	1 (4.8)	0	1 (0.8)	2 (0.4)	0
Psychiatric Disorders	**9 (3.9)**	**0**	**1 (0.5)**	**3 (2.5)**	**13 (2.8)**	**0**
Abnormal Dreams	1 (0.4)	0	0	0	1 (0.2)	0
Anxiety	1 (0.4)	0	0	1 (0.8)	2 (0.4)	0
Disorientation	0	0	1 (0.5)	0	1 (0.2)	0
Insomnia	7 (3.0)	0	0	1 (0.8)	8 (1.7)	0
Middle Insomnia	0	0	0	1 (0.8)	1 (0.2)	0
Renal And Urinary Disorders	**11 (4.7)**	**0**	**0**	**5 (4.2)**	**16 (3.5)**	**0**
Dysuria	0	0	0	3 (2.5)	3 (0.6)	0
Micturition Urgency	0	0	0	1 (0.8)	1 (0.2)	0
Pollakiuria	11 (4.7)	0	0	1 (0.8)	12 (2.6)	0
Reproductive System And Breast Disorders	**1 (0.4)**	**0**	**0**	**2 (1.7)**	**3 (0.6)**	**0**
Menstruation Irregular	1 (0.4)	0	0	0	1 (0.2)	0
Vaginal Discharge	0	0	0	2 (1.7)	2 (0.4)	0
Respiratory, Thoracic And Mediastinal Disorders	**4 (1.7)**	**1 (4.8)**	**3 (1.5)**	**2 (1.7)**	**10 (2.2)**	**1 (2 1)**
Cough	0	0	2 (1.0)	0	2 (0.4)	0
Dyspnoea	1 (0.4)	0	0	1 (0.8)	2 (0.4)	0
Nasal Congestion	0	0	1 (0.5)	0	1 (0.2)	0
Nasal Dryness	0	1 (4.8)	0	0	1 (0.2)	1 (2 1)
Oropharyngeal Pain	2 (0.9)	0	0	1 (0.8)	3 (0.6)	0
Painful Respiration	1 (0.4)	0	0	0	1 (0.2)	0
Skin And Subcutaneous Tissue Disorders	**17 (7.3)**	**1 (4.8)**	**6 (2.9)**	**3 (2.5)**	**27 (5.8)**	**1 (2 1)**

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Posaconazole Clinical Pharmacology Integrated Analysis of Safety - FINAL
All Treated Healthy Volunteers
Summary of Treatment Related Treatment Emergent Adverse Events
Number (%) of Subjects

	POS 400mg BID Suspension Fed n = 233	Other POS Suspension Fed >=800mg/day n = 21	POS <800mg/day n = 206	POS+Other n = 118	Total POS n = 462	Placebo n = 48
Acne	2 (0.9)	0	0	0	2 (0.4)	0
Dry Skin	12 (5.2)	1 (4.8)	3 (1.5)	0	16 (3.5)	0
Hyperhidrosis	2 (0.9)	0	0	2 (1.7)	4 (0.9)	0
Pruritus	0	0	2 (1.0)	1 (0.8)	3 (0.6)	0
Rash	1 (0.4)	0	0	0	1 (0.2)	0
Seborrhoea	0	0	1 (0.5)	0	1 (0.2)	0
Skin Irritation	0	0	0	0	0	1 (2.1)
Vascular Disorders	**1 (0.4)**	**0**	**1 (0.5)**	**8 (6.8)**	**10 (2.2)**	**0**
Flushing	0	0	0	7 (5.9)	7 (1.5)	0
Hot Flush	1 (0.4)	0	1 (0.5)	1 (0.8)	3 (0.6)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-9　投与中止に至った有害事象の一覧

健康被験者へのポサコナゾール経口懸濁液投与試験（計 20 試験）

Protocol No.	Subject No. (Posaconazole dose)	Adverse event that resulted in discontinuation (Preferred Term†)	Relationship to study drug
I95-099	[redacted] (200 mg SD)	Gamma-GT Increased SGOT Increased SGPT Increased	Possible Possible Possible
	[redacted] (200 mg SD)	ECG Abnormal‡	Possible
	[redacted] (200 mg SD)	Fracture	Unrelated
I96-089	[redacted] (400 mg BID MD)	Tooth Disorder	Unrelated
I97-016	[redacted] (200 mg QD MD)	Influenza Like Symptoms	Unrelated
I96-207	[redacted] (200 mg QD MD)	Leukopenia	Possible
	[redacted] (200 mg QD MD)	Back Pain Eye Abnormality§ Lymphadenopathy Cervical Dizziness Fever Headache	Probable Probable Possible Possible Related Possible
	[redacted] (200 mg QD MD)	Leukopenia	Unrelated
	[redacted] (200 mg QD MD)	Leukopenia	Unrelated
P02862	[redacted] (400 mg BID MD)	Hepatic Enzymes Increased	Possible
P04547	[redacted]	Diarrhoea Pyrexia Chills Fatigue Anorexia	Possible Possible Possible Possible Possible
	[redacted]	Fatigue Eyelid Oedema Painful Respiration	Probable Probable Probable
P05270	[redacted]	Alanine Aminotransferase Increased Aspartate Aminotransferase Increased	Probable Probable
	[redacted]	Alanine Aminotransferase Increased	Probable

SD = Single Dose, MD = Multiple Dose; BID = twice daily; QD = once daily; Gamma-GT = gamma-glutamyl transferase; SGOT = serum glutamic oxaloacetic transaminase (same as AST); SGPT = serum glutamic pyruvic transaminase (same as ALT).

† 各試験の総括報告書に添付されている被験者一覧の Preferred Term を記載した

‡ 報告事象名（literal term）は Flattening of T-waves

§ 報告事象名（literal term）は Eye Strain

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付録 2.7.4-10 有害事象の要約

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764 試験及び P07783 試験パート 1）

	100 mg SD P04975 n=16		100 mg SD P07691 n=23		Total 100 mg SD n=39		300 mg SD P07783 n=13		400 mg SD P07764 n=21		Combined n=73	
Category												
Treatment Emergent AE	5	(31)	5	(22)	10	(26)	3	(23)	19	(90)	32	(44)
Treatment-Related Treatment Emergent AE	0		4	(17)	4	(10)	0		14	(67)	18	(25)
Serious AE	0		0		0		0		0		0	
Death	0		0		0		0		0		0	
Severe/Life-Threatening Treatment Emergent AE	0		0		0		0		0		0	
Study Drug Discontinuation due to AE	1	(6)	0		1	(3)	0		0		1	(1)

SD = Single Dose, n = number of subjects, AE = Adverse Event
Note: Only subjects treated with POS solid oral formulations are included

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付録 2.7.4-11 有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764 試験及び P07783 試験パート 1）

	100 mg SD P04975 n=16		100 mg SD P07691 n=23		Total 100 mg SD n=39		300 mg SD P07783 n=13		400 mg SD P07764 n=21		Combined n=73	
Subjects Reporting Any Adverse Event	5	(31)	5	(22)	10	(26)	3	(23)	19	(90)	32	(44)
Eye disorders	0		2	(9)	2	(5)	0		1	(5)	3	(4)
Conjunctivitis	0		2	(9)	2	(5)	0		0		2	(3)
Eye swelling	0		0		0		0		1	(5)	1	(1)
Gastrointestinal Disorders	2	(13)	4	(17)	6	(15)	0		10	(48)	16	(22)
Abdominal distension	0		1	(4)	1	(3)	0		1	(5)	2	(3)
Abdominal pain upper	0		0		0		0		1	(5)	1	(1)
Constipation	0		3	(13)	3	(8)	0		0		3	(4)
Diarrhoea	1	(6)	0		1	(3)	0		7	(33)	8	(11)
Dysphagia	0		0		0		0		1	(5)	1	(1)
Flatulence	0		0		0		0		5	(24)	5	(7)
Haematochezia	0		0		0		0		1	(5)	1	(1)
Nausea	0		1	(4)	1	(3)	0		2	(10)	3	(4)
Toothache	1	(6)	0		1	(3)	0		0		1	(1)
Vomiting	0		0		0		0		1	(5)	1	(1)
General disorders and administration site conditions	0		1	(4)	1	(3)	0		6	(29)	7	(10)
Fatigue	0		1	(4)	1	(3)	0		1	(5)	2	(3)
Feeling jittery	0		0		0		0		3	(14)	3	(4)
Infusion site erythema	0		0		0		0		1	(5)	1	(1)
Infusion site swelling	0		0		0		0		1	(5)	1	(1)
Irritability	0		0		0		0		1	(5)	1	(1)
Infections and infestations	2	(13)	0		2	(5)	0		0		2	(3)
Nasopharyngitis	1	(6)	0		1	(3)	0		0		1	(1)
Viral infection	1	(6)	0		1	(3)	0		0		1	(1)
Injury, poisoning and procedural complications	1	(6)	1	(4)	2	(5)	1	(8)	8	(38)	11	(15)
Arthropod bite	0		0		0		1	(8)	0		1	(1)
Contusion	0		1	(4)	1	(3)	0		6	(29)	7	(10)
Corneal abrasion	1	(6)	0		1	(3)	0		0		1	(1)
Excoriation	0		0		0		0		2	(10)	2	(3)
Fall	0		0		0		0		1	(5)	1	(1)
Laceration	0		0		0		0		1	(5)	1	(1)
Scratch	0		0		0		0		1	(5)	1	(1)
Investigations	0		0		0		0		1	(5)	1	(1)
Blood creatine phosphokinase increased	0		0		0		0		1	(5)	1	(1)

付録 2.7.4-11　有害事象の発現例数（%）（いずれかの投与群で発現割合0%超）

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764試験及び P07783試験パート1）（続き）

	100 mg SD P04975 n=16		100 mg SD P07691 n=23		Total 100 mg SD n=39		300 mg SD P07783 n=13		400 mg SD P07764 n=21		Combined n=73	
Musculoskeletal and connective tissue disorders	1	(6)	1	(4)	2	(5)	0		2	(10)	4	(5)
Arthralgia	0		0		0		0		1	(5)	1	(1)
Back pain	0		0		0		0		1	(5)	1	(1)
Myalgia	1	(6)	0		1	(3)	0		0		1	(1)
Neck pain	0		0		0		0		1	(5)	1	(1)
Pain in extremity	0		1	(4)	1	(3)	0		0		1	(1)
Nervous system disorders	2	(13)	0		2	(5)	1	(8)	12	(57)	15	(21)
Dizziness	0		0		0		0		2	(10)	2	(3)
Dystonia	0		0		0		0		1	(5)	1	(1)
Headache	2	(13)	0		2	(5)	0		2	(10)	4	(5)
Migraine	0		0		0		1	(8)	0		1	(1)
Oromandibular dystonia	0		0		0		0		2	(10)	2	(3)
Somnolence	0		0		0		0		8	(38)	8	(11)
Psychiatric disorders	0		0		0		0		3	(14)	3	(4)
Anxiety	0		0		0		0		1	(5)	1	(1)
Insomnia	0		0		0		0		1	(5)	1	(1)
Restlessness	0		0		0		0		1	(5)	1	(1)
Reproductive system and breast disorders	0		0		0		2	(15)	0		2	(3)
Dysmenorrhoea	0		0		0		2	(15)	0		2	(3)
Respiratory, thoracic and mediastinal disorders	1	(6)	0		1	(3)	0		2	(10)	3	(4)
Nasal congestion	0		0		0		0		2	(10)	2	(3)
Oropharyngeal pain	1	(6)	0		1	(3)	0		0		1	(1)
Skin and subcutaneous tissue disorders	1	(6)	0		1	(3)	0		3	(14)	4	(5)
Dermatitis contact	1	(6)	0		1	(3)	0		0		1	(1)
Erythema	0		0		0		0		3	(14)	3	(4)
Vascular disorders	0		1	(4)	1	(3)	0		0		1	(1)
Flushing	0		1	(4)	1	(3)	0		0		1	(1)

SD = Single Dose, n = number of subjects, AE = Adverse Event
Note: Only subjects treated with POS solid oral formulations are included

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付録 2.7.4-12 副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール新錠剤

単回投与試験（P04975、P07691、P07764 試験及び P07783 試験パート 1）

	100 mg SD P04975 n=16	100 mg SD P07691 n=23	Total 100 mg SD n=39	300 mg SD P07783 n=13	400 mg SD P07764 n=21	Combined n=73
Subjects Reporting Any Adverse Event	0	4 (17)	4 (10)	0	14 (67)	18 (25)
Eye disorders	0	1 (4)	1 (3)	0	0	1 (1)
Conjunctivitis	0	1 (4)	1 (3)	0	0	1 (1)
Gastrointestinal disorders	0	3 (13)	3 (8)	0	6 (29)	9 (12)
Constipation	0	2 (9)	2 (5)	0	0	2 (3)
Diarrhoea	0	0	0	0	5 (24)	5 (7)
Flatulence	0	0	0	0	3 (14)	3 (4)
Nausea	0	1 (4)	1 (3)	0	1 (5)	2 (3)
Vomiting	0	0	0	0	1 (5)	1 (1)
General disorders and administration site conditions	0	1 (4)	1 (3)	0	3 (14)	4 (5)
Fatigue	0	1 (4)	1 (3)	0	1 (5)	2 (3)
Feeling jittery	0	0	0	0	1 (5)	1 (1)
Irritability	0	0	0	0	1 (5)	1 (1)
Nervous system disorders	0	0	0	0	10 (48)	10 (14)
Dizziness	0	0	0	0	1 (5)	1 (1)
Dystonia	0	0	0	0	1 (5)	1 (1)
Headache	0	0	0	0	1 (5)	1 (1)
Oromandibular dystonia	0	0	0	0	2 (10)	2 (3)
Somnolence	0	0	0	0	7 (33)	7 (10)
Psychiatric disorders	0	0	0	0	2 (10)	2 (3)
Anxiety	0	0	0	0	1 (5)	1 (1)
Insomnia	0	0	0	0	1 (5)	1 (1)
Vascular disorders	0	1 (4)	1 (3)	0	0	1 (1)
Flushing	0	1 (4)	1 (3)	0	0	1 (1)

SD = Single Dose, n = number of subjects, AE = Adverse Event
Note: Only subjects treated with POS solid oral formulations are included

Confidential

付録 2.7.4-13 有害事象の要約

健康被験者へのポサコナゾール新錠剤

反復投与試験（P05637 試験及び P07783 試験パート 2）

	200 mg MD P05637 n=10		300 mg MD P07783 n=12		400 mg MD P05637 n=9		Combined n=31	
Category								
Treatment Emergent AE	6	(60)	9	(75)	5	(56)	20	(65)
Treatment-Related Treatment Emergent AE	6	(60)	8	(67)	4	(44)	18	(58)
Serious AE	0		0		0		0	
Death	0		0		0		0	
Severe/Life-Threatening Treatment Emergent AE	0		0		0		0	
Study Drug Discontinuation due to AE	2	(20)	1	(8)	1	(11)	4	(13)

MD = Multiple Dose, n = number of subjects, AE = Adverse Event

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付録 2.7.4-14 有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール新錠剤

反復投与試験（P05637 試験及び P07783 試験パート 2）

	200 mg MD P05637 n=10		300 mg MD P07783 n=12		400 mg MD P05637 n=9		Combined n=31	
Subjects Reporting Any Adverse Event	6	(60)	9	(75)	5	(56)	20	(65)
Eye disorders	0		2	(17)	0		2	(6)
Dry eye	0		1	(8)	0		1	(3)
Vision blurred	0		2	(17)	0		2	(6)
Gastrointestinal disorders	1	(10)	7	(58)	4	(44)	12	(39)
Abdominal distension	0		1	(8)	0		1	(3)
Abdominal pain	0		2	(17)	0		2	(6)
Constipation	0		2	(17)	0		2	(6)
Diarrhoea	0		3	(25)	3	(33)	6	(19)
Dry mouth	0		0		1	(11)	1	(3)
Nausea	0		3	(25)	1	(11)	4	(13)
Toothache	1	(10)	1	(8)	0		2	(6)
General disorders and administration site conditions	0		3	(25)	0		3	(10)
Chest pain	0		2	(17)	0		2	(6)
Fatigue	0		2	(17)	0		2	(6)
Infections and infestations	0		2	(17)	0		2	(6)
Upper respiratory tract infection	0		1	(8)	0		1	(3)
Urinary tract infection	0		1	(8)	0		1	(3)
Investigations	5	(50)	1	(8)	1	(11)	7	(23)
Hepatic enzyme increased	5	(50)	1	(8)	1	(11)	7	(23)
Musculoskeletal and connective tissue disorders	0		2	(17)	1	(11)	3	(10)
Arthralgia	0		1	(8)	0		1	(3)
Back pain	0		1	(8)	0		1	(3)
Myalgia	0		1	(8)	1	(11)	2	(6)
Nervous system disorders	1	(10)	3	(25)	1	(11)	5	(16)
Dizziness	1	(10)	1	(8)	0		2	(6)
Headache	0		0		1	(11)	1	(3)
Migraine	0		1	(8)	0		1	(3)
Paraesthesia	0		1	(8)	0		1	(3)
Somnolence	0		1	(8)	0		1	(3)
Tension headache	0		1	(8)	0		1	(3)
Renal and urinary disorders	0		2	(17)	0		2	(6)
Dysuria	0		1	(8)	0		1	(3)
Urinary incontinence	0		1	(8)	0		1	(3)
Reproductive system and breast disorders	0		1	(8)	0		1	(3)
Dysmenorrhoea	0		1	(8)	0		1	(3)
Skin and subcutaneous tissue disorders	0		3	(25)	0		3	(10)
Dry skin	0		2	(17)	0		2	(6)
Erythema	0		1	(8)	0		1	(3)
Hyperhidrosis	0		1	(8)	0		1	(3)
Pruritus	0		1	(8)	0		1	(3)

MD = Multiple Dose, n = number of subjects

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付録 2.7.4-15 副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール新錠剤

反復投与試験（P05637 試験及び P07783 試験パート 2）

	200 mg MD P05637 n=10		300 mg MD P07783 n=12		400 mg MD P05637 n=9		Combined n=31	
Subjects Reporting Any Adverse Event	6	(60)	8	(67)	4	(44)	18	(58)
Eye disorders	0		1	(8)	0		1	(3)
Dry eye	0		1	(8)	0		1	(3)
Vision blurred	0		1	(8)	0		1	(3)
Gastrointestinal disorders	0		6	(50)	4	(44)	10	(32)
Abdominal distension	0		1	(8)	0		1	(3)
Abdominal pain	0		2	(17)	0		2	(6)
Constipation	0		2	(17)	0		2	(6)
Diarrhoea	0		3	(25)	3	(33)	6	(19)
Dry mouth	0		0		1	(11)	1	(3)
Nausea	0		3	(25)	1	(11)	4	(13)
General disorders and administration site conditions	0		3	(25)	0		3	(10)
Chest pain	0		1	(8)	0		1	(3)
Fatigue	0		2	(17)	0		2	(6)
Infections and infestations	0		1	(8)	0		1	(3)
Upper respiratory tract infection	0		1	(8)	0		1	(3)
Investigations	5	(50)	1	(8)	1	(11)	7	(23)
Hepatic enzyme increased	5	(50)	1	(8)	1	(11)	7	(23)
Musculoskeletal and connective tissue disorders	0		1	(8)	0		1	(3)
Back pain	0		1	(8)	0		1	(3)
Nervous system disorders	1	(10)	2	(17)	1	(11)	4	(13)
Dizziness	1	(10)	1	(8)	0		2	(6)
Headache	0		0		1	(11)	1	(3)
Somnolence	0		1	(8)	0		1	(3)
Tension headache	0		1	(8)	0		1	(3)
Renal and urinary disorders	0		1	(8)	0		1	(3)
Urinary incontinence	0		1	(8)	0		1	(3)
Skin and subcutaneous tissue disorders	0		2	(17)	0		2	(6)
Dry skin	0		2	(17)	0		2	(6)
Pruritus	0		1	(8)	0		1	(3)

MD = Multiple Dose, n = number of subjects

Confidential

付録 2.7.4-16 有害事象の要約

健康被験者へのポサコナゾール静注用溶液

投与試験（P04985、P06356 及び P07783 試験）

Category	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
Treatment Emergent AE	4 (44)	3 (33)	6 (33)	3 (33)	8 (36)	5 (100)	29 (40)
Treatment-Related Treatment Emergent AE	1 (11)	0	4 (22)	3 (33)	7 (32)	4 (80)	19 (26)
Serious AE	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Severe/Life-Threatening Treatment Emergent AE	0	0	0	0	0	0	0
Study Drug Discontinuation due to AE	0	0	0	0	0	2 (40)	2 (3)

SD = Single Dose; MD = Multiple Dose
Column "POS IV 200mg SD": subjects from P04985 and P06356
Column "POS IV 300mg SD": subjects from P06356 and P07783. All other data are from P06356

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付録 2.7.4-17 有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール静注用溶液

投与試験（P04985、P06356 及び P07783 試験）

	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	4 (44)	3 (33)	6 (33)	3 (33)	8 (36)	5 (100)	29 (40)
Gastrointestinal disorders	1 (11)	0	3 (17)	0	1 (5)	1 (20)	6 (8)
Diarrhoea	0	0	2 (11)	0	0	0	2 (3)
Nausea	1 (11)	0	2 (11)	0	1 (5)	1 (20)	5 (7)
Vomiting	1 (11)	0	1 (6)	0	0	0	2 (3)
General disorders and administration site conditions	3 (33)	1 (11)	6 (33)	2 (22)	3 (14)	4 (80)	19 (26)
Catheter site pain	1 (11)	1 (11)	1 (6)	0	0	0	3 (4)
Catheter site related reaction	0	0	1 (6)	0	0	0	1 (1)
Fatigue	1 (11)	0	1 (6)	0	0	0	2 (3)
Infusion site pain	0	0	1 (6)	0	0	0	1 (1)
Infusion site paraesthesia	0	0	1 (6)	0	0	0	1 (1)
Infusion site reaction	1 (11)	0	1 (6)	2 (22)	3 (14)	4 (80)	11 (15)
Malaise	0	0	0	0	0	1 (20)	1 (1)
Oedema peripheral	0	0	1 (6)	0	0	0	1 (1)
Pyrexia	0	0	0	0	0	1 (20)	1 (1)
Infections and infestations	0	0	1 (6)	1 (11)	1 (5)	0	3 (4)
Nasopharyngitis	0	0	1 (6)	1 (11)	1 (5)	0	3 (4)
Injury, poisoning and procedural complications	0	0	0	0	1 (5)	1 (20)	2 (3)
Procedural pain	0	0	0	0	0	1 (20)	1 (1)
Thermal burn	0	0	0	0	1 (5)	0	1 (1)
Investigations	0	0	1 (6)	0	0	0	1 (1)
Liver function test abnormal	0	0	1 (6)	0	0	0	1 (1)
Metabolism and nutrition disorders	0	0	1 (6)	0	0	0	1 (1)
Decreased appetite	0	0	1 (6)	0	0	0	1 (1)
Musculoskeletal and connective tissue disorders	1 (11)	0	1 (6)	0	0	0	2 (3)
Musculoskeletal chest pain	1 (11)	0	0	0	0	0	1 (1)
Myalgia	0	0	1 (6)	0	0	0	1 (1)
Nervous system disorders	0	2 (22)	3 (17)	2 (22)	4 (18)	2 (40)	13 (18)
Dizziness	0	0	1 (6)	0	0	0	1 (1)
Headache	0	1 (11)	1 (6)	1 (11)	1 (5)	2 (40)	6 (8)
Mental impairment	0	0	0	0	1 (5)	0	1 (1)
Migraine	0	0	0	0	1 (5)	0	1 (1)
Paraesthesia	0	0	0	1 (11)	0	0	1 (1)
Somnolence	0	1 (11)	1 (6)	0	0	0	2 (3)
Tension headache	0	0	0	0	2 (9)	0	2 (3)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (5)	1 (20)	2 (3)
Dermatitis	0	0	0	0	1 (5)	0	1 (1)
Erythema	0	0	0	0	0	1 (20)	1 (1)
Vascular disorders	0	0	1 (6)	0	2 (9)	3 (60)	6 (8)
Phlebitis	0	0	0	0	1 (5)	0	1 (1)
Thrombophlebitis	0	0	1 (6)	0	1 (5)	3 (60)	5 (7)

SD = Single Dose; MD = Multiple Dose
Column "POS IV 200mg SD": data are from P04985 and P06356
Column "POS IV 300mg SD": data are from P06356 and P07783. All other data are from P06356

付録 2.7.4-18 副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

健康被験者へのポサコナゾール静注用溶液

投与試験（P04985、P06356 及び P07783 試験）

	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	1 (11)	0	4 (22)	3 (33)	7 (32)	4 (80)	19 (26)
Gastrointestinal disorders	0	0	0	0	1 (5)	0	1 (1)
Nausea	0	0	0	0	1 (5)	0	1 (1)
General disorders and administration site conditions	1 (11)	0	4 (22)	2 (22)	3 (14)	4 (80)	14 (19)
Infusion site pain	0	0	1 (6)	0	0	0	1 (1)
Infusion site paraesthesia	0	0	1 (6)	0	0	0	1 (1)
Infusion site reaction	1 (11)	0	1 (6)	2 (22)	3 (14)	4 (80)	11 (15)
Malaise	0	0	0	0	0	1 (20)	1 (1)
Oedema peripheral	0	0	1 (6)	0	0	0	1 (1)
Pyrexia	0	0	0	0	0	1 (20)	1 (1)
Investigations	0	0	1 (6)	0	0	0	1 (1)
Liver function test abnormal	0	0	1 (6)	0	0	0	1 (1)
Nervous system disorders	0	0	1 (6)	2 (22)	4 (18)	0	7 (10)
Headache	0	0	1 (6)	1 (11)	1 (5)	0	3 (4)
Mental impairment	0	0	0	0	1 (5)	0	1 (1)
Paraesthesia	0	0	0	1 (11)	0	0	1 (1)
Tension headache	0	0	0	0	2 (9)	0	2 (3)
Vascular disorders	0	0	1 (6)	0	2 (9)	3 (60)	6 (8)
Phlebitis	0	0	0	0	1 (5)	0	1 (1)
Thrombophlebitis	0	0	1 (6)	0	1 (5)	3 (60)	5 (7)

SD: = Single Dose; MD = Multiple Dose
Column "POS IV 200mg SD": data are from P04985 and P06356
Column "POS IV 300mg SD": data are from P06356 and P07783. All other data are from P06356

付録 2.7.4-19 有害事象及び重度／生命を脅かす有害事象の発現例数（%）
（いずれかの投与群で発現割合 0%超）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）
Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Subjects Reporting Any Adverse Event	**595 (98.3)**	**448 (74.0)**	**531 (98.5)**	**381 (70.7)**	**58 (100.0)**	**47 (81.0)**
Blood And Lymphatic System Disorders	**380 (62.8)**	**239 (39.5)**	**330 (61.2)**	**211 (39.1)**	**41 (70.7)**	**28 (48.3)**
Anaemia	161 (26.6)	67 (11.1)	136 (25.2)	48 (8.9)	19 (32.8)	12 (20.7)
Bone Marrow Disorder	0	0	1 (0.2)	1 (0.2)	0	0
Bone Marrow Failure	5 (0.8)	3 (0.5)	0	0	0	0
Coagulation Factor Deficiency	1 (0.2)	0	0	0	0	0
Coagulopathy	12 (2.0)	0	14 (2.6)	4 (0.7)	1 (1.7)	1 (1.7)
Disseminated Intravascular Coagulation	3 (0.5)	2 (0.3)	5 (0.9)	4 (0.7)	0	0
Eosinophilia	1 (0.2)	0	0	0	0	0
Febrile Neutropenia	118 (19.5)	49 (8.1)	85 (15.8)	40 (7.4)	23 (39.7)	7 (12.1)
Granulocytopenia	1 (0.2)	1 (0 2)	3 (0.6)	1 (0.2)	0	0
Haemolysis	5 (0.8)	1 (0 2)	4 (0.7)	2 (0.4)	0	0
Haemolytic Anaemia	0	0	1 (0.2)	0	0	0
Haemolytic Uraemic Syndrome	6 (1.0)	5 (0.8)	3 (0.6)	1 (0.2)	0	0
Haemorrhagic Diathesis	2 (0.3)	0	4 (0.7)	2 (0.4)	0	0
Haemorrhagic Disorder	1 (0.2)	0	0	0	0	0
Hypercoagulation	1 (0.2)	0	0	0	0	0
Hypofibrinogenaemia	1 (0.2)	0	1 (0.2)	0	1 (1.7)	0
Hypoglobulinaemia	1 (0.2)	0	1 (0.2)	0	0	0
Hypoprothrombinaemia	2 (0.3)	0	5 (0.9)	0	0	0
Increased Tendency To Bruise	0	0	2 (0.4)	0	0	0
Iron Deficiency Anaemia	0	0	1 (0.2)	0	0	0
Leukocytosis	3 (0.5)	1 (0.2)	6 (1.1)	1 (0.2)	0	0
Leukopenia	36 (6.0)	19 (3 1)	41 (7.6)	20 (3.7)	5 (8.6)	5 (8.6)
Lymph Node Pain	3 (0.5)	0	0	0	1 (1.7)	0
Lymphadenitis	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Lymphadenopathy	11 (1.8)	1 (0 2)	9 (1.7)	2 (0.4)	2 (3.4)	1 (1.7)
Lymphopenia	0	0	1 (0.2)	1 (0.2)	1 (1.7)	0
Macrocytosis	1 (0.2)	0	1 (0.2)	0	0	0
Microangiopathic Haemolytic Anaemia	0	0	1 (0.2)	1 (0.2)	0	0
Monocytosis	0	0	1 (0.2)	0	0	0
Neutropenia	145 (24.0)	95 (15.7)	127 (23.6)	79 (14.7)	23 (39.7)	19 (32.8)
Pancytopenia	18 (3.0)	9 (1 5)	21 (3.9)	13 (2.4)	1 (1.7)	1 (1.7)
Polychromasia	0	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Polycythaemia	0	0	1 (0.2)	0	0	0
Protein Deficiency Anaemia	1 (0.2)	0	0	0	0	0
Red Cell Fragmentation Syndrome	1 (0.2)	0	0	0	0	0
Retroperitoneal Lymphadenopathy	1 (0.2)	0	0	0	0	0
Splenomegaly	11 (1.8)	0	7 (1.3)	1 (0.2)	0	0
Thrombocytopenia	189 (31.2)	143 (23.6)	161 (29.9)	117 (21.7)	21 (36.2)	16 (27.6)
Thrombocytosis	0	0	2 (0.4)	1 (0.2)	1 (1.7)	0
Thrombotic Microangiopathy	0	0	1 (0.2)	1 (0.2)	0	0
Thrombotic Thrombocytopenic Purpura	9 (1.5)	8 (1.3)	3 (0.6)	2 (0.4)	0	0
Cardiac Disorders	**144 (23.8)**	**46 (7.6)**	**139 (25.8)**	**40 (7.4)**	**14 (24.1)**	**5 (8.6)**
Acute Myocardial Infarction	3 (0.5)	1 (0 2)	0	0	0	0
Angina Pectoris	4 (0.7)	1 (0 2)	4 (0.7)	0	0	0
Aortic Valve Incompetence	1 (0.2)	0	1 (0.2)	0	0	0
Arrhythmia	4 (0.7)	2 (0 3)	2 (0.4)	0	0	0
Arrhythmia Supraventricular	0	0	1 (0.2)	1 (0.2)	0	0
Arteriosclerosis Coronary Artery	1 (0.2)	0	0	0	0	0
Atrial Fibrillation	11 (1.8)	8 (1.3)	17 (3.2)	8 (1.5)	2 (3.4)	2 (3.4)
Atrial Flutter	3 (0.5)	1 (0 2)	3 (0.6)	2 (0.4)	0	0
Atrial Hypertrophy	1 (0.2)	0	0	0	0	0
Atrial Tachycardia	1 (0.2)	0	0	0	0	0
Atrioventricular Block	0	0	1 (0.2)	1 (0.2)	0	0
Atrioventricular Block Complete	1 (0.2)	1 (0 2)	0	0	0	0
Atrioventricular Block Second Degree	1 (0.2)	0	0	0	0	0
Bradycardia	10 (1.7)	4 (0.7)	8 (1.5)	1 (0.2)	2 (3.4)	0
Bundle Branch Block	0	0	1 (0.2)	0	0	0
Bundle Branch Block Left	2 (0.3)	0	3 (0.6)	1 (0.2)	0	0
Bundle Branch Block Right	1 (0.2)	0	3 (0.6)	1 (0.2)	0	0
Cardiac Arrest	7 (1.2)	7 (1 2)	6 (1.1)	6 (1.1)	1 (1.7)	1 (1.7)
Cardiac Disorder	1 (0.2)	0	0	0	0	0
Cardiac Failure	4 (0.7)	3 (0 5)	4 (0.7)	3 (0.6)	0	0
Cardiac Failure Congestive	3 (0.5)	2 (0 3)	5 (0.9)	4 (0.7)	0	0
Cardiac Flutter	0	0	1 (0.2)	0	0	0
Cardiac Hypertrophy	2 (0.3)	0	0	0	0	0
Cardiac Tamponade	0	0	1 (0.2)	0	0	0
Cardio-Respiratory Arrest	3 (0.5)	3 (0 5)	6 (1.1)	6 (1.1)	0	0
Cardiomegaly	6 (1.0)	1 (0 2)	0	0	1 (1.7)	0
Cardiomyopathy	1 (0.2)	0	1 (0.2)	0	1 (1.7)	1 (1.7)

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Cardiopulmonary Failure	1 (0.2)	1 (0 2)	0	0	0	0
Cardiotoxicity	0	0	1 (0.2)	1 (0.2)	0	0
Cardiovascular Disorder	0	0	1 (0.2)	1 (0.2)	0	0
Cardiovascular Insufficiency	3 (0.5)	3 (0 5)	2 (0.4)	1 (0.2)	0	0
Congestive Cardiomyopathy	1 (0.2)	1 (0 2)	0	0	0	0
Cor Pulmonale	0	0	1 (0.2)	0	0	0
Coronary Artery Stenosis	1 (0.2)	0	0	0	0	0
Cyanosis	0	0	1 (0.2)	0	0	0
Defect Conduction Intraventricular	0	0	1 (0.2)	0	0	0
Endocarditis Noninfective	0	0	1 (0.2)	1 (0.2)	0	0
Extrasystoles	1 (0.2)	0	4 (0.7)	0	0	0
Intracardiac Mass	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Left Atrial Dilatation	1 (0.2)	1 (0 2)	0	0	0	0
Left Ventricular Dysfunction	4 (0.7)	1 (0 2)	5 (0.9)	0	0	0
Left Ventricular Hypertrophy	2 (0.3)	1 (0.2)	1 (0.2)	0	0	0
Mitral Valve Disease	1 (0.2)	0	0	0	0	0
Mitral Valve Incompetence	4 (0.7)	1 (0 2)	1 (0.2)	0	0	0
Myocardial Infarction	3 (0.5)	3 (0 5)	0	0	0	0
Myocardial Ischaemia	2 (0.3)	1 (0 2)	0	0	0	0
Myocarditis	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Palpitations	5 (0.8)	1 (0 2)	6 (1.1)	0	1 (1.7)	0
Pericardial Effusion	8 (1.3)	0	17 (3.2)	3 (0.6)	1 (1.7)	0
Pericardial Mass	0	0	1 (0.2)	0	0	0
Pericardial Rub	0	0	1 (0.2)	0	0	0
Pericarditis	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Restrictive Cardiomyopathy	1 (0.2)	0	0	0	0	0
Right Atrial Enlargement	0	0	1 (0.2)	0	0	0
Right Ventricular Enlargement	0	0	1 (0.2)	0	0	0
Right Ventricular Hypertrophy	0	0	1 (0.2)	0	0	0
Sinus Arrhythmia	1 (0.2)	0	0	0	0	0
Sinus Bradycardia	1 (0.2)	0	1 (0.2)	0	2 (3.4)	0
Sinus Tachycardia	11 (1.8)	2 (0 3)	10 (1.9)	3 (0.6)	2 (3.4)	0
Subendocardial Ischaemia	0	0	2 (0.4)	1 (0.2)	0	0
Supraventricular Extrasystoles	3 (0.5)	0	1 (0.2)	0	0	0
Supraventricular Tachycardia	4 (0.7)	3 (0 5)	3 (0.6)	2 (0.4)	1 (1.7)	1 (1.7)
Tachycardia	65 (10.7)	6 (1.0)	69 (12.8)	4 (0.7)	5 (8.6)	3 (5.2)
Tachycardia Paroxysmal	0	0	1 (0.2)	0	0	0
Torsade De Pointes	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Tricuspid Valve Incompetence	2 (0.3)	0	0	0	0	0
Ventricular Dysfunction	0	0	1 (0.2)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Ventricular Extrasystoles	9 (1.5)	2 (0 3)	1 (0.2)	0	1 (1.7)	0
Ventricular Hypertrophy	0	0	1 (0.2)	0	0	0
Ventricular Hypokinesia	0	0	1 (0.2)	0	0	0
Ventricular Tachycardia	1 (0.2)	0	1 (0.2)	0	0	0
Congenital, Familial And Genetic Disorders	**3 (0.5)**	**0**	**1 (0.2)**	**0**	**0**	**0**
Antithrombin III Deficiency	0	0	1 (0.2)	0	0	0
Chimerism	1 (0.2)	0	0	0	0	0
Epidermolysis	1 (0.2)	0	0	0	0	0
Factor II Deficiency	1 (0.2)	0	0	0	0	0
Ear And Labyrinth Disorders	**52 (8.6)**	**3 (0.5)**	**36 (6.7)**	**2 (0.4)**	**4 (6.9)**	**0**
Deafness	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Ear Congestion	0	0	3 (0.6)	0	1 (1.7)	0
Ear Discomfort	4 (0.7)	0	4 (0.7)	1 (0.2)	0	0
Ear Disorder	2 (0.3)	0	0	0	0	0
Ear Haemorrhage	2 (0.3)	0	1 (0.2)	0	0	0
Ear Pain	17 (2.8)	0	12 (2.2)	0	1 (1.7)	0
Ear Pruritus	1 (0.2)	0	0	0	1 (1.7)	0
Ear Swelling	1 (0.2)	0	1 (0.2)	0	0	0
Eustachian Tube Obstruction	0	0	0	0	1 (1.7)	0
Excessive Cerumen Production	1 (0.2)	0	0	0	0	0
Hypoacusis	8 (1.3)	2 (0 3)	2 (0.4)	0	0	0
Middle Ear Effusion	2 (0.3)	0	0	0	0	0
Otorrhoea	2 (0.3)	0	0	0	0	0
Sudden Hearing Loss	1 (0.2)	0	0	0	0	0
Tinnitus	5 (0.8)	0	3 (0.6)	0	0	0
Vertigo	10 (1.7)	1 (0 2)	9 (1.7)	0	0	0
Endocrine Disorders	**32 (5.3)**	**1 (0.2)**	**35 (6.5)**	**0**	**1 (1.7)**	**1 (1.7)**
Addison's Disease	1 (0.2)	0	0	0	0	0
Adrenal Insufficiency	2 (0.3)	0	2 (0.4)	0	1 (1.7)	1 (1.7)
Adrenal Mass	1 (0.2)	0	1 (0.2)	0	0	0
Adrenomegaly	0	0	1 (0.2)	0	0	0
Androgen Deficiency	1 (0.2)	0	0	0	0	0
Cushing's Syndrome	1 (0.2)	1 (0.2)	0	0	0	0
Cushingoid	24 (4.0)	0	26 (4.8)	0	0	0
Euthyroid Sick Syndrome	0	0	1 (0.2)	0	0	0
Goitre	1 (0.2)	0	1 (0.2)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Hypogonadism	3 (0.5)	0	1 (0.2)	0	0	0
Hypothyroidism	0	0	2 (0.4)	0	0	0
Inappropriate Antidiuretic Hormone Secretion	0	0	2 (0.4)	0	0	0
Steroid Withdrawal Syndrome	0	0	1 (0.2)	0	0	0
Thyroid Cyst	1 (0.2)	0	0	0	0	0
Eye Disorders	**125 (20.7)**	**4 (0.7)**	**135 (25.0)**	**14 (2.6)**	**10 (17.2)**	**0**
Abnormal Sensation In Eye	1 (0.2)	0	0	0	0	0
Blepharitis	0	0	0	0	1 (1.7)	0
Cataract	3 (0.5)	0	4 (0.7)	0	0	0
Choroiditis	0	0	1 (0.2)	1 (0.2)	0	0
Conjunctival Deposit	0	0	0	0	1 (1.7)	0
Conjunctival Discolouration	0	0	1 (0.2)	0	0	0
Conjunctival Disorder	0	0	1 (0.2)	0	0	0
Conjunctival Haemorrhage	8 (1.3)	0	14 (2.6)	2 (0.4)	1 (1.7)	0
Conjunctival Hyperaemia	2 (0.3)	0	0	0	0	0
Conjunctival Irritation	0	0	1 (0.2)	0	0	0
Conjunctival Oedema	1 (0.2)	0	1 (0.2)	0	0	0
Conjunctivitis Allergic	0	0	1 (0.2)	0	0	0
Corneal Degeneration	0	0	1 (0.2)	1 (0.2)	0	0
Corneal Irritation	0	0	1 (0.2)	0	0	0
Corneal Oedema	0	0	1 (0.2)	0	0	0
Diabetic Retinopathy	0	0	1 (0.2)	0	0	0
Diplopia	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Dry Eye	22 (3.6)	0	26 (4.8)	1 (0.2)	1 (1.7)	0
Episcleritis	0	0	1 (0.2)	0	0	0
Erythema Of Eyelid	2 (0.3)	0	0	0	0	0
Exophthalmos	0	0	1 (0.2)	0	0	0
Eye Discharge	1 (0.2)	0	3 (0.6)	0	0	0
Eye Disorder	0	0	1 (0.2)	0	0	0
Eye Haemorrhage	3 (0.5)	0	7 (1.3)	1 (0.2)	2 (3.4)	0
Eye Inflammation	0	0	1 (0.2)	0	0	0
Eye Irritation	12 (2.0)	0	6 (1.1)	0	1 (1.7)	0
Eye Movement Disorder	1 (0.2)	0	0	0	0	0
Eye Oedema	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Eye Pain	9 (1.5)	0	11 (2.0)	1 (0.2)	1 (1.7)	0
Eye Pruritus	4 (0.7)	1 (0 2)	5 (0.9)	0	0	0
Eye Swelling	4 (0.7)	0	2 (0.4)	0	1 (1.7)	0
Eyelid Oedema	4 (0.7)	0	2 (0.4)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Eyelid Pain	0	0	0	0	1 (1.7)	0
Foreign Body Sensation In Eyes	2 (0.3)	0	0	0	1 (1.7)	0
Glaucoma	1 (0.2)	1 (0 2)	0	0	0	0
Halo Vision	2 (0.3)	0	0	0	0	0
Iridocyclitis	0	0	1 (0.2)	0	0	0
Iritis	1 (0.2)	0	1 (0.2)	0	0	0
Keratitis	1 (0.2)	0	0	0	0	0
Lacrimation Decreased	0	0	1 (0.2)	0	0	0
Lacrimation Increased	6 (1.0)	0	9 (1.7)	0	1 (1.7)	0
Mydriasis	1 (0.2)	0	2 (0.4)	2 (0.4)	0	0
Myopia	1 (0.2)	0	0	0	0	0
Ocular Discomfort	2 (0.3)	0	3 (0.6)	0	0	0
Ocular Hyperaemia	5 (0.8)	0	3 (0.6)	0	2 (3.4)	0
Ophthalmoplegia	1 (0.2)	0	1 (0.2)	0	0	0
Orbital Oedema	0	0	1 (0.2)	0	0	0
Periorbital Oedema	3 (0.5)	0	1 (0.2)	0	0	0
Photophobia	6 (1.0)	0	7 (1.3)	1 (0.2)	0	0
Photopsia	1 (0.2)	0	2 (0.4)	0	0	0
Punctate Keratitis	0	0	1 (0.2)	0	0	0
Pupils Unequal	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Retinal Exudates	1 (0.2)	0	0	0	1 (1.7)	0
Retinal Haemorrhage	5 (0.8)	0	3 (0.6)	0	1 (1.7)	0
Retinal Oedema	1 (0.2)	0	0	0	0	0
Retinopathy Haemorrhagic	0	0	1 (0.2)	0	0	0
Scleral Discolouration	1 (0.2)	0	2 (0.4)	0	0	0
Scleral Haemorrhage	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Scleral Oedema	0	0	1 (0.2)	0	0	0
Vision Blurred	26 (4.3)	1 (0 2)	31 (5.8)	0	3 (5.2)	0
Visual Acuity Reduced	4 (0.7)	0	5 (0.9)	1 (0.2)	0	0
Visual Impairment	9 (1.5)	1 (0 2)	9 (1.7)	0	3 (5.2)	0
Vitreous Detachment	0	0	1 (0.2)	0	0	0
Vitreous Floaters	2 (0.3)	0	1 (0.2)	0	1 (1.7)	0
Vitreous Haemorrhage	1 (0.2)	0	1 (0.2)	0	0	0
Gastrointestinal Disorders	**488 (80.7)**	**111 (18.3)**	**429 (79.6)**	**102 (18.9)**	**55 (94.8)**	**12 (20.7)**
Abdominal Compartment Syndrome	0	0	1 (0.2)	1 (0.2)	0	0
Abdominal Discomfort	26 (4.3)	0	8 (1.5)	1 (0.2)	2 (3.4)	0
Abdominal Distension	40 (6.6)	3 (0 5)	44 (8.2)	4 (0.7)	4 (6.9)	0
Abdominal Hernia	1 (0.2)	0	0	0	0	0
Abdominal Mass	0	0	1 (0.2)	0	0	0

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All Randomized Subjects
Summary of Treatment Emergent Adverse Events
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Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Abdominal Pain	113 (18.7)	16 (2.6)	112 (20.8)	17 (3.2)	15 (25.9)	0
Abdominal Pain Lower	11 (1.8)	1 (0 2)	7 (1.3)	0	0	0
Abdominal Pain Upper	44 (7.3)	5 (0.8)	43 (8.0)	5 (0.9)	14 (24.1)	0
Abdominal Rigidity	1 (0.2)	0	3 (0.6)	1 (0.2)	0	0
Abdominal Tenderness	10 (1.7)	1 (0.2)	11 (2.0)	1 (0.2)	2 (3.4)	0
Acute Abdomen	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Anal Fissure	9 (1.5)	2 (0.3)	2 (0.4)	0	2 (3.4)	0
Anal Fistula	0	0	0	0	1 (1.7)	1 (1.7)
Anal Haemorrhage	1 (0.2)	0	0	0	2 (3.4)	0
Anal Incontinence	6 (1.0)	2 (0 3)	12 (2.2)	2 (0.4)	0	0
Anal Inflammation	0	0	1 (0.2)	0	0	0
Anal Pruritus	2 (0.3)	0	0	0	0	0
Anal Ulcer	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Anorectal Discomfort	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Aphthous Ulcer	5 (0.8)	0	2 (0.4)	0	2 (3.4)	0
Aptyalism	2 (0.3)	0	0	0	0	0
Ascites	23 (3.8)	5 (0.8)	15 (2.8)	6 (1.1)	1 (1.7)	0
Breath Odour	1 (0.2)	0	0	0	0	0
Change Of Bowel Habit	1 (0.2)	1 (0 2)	0	0	0	0
Chapped Lips	3 (0.5)	0	4 (0.7)	0	2 (3.4)	0
Cheilitis	2 (0.3)	0	1 (0.2)	0	0	0
Colitis	15 (2.5)	2 (0 3)	11 (2.0)	5 (0.9)	3 (5.2)	1 (1.7)
Colitis Ulcerative	2 (0.3)	1 (0 2)	0	0	0	0
Constipation	125 (20.7)	1 (0 2)	95 (17.6)	2 (0.4)	6 (10.3)	1 (1.7)
Crohn's Disease	1 (0.2)	1 (0.2)	0	0	0	0
Dental Alveolar Anomaly	0	0	1 (0.2)	0	0	0
Diarrhoea	251 (41.5)	22 (3.6)	213 (39 5)	24 (4.5)	36 (62.1)	3 (5.2)
Diarrhoea Haemorrhagic	4 (0.7)	3 (0 5)	8 (1.5)	5 (0.9)	0	0
Diverticulum	1 (0.2)	0	1 (0.2)	0	0	0
Diverticulum Intestinal	1 (0.2)	0	0	0	0	0
Dry Mouth	32 (5.3)	1 (0 2)	27 (5.0)	0	2 (3.4)	0
Duodenal Perforation	1 (0.2)	1 (0.2)	0	0	0	0
Duodenitis	5 (0.8)	0	2 (0.4)	0	1 (1.7)	0
Duodenitis Haemorrhagic	0	0	1 (0.2)	1 (0.2)	0	0
Dyschezia	3 (0.5)	0	0	0	0	0
Dyspepsia	51 (8.4)	1 (0 2)	50 (9.3)	2 (0.4)	5 (8.6)	0
Dysphagia	9 (1.5)	2 (0 3)	20 (3.7)	6 (1.1)	4 (6.9)	0
Enteritis	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Enterocolitis	2 (0.3)	0	1 (0.2)	0	0	0
Epigastric Discomfort	4 (0.7)	0	3 (0.6)	0	0	0

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All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Erosive Oesophagitis	1 (0.2)	1 (0 2)	0	0	0	0
Eructation	3 (0.5)	0	0	0	0	0
Faecal Volume Increased	1 (0.2)	0	0	0	0	0
Faecaloma	0	0	1 (0.2)	0	0	0
Faeces Discoloured	1 (0.2)	0	0	0	0	0
Faeces Hard	0	0	0	0	1 (1.7)	0
Flatulence	18 (3.0)	0	28 (5.2)	0	2 (3.4)	0
Frequent Bowel Movements	1 (0.2)	0	1 (0.2)	0	0	0
Gastric Disorder	3 (0.5)	1 (0 2)	1 (0.2)	0	5 (8.6)	0
Gastric Haemorrhage	1 (0.2)	1 (0.2)	0	0	0	0
Gastric Ulcer	2 (0.3)	1 (0 2)	3 (0.6)	1 (0.2)	0	0
Gastric Ulcer Haemorrhage	2 (0.3)	2 (0 3)	1 (0.2)	1 (0.2)	0	0
Gastric Varices	1 (0.2)	0	0	0	0	0
Gastritis	24 (4.0)	0	21 (3.9)	3 (0.6)	1 (1.7)	0
Gastritis Erosive	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Gastritis Haemorrhagic	1 (0.2)	1 (0 2)	0	0	0	0
Gastroenteritis Eosinophilic	0	0	1 (0.2)	0	0	0
Gastrointestinal Disorder	1 (0.2)	0	0	0	0	0
Gastrointestinal Haemorrhage	23 (3.8)	13 (2.1)	19 (3.5)	14 (2.6)	0	0
Gastrointestinal Hypomotility	1 (0.2)	0	0	0	0	0
Gastrointestinal Inflammation	0	0	1 (0.2)	0	1 (1.7)	0
Gastrointestinal Obstruction	1 (0.2)	0	0	0	0	0
Gastrointestinal Pain	1 (0.2)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Gastrointestinal Sounds Abnormal	4 (0.7)	0	7 (1.3)	1 (0.2)	0	0
Gastrointestinal Ulcer Haemorrhage	2 (0.3)	1 (0 2)	0	0	0	0
Gastrooesophageal Reflux Disease	20 (3.3)	1 (0.2)	13 (2.4)	1 (0.2)	0	0
Gingival Bleeding	25 (4.1)	1 (0 2)	11 (2.0)	1 (0.2)	1 (1.7)	0
Gingival Erosion	0	0	0	0	1 (1.7)	0
Gingival Hypertrophy	1 (0.2)	0	1 (0.2)	0	0	0
Gingival Pain	2 (0.3)	0	4 (0.7)	0	0	0
Gingival Swelling	2 (0.3)	0	1 (0.2)	0	0	0
Gingival Ulceration	1 (0.2)	0	0	0	1 (1.7)	0
Glossitis	0	0	1 (0.2)	1 (0.2)	0	0
Glossodynia	4 (0.7)	0	1 (0.2)	0	0	0
Haematemesis	14 (2.3)	5 (0.8)	8 (1.5)	4 (0.7)	0	0
Haematochezia	17 (2.8)	1 (0 2)	9 (1.7)	3 (0.6)	2 (3.4)	0
Haemorrhoidal Haemorrhage	9 (1.5)	0	4 (0.7)	1 (0.2)	0	0
Haemorrhoids	38 (6.3)	4 (0.7)	32 (5.9)	0	11 (19.0)	1 (1.7)
Haemorrhoids Thrombosed	1 (0.2)	0	0	0	0	0
Hiatus Hernia	3 (0.5)	0	3 (0.6)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Hyperchlorhydria	1 (0.2)	0	0	0	0	0
Hypoaesthesia Oral	3 (0.5)	0	1 (0.2)	0	0	0
Ileus	4 (0.7)	3 (0 5)	5 (0.9)	5 (0.9)	0	0
Ileus Paralytic	1 (0.2)	0	3 (0.6)	2 (0.4)	0	0
Impaired Gastric Emptying	3 (0.5)	0	2 (0.4)	0	0	0
Inguinal Hernia	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Intestinal Angioedema	0	0	1 (0.2)	0	0	0
Intestinal Haemorrhage	1 (0.2)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Intestinal Infarction	1 (0.2)	1 (0 2)	0	0	0	0
Intestinal Ischaemia	1 (0.2)	1 (0 2)	0	0	0	0
Intestinal Mass	0	0	1 (0.2)	1 (0.2)	0	0
Intestinal Obstruction	3 (0.5)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Intestinal Ulcer	2 (0.3)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Intra-Abdominal Fluid Collection	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Intra-Abdominal Haematoma	1 (0.2)	0	1 (0.2)	0	0	0
Irritable Bowel Syndrome	1 (0.2)	0	0	0	0	0
Leukoplakia Oral	2 (0.3)	0	4 (0.7)	0	0	0
Lip Blister	2 (0.3)	0	0	0	0	0
Lip Dry	3 (0.5)	0	10 (1.9)	0	0	0
Lip Exfoliation	1 (0.2)	0	0	0	0	0
Lip Haematoma	0	0	1 (0.2)	0	0	0
Lip Haemorrhage	0	0	2 (0.4)	0	1 (1.7)	0
Lip Pain	2 (0.3)	0	2 (0.4)	0	0	0
Lip Swelling	1 (0.2)	0	0	0	0	0
Lip Ulceration	4 (0.7)	0	2 (0.4)	0	0	0
Loose Tooth	0	0	2 (0.4)	0	0	0
Lower Gastrointestinal Haemorrhage	1 (0.2)	0	0	0	0	0
Malabsorption	1 (0.2)	1 (0 2)	0	0	0	0
Melaena	14 (2.3)	4 (0.7)	12 (2.2)	2 (0.4)	1 (1.7)	1 (1.7)
Mouth Haemorrhage	17 (2.8)	2 (0 3)	4 (0.7)	1 (0.2)	2 (3.4)	0
Mouth Ulceration	22 (3.6)	0	16 (3.0)	0	4 (6.9)	0
Mucous Stools	0	0	1 (0.2)	0	0	0
Nausea	243 (40.2)	26 (4.3)	203 (37.7)	10 (1.9)	33 (56.9)	3 (5.2)
Neutropenic Colitis	6 (1.0)	4 (0.7)	1 (0.2)	1 (0.2)	2 (3.4)	1 (1.7)
Odynophagia	7 (1.2)	0	3 (0.6)	1 (0.2)	1 (1.7)	0
Oedema Mouth	0	0	1 (0.2)	0	0	0
Oesophageal Pain	0	0	2 (0.4)	0	1 (1.7)	0
Oesophageal Ulcer	2 (0.3)	1 (0.2)	0	0	0	0
Oesophagitis	11 (1.8)	2 (0 3)	6 (1.1)	1 (0.2)	0	0
Oesophagitis Ulcerative	1 (0.2)	0	0	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Oral Discomfort	1 (0.2)	0	1 (0.2)	0	0	0
Oral Disorder	12 (2.0)	0	8 (1.5)	0	1 (1.7)	0
Oral Mucosal Blistering	5 (0.8)	0	1 (0.2)	0	2 (3.4)	1 (1.7)
Oral Mucosal Discolouration	0	0	1 (0.2)	0	0	0
Oral Mucosal Erythema	6 (1.0)	0	4 (0.7)	0	0	0
Oral Mucosal Exfoliation	1 (0.2)	0	1 (0.2)	0	0	0
Oral Mucosal Hypertrophy	0	0	1 (0.2)	0	0	0
Oral Pain	26 (4.3)	2 (0 3)	24 (4.5)	2 (0.4)	3 (5.2)	1 (1.7)
Palatal Disorder	0	0	1 (0.2)	0	0	0
Palatal Swelling	1 (0.2)	0	0	0	0	0
Pancreatitis	1 (0.2)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Pancreatitis Acute	1 (0.2)	1 (0 2)	0	0	0	0
Paraesthesia Oral	1 (0.2)	0	1 (0.2)	0	0	0
Parotid Gland Enlargement	0	0	1 (0.2)	0	1 (1.7)	0
Perianal Erythema	2 (0.3)	0	0	0	0	0
Periodontal Disease	1 (0.2)	0	0	0	0	0
Pneumoperitoneum	1 (0.2)	0	0	0	0	0
Proctalgia	9 (1.5)	0	17 (3.2)	2 (0.4)	5 (8.6)	1 (1.7)
Proctitis	2 (0.3)	0	1 (0.2)	0	1 (1.7)	0
Proctitis Ulcerative	0	0	1 (0.2)	0	0	0
Rectal Discharge	0	0	1 (0.2)	0	0	0
Rectal Fissure	1 (0.2)	0	0	0	0	0
Rectal Haemorrhage	15 (2.5)	3 (0.5)	7 (1.3)	1 (0.2)	2 (3.4)	0
Rectal Lesion	0	0	1 (0.2)	0	0	0
Rectal Prolapse	0	0	1 (0.2)	0	0	0
Rectal Tenesmus	1 (0.2)	1 (0 2)	0	0	0	0
Rectal Ulcer	0	0	1 (0.2)	0	0	0
Retching	6 (1.0)	0	5 (0.9)	0	0	0
Retroperitoneal Haemorrhage	2 (0.3)	0	0	0	0	0
Saliva Altered	1 (0.2)	0	1 (0.2)	0	0	0
Salivary Gland Calculus	0	0	1 (0.2)	0	0	0
Salivary Gland Mass	1 (0.2)	0	0	0	0	0
Salivary Gland Pain	0	0	1 (0.2)	0	0	0
Salivary Hypersecretion	1 (0.2)	0	2 (0.4)	0	1 (1.7)	0
Sensitivity Of Teeth	1 (0.2)	0	0	0	0	0
Small Intestinal Obstruction	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Small Intestinal Stenosis	0	0	1 (0.2)	0	0	0
Stomach Mass	1 (0.2)	0	0	0	0	0
Stomatitis	18 (3.0)	1 (0 2)	9 (1.7)	1 (0.2)	6 (10.3)	0
Subileus	1 (0.2)	1 (0 2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Swollen Tongue	0	0	1 (0.2)	1 (0.2)	0	0
Tongue Blistering	1 (0.2)	0	0	0	0	0
Tongue Coated	10 (1.7)	0	4 (0.7)	0	0	0
Tongue Discolouration	3 (0.5)	0	2 (0.4)	0	0	0
Tongue Discomfort	1 (0.2)	0	0	0	0	0
Tongue Disorder	1 (0.2)	0	1 (0.2)	0	0	0
Tongue Erythema	2 (0.3)	0	1 (0.2)	0	0	0
Tongue Haematoma	2 (0.3)	0	0	0	1 (1.7)	0
Tongue Haemorrhage	1 (0.2)	0	0	0	0	0
Tongue Ulceration	4 (0.7)	0	9 (1.7)	0	3 (5.2)	0
Tooth Discolouration	1 (0.2)	0	0	0	0	0
Tooth Loss	0	0	2 (0.4)	0	0	0
Toothache	9 (1.5)	0	13 (2.4)	0	2 (3.4)	0
Trichoglossia	4 (0.7)	0	2 (0.4)	0	0	0
Umbilical Hernia	1 (0.2)	0	0	0	0	0
Upper Gastrointestinal Haemorrhage	4 (0.7)	2 (0 3)	0	0	0	0
Uvulitis	1 (0.2)	0	0	0	0	0
Vomiting	178 (29.4)	16 (2.6)	175 (32 5)	14 (2.6)	24 (41.4)	0
General Disorders And Administration Site Conditions	**466 (77.0)**	**121 (20.0)**	**413 (76.6)**	**104 (19.3)**	**55 (94.8)**	**15 (25.9)**
Adverse Drug Reaction	1 (0.2)	1 (0 2)	0	0	0	0
Application Site Burn	1 (0.2)	0	0	0	0	0
Application Site Discomfort	1 (0.2)	0	0	0	0	0
Asthenia	60 (9.9)	12 (2.0)	60 (11.1)	12 (2.2)	3 (5.2)	1 (1.7)
Atrophy	0	0	1 (0.2)	0	0	0
Axillary Pain	0	0	1 (0.2)	0	0	0
Catheter Site Bruise	1 (0.2)	0	3 (0.6)	1 (0.2)	0	0
Catheter Site Discharge	3 (0.5)	0	0	0	1 (1.7)	0
Catheter Site Erosion	0	0	1 (0.2)	0	0	0
Catheter Site Erythema	39 (6.4)	0	32 (5.9)	0	11 (19.0)	1 (1.7)
Catheter Site Haematoma	3 (0.5)	1 (0 2)	5 (0.9)	0	0	0
Catheter Site Haemorrhage	15 (2.5)	1 (0 2)	6 (1.1)	0	1 (1.7)	0
Catheter Site Inflammation	8 (1.3)	0	3 (0.6)	0	7 (12.1)	1 (1.7)
Catheter Site Oedema	0	0	2 (0.4)	0	0	0
Catheter Site Pain	33 (5.5)	0	33 (6.1)	0	3 (5.2)	0
Catheter Site Phlebitis	2 (0.3)	0	2 (0.4)	0	0	0
Catheter Site Pruritus	3 (0.5)	0	1 (0.2)	0	1 (1.7)	0
Catheter Site Rash	1 (0.2)	0	0	0	0	0
Catheter Site Related Reaction	4 (0.7)	0	5 (0.9)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Catheter Site Swelling	3 (0.5)	0	1 (0.2)	0	0	0
Chest Discomfort	8 (1.3)	0	6 (1.1)	0	3 (5.2)	0
Chest Pain	52 (8.6)	6 (1.0)	35 (6.5)	6 (1.1)	3 (5.2)	0
Chills	117 (19.3)	8 (1 3)	81 (15.0)	2 (0.4)	17 (29.3)	2 (3.4)
Complication Associated With Device	4 (0.7)	0	6 (1.1)	0	0	0
Crepitations	4 (0.7)	0	5 (0.9)	0	0	0
Death	0	0	1 (0.2)	1 (0.2)	0	0
Device Related Thrombosis	3 (0.5)	0	3 (0.6)	0	0	0
Disease Progression	4 (0.7)	2 (0.3)	5 (0.9)	2 (0.4)	0	0
Drug Interaction	2 (0.3)	2 (0 3)	1 (0.2)	1 (0.2)	0	0
Drug Intolerance	1 (0.2)	0	2 (0.4)	2 (0.4)	0	0
Drug Withdrawal Syndrome	1 (0.2)	0	2 (0.4)	0	0	0
Early Satiety	0	0	3 (0.6)	0	0	0
Effusion	1 (0.2)	0	0	0	0	0
Exercise Tolerance Decreased	2 (0.3)	0	1 (0.2)	0	0	0
Face Oedema	6 (1.0)	0	8 (1.5)	0	0	0
Facial Pain	3 (0.5)	0	5 (0.9)	0	0	0
Fatigue	104 (17.2)	16 (2.6)	103 (19.1)	8 (1.5)	3 (5.2)	0
Feeling Cold	4 (0.7)	0	8 (1.5)	0	0	0
Feeling Hot	1 (0.2)	0	0	0	0	0
Feeling Jittery	4 (0.7)	0	2 (0.4)	0	0	0
Gait Disturbance	9 (1.5)	0	11 (2.0)	2 (0.4)	0	0
Gait Inability	0	0	1 (0.2)	0	0	0
General Physical Health Deterioration	3 (0.5)	2 (0.3)	1 (0.2)	1 (0.2)	0	0
General Symptom	1 (0.2)	0	0	0	0	0
Generalised Oedema	15 (2.5)	2 (0.3)	19 (3.5)	4 (0.7)	1 (1.7)	0
Granuloma	3 (0.5)	0	0	0	0	0
Gravitational Oedema	0	0	1 (0.2)	0	0	0
Hyperpyrexia	0	0	0	0	1 (1.7)	1 (1.7)
Hyperthermia	4 (0.7)	1 (0 2)	1 (0.2)	1 (0.2)	3 (5.2)	0
Hypothermia	2 (0.3)	1 (0 2)	4 (0.7)	1 (0.2)	0	0
Impaired Healing	1 (0.2)	0	1 (0.2)	0	0	0
Induration	2 (0.3)	0	1 (0.2)	0	0	0
Inflammation	2 (0.3)	0	0	0	0	0
Influenza Like Illness	2 (0.3)	0	2 (0.4)	0	0	0
Infusion Site Erythema	0	0	1 (0.2)	0	0	0
Infusion Site Extravasation	0	0	2 (0.4)	0	0	0
Infusion Site Haemorrhage	1 (0.2)	0	0	0	0	0
Infusion Site Inflammation	1 (0.2)	0	0	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Infusion Site Pain	6 (1.0)	0	0	0	0	0
Infusion Site Swelling	0	0	1 (0.2)	0	0	0
Infusion Site Vesicles	1 (0.2)	0	0	0	0	0
Injection Site Haemorrhage	0	0	1 (0.2)	0	0	0
Injection Site Inflammation	0	0	1 (0.2)	0	0	0
Injection Site Irritation	1 (0.2)	0	2 (0.4)	0	0	0
Injection Site Nodule	0	0	1 (0.2)	0	0	0
Injection Site Pain	0	0	1 (0.2)	0	0	0
Injection Site Reaction	0	0	1 (0.2)	0	0	0
Injection Site Vesicles	0	0	0	0	1 (1.7)	0
Localised Oedema	2 (0.3)	0	2 (0.4)	0	1 (1.7)	0
Malaise	15 (2.5)	0	10 (1.9)	1 (0.2)	2 (3.4)	0
Mass	2 (0.3)	0	0	0	0	0
Mucosa Vesicle	1 (0.2)	0	1 (0.2)	0	0	0
Mucosal Haemorrhage	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Mucosal Hyperaemia	1 (0.2)	0	0	0	0	0
Mucosal Inflammation	99 (16.4)	17 (2.8)	65 (12.1)	14 (2.6)	14 (24.1)	1 (1.7)
Mucous Membrane Disorder	1 (0.2)	0	0	0	0	0
Multi-Organ Disorder	1 (0.2)	1 (0 2)	0	0	0	0
Multiple Organ Dysfunction Syndrome	15 (2.5)	15 (2.5)	9 (1.7)	9 (1.7)	2 (3.4)	2 (3.4)
Necrosis	3 (0.5)	1 (0 2)	0	0	0	0
Nodule	2 (0.3)	0	3 (0.6)	1 (0.2)	0	0
Non-Cardiac Chest Pain	0	0	0	0	1 (1.7)	0
Obstruction	1 (0.2)	0	0	0	3 (5.2)	0
Oedema	39 (6.4)	1 (0 2)	48 (8.9)	5 (0.9)	4 (6.9)	0
Oedema Mucosal	0	0	1 (0.2)	0	0	0
Oedema Peripheral	96 (15.9)	4 (0.7)	79 (14.7)	2 (0.4)	12 (20.7)	0
Pain	42 (6.9)	4 (0.7)	26 (4.8)	2 (0.4)	5 (8.6)	0
Paradoxical Drug Reaction	0	0	1 (0.2)	0	0	0
Performance Status Decreased	2 (0.3)	2 (0.3)	0	0	0	0
Peripheral Swelling	16 (2.6)	2 (0 3)	12 (2.2)	0	1 (1.7)	0
Puncture Site Pain	3 (0.5)	0	0	0	0	0
Puncture Site Reaction	3 (0.5)	0	0	0	0	0
Pyrexia	266 (44.0)	45 (7.4)	251 (46.6)	52 (9.6)	31 (53.4)	10 (17.2)
Secretion Discharge	1 (0.2)	0	1 (0.2)	0	0	0
Sudden Death	0	0	1 (0.2)	1 (0.2)	0	0
Swelling	1 (0.2)	0	1 (0.2)	0	0	0
Tenderness	2 (0.3)	0	0	0	0	0
Therapeutic Product Ineffective	0	0	1 (0.2)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Therapy Non-Responder	4 (0.7)	4 (0.7)	3 (0.6)	2 (0.4)	0	0
Thirst	5 (0.8)	0	4 (0.7)	1 (0.2)	0	0
Ulcer	2 (0.3)	0	0	0	0	0
Ulcer Haemorrhage	0	0	1 (0.2)	0	0	0
Vessel Puncture Site Inflammation	0	0	1 (0.2)	0	0	0
Vessel Puncture Site Pain	2 (0.3)	0	2 (0.4)	0	0	0
Xerosis	1 (0.2)	0	0	0	0	0
Hepatobiliary Disorders	**96 (15.9)**	**37 (6.1)**	**77 (14.3)**	**28 (5.2)**	**12 (20.7)**	**5 (8.6)**
Acute Hepatic Failure	1 (0.2)	1 (0 2)	0	0	0	0
Cholecystitis	1 (0.2)	0	2 (0.4)	1 (0.2)	1 (1.7)	0
Cholecystitis Acute	0	0	0	0	1 (1.7)	1 (1.7)
Cholelithiasis	7 (1.2)	1 (0 2)	7 (1.3)	0	2 (3.4)	0
Cholestasis	5 (0.8)	2 (0 3)	2 (0.4)	0	0	0
Drug-Induced Liver Injury	0	0	1 (0.2)	1 (0.2)	0	0
Gallbladder Enlargement	0	0	1 (0.2)	0	0	0
Gallbladder Polyp	2 (0.3)	0	0	0	0	0
Hepatic Cyst	2 (0.3)	0	2 (0.4)	0	0	0
Hepatic Failure	8 (1.3)	7 (1 2)	4 (0.7)	4 (0.7)	0	0
Hepatic Function Abnormal	3 (0.5)	2 (0 3)	8 (1.5)	3 (0.6)	0	0
Hepatic Lesion	4 (0.7)	0	0	0	0	0
Hepatic Necrosis	1 (0.2)	1 (0.2)	0	0	0	0
Hepatic Steatosis	1 (0.2)	0	2 (0.4)	0	0	0
Hepatitis	1 (0.2)	0	3 (0.6)	2 (0.4)	0	0
Hepatitis Acute	1 (0.2)	1 (0 2)	0	0	0	0
Hepatocellular Injury	3 (0.5)	3 (0 5)	0	0	0	0
Hepatomegaly	10 (1.7)	0	5 (0.9)	0	1 (1.7)	0
Hepatosplenomegaly	3 (0.5)	0	3 (0.6)	0	0	0
Hepatotoxicity	4 (0.7)	3 (0 5)	4 (0.7)	0	0	0
Hyperbilirubinaemia	28 (4.6)	16 (2.6)	26 (4.8)	13 (2.4)	8 (13.8)	4 (6.9)
Hypertransaminasaemia	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Jaundice	27 (4.5)	6 (1.0)	24 (4.5)	5 (0.9)	1 (1.7)	0
Jaundice Cholestatic	1 (0.2)	0	0	0	0	0
Liver Disorder	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Liver Injury	2 (0.3)	1 (0 2)	0	0	0	0
Ocular Icterus	11 (1.8)	1 (0.2)	3 (0.6)	0	0	0
Perihepatic Discomfort	1 (0.2)	0	0	0	0	0
Portal Hypertension	1 (0.2)	0	2 (0.4)	0	0	0
Portal Vein Thrombosis	1 (0.2)	0	1 (0.2)	0	0	0
Venoocclusive Liver Disease	0	0	1 (0.2)	0	0	0

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Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Immune System Disorders	**111 (18.3)**	**50 (8.3)**	**111 (20.6)**	**53 (9.8)**	**3 (5.2)**	**2 (3.4)**
Acute Graft Versus Host Disease In Liver	0	0	1 (0.2)	1 (0.2)	0	0
Acute Graft Versus Host Disease In Skin	0	0	1 (0.2)	0	0	0
Anaphylactic Reaction	1 (0.2)	1 (0 2)	2 (0.4)	2 (0.4)	0	0
Chronic Graft Versus Host Disease	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Contrast Media Allergy	1 (0.2)	0	0	0	0	0
Drug Hypersensitivity	14 (2.3)	1 (0 2)	7 (1.3)	1 (0.2)	3 (5.2)	2 (3.4)
Graft Versus Host Disease	61 (10.1)	31 (5.1)	55 (10.2)	28 (5.2)	0	0
Graft Versus Host Disease In Gastrointestinal Tract	27 (4.5)	15 (2.5)	21 (3.9)	12 (2.2)	0	0
Graft Versus Host Disease In Liver	14 (2.3)	10 (1.7)	10 (1.9)	5 (0.9)	0	0
Graft Versus Host Disease In Lung	0	0	5 (0.9)	3 (0.6)	0	0
Graft Versus Host Disease In Skin	25 (4.1)	9 (1 5)	27 (5.0)	6 (1.1)	0	0
Hypersensitivity	1 (0.2)	0	5 (0.9)	0	0	0
Hypogammaglobulinaemia	3 (0.5)	1 (0 2)	3 (0.6)	0	0	0
Immune System Disorder	0	0	1 (0.2)	1 (0.2)	0	0
Sarcoidosis	1 (0.2)	0	0	0	0	0
Seasonal Allergy	2 (0.3)	0	2 (0.4)	0	0	0
Transplant Rejection	3 (0.5)	2 (0 3)	0	0	0	0
Infections And Infestations	**437 (72.2)**	**191 (31.6)**	**414 (76.8)**	**166 (30.8)**	**51 (87.9)**	**24 (41.4)**
Abscess Fungal	0	0	1 (0.2)	1 (0.2)	0	0
Abscess Jaw	0	0	1 (0.2)	0	0	0
Abscess Limb	1 (0.2)	0	3 (0.6)	1 (0.2)	0	0
Abscess Neck	1 (0.2)	0	1 (0.2)	0	0	0
Acarodermatitis	1 (0.2)	0	1 (0.2)	0	0	0
Acid Fast Bacilli Infection	1 (0.2)	1 (0 2)	0	0	0	0
Acinetobacter Bacteraemia	0	0	1 (0.2)	0	0	0
Acinetobacter Infection	0	0	4 (0.7)	1 (0.2)	0	0
Acute Sinusitis	3 (0.5)	1 (0 2)	3 (0.6)	0	0	0
Adenovirus Infection	0	0	3 (0.6)	0	0	0
Alpha Haemolytic Streptococcal Infection	1 (0.2)	0	5 (0.9)	0	0	0
Amoebic Dysentery	1 (0.2)	0	0	0	0	0
Anal Abscess	5 (0.8)	1 (0.2)	5 (0.9)	0	0	0
Anal Infection	0	0	1 (0.2)	0	0	0
Angular Cheilitis	0	0	1 (0.2)	0	0	0

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Anorectal Cellulitis	0	0	1 (0.2)	0	0	0
Anorectal Infection	1 (0.2)	1 (0 2)	0	0	1 (1.7)	0
Aspergilloma	0	0	1 (0.2)	1 (0.2)	0	0
Aspergillus Infection	5 (0.8)	3 (0 5)	14 (2.6)	10 (1.9)	1 (1.7)	1 (1.7)
Atypical Pneumonia	1 (0.2)	1 (0 2)	0	0	0	0
Bacillus Bacteraemia	1 (0.2)	0	0	0	0	0
Bacillus Infection	1 (0.2)	0	0	0	0	0
Bacteraemia	56 (9.3)	36 (6.0)	45 (8.3)	19 (3.5)	8 (13.8)	6 (10.3)
Bacterial Disease Carrier	2 (0.3)	0	1 (0.2)	0	0	0
Bacterial Infection	14 (2.3)	5 (0.8)	12 (2.2)	3 (0.6)	1 (1.7)	1 (1.7)
Bacterial Sepsis	5 (0.8)	4 (0.7)	5 (0.9)	3 (0.6)	1 (1.7)	0
Bacteriuria	0	0	1 (0.2)	0	0	0
Bartholin's Abscess	1 (0.2)	0	0	0	0	0
Bartholinitis	1 (0.2)	0	0	0	0	0
Bk Virus Infection	1 (0.2)	1 (0 2)	0	0	0	0
Body Tinea	0	0	2 (0.4)	0	0	0
Bronchiolitis	4 (0.7)	0	0	0	0	0
Bronchitis	14 (2.3)	2 (0 3)	10 (1.9)	3 (0.6)	0	0
Bronchopulmonary Aspergillosis	3 (0.5)	3 (0.5)	9 (1.7)	9 (1.7)	2 (3.4)	2 (3.4)
Campylobacter Infection	1 (0.2)	0	0	0	0	0
Candida Infection	9 (1.5)	1 (0 2)	9 (1.7)	4 (0.7)	1 (1.7)	0
Candida Sepsis	1 (0.2)	1 (0 2)	0	0	0	0
Catheter Site Cellulitis	4 (0.7)	0	3 (0.6)	1 (0.2)	1 (1.7)	0
Catheter Site Infection	10 (1.7)	1 (0 2)	9 (1.7)	3 (0.6)	1 (1.7)	0
Cavernous Sinus Thrombosis	0	0	1 (0.2)	1 (0.2)	0	0
Cellulitis	15 (2.5)	4 (0.7)	17 (3.2)	4 (0.7)	1 (1.7)	0
Cellulitis Staphylococcal	1 (0.2)	0	0	0	0	0
Cerebral Fungal Infection	0	0	1 (0.2)	0	0	0
Cerebral Toxoplasmosis	1 (0.2)	0	2 (0.4)	2 (0.4)	0	0
Chlamydial Infection	0	0	1 (0.2)	0	0	0
Chronic Sinusitis	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Citrobacter Infection	1 (0.2)	0	0	0	0	0
Clostridial Infection	5 (0.8)	2 (0 3)	0	0	0	0
Clostridium Bacteraemia	0	0	1 (0.2)	1 (0.2)	0	0
Clostridium Colitis	1 (0.2)	0	0	0	0	0
Clostridium Difficile Colitis	8 (1.3)	1 (0 2)	10 (1.9)	2 (0.4)	1 (1.7)	0
Clostridium Difficile Infection	9 (1.5)	1 (0 2)	7 (1.3)	0	1 (1.7)	0
Conjunctivitis	23 (3.8)	1 (0 2)	22 (4.1)	1 (0.2)	0	0
Corynebacterium Bacteraemia	1 (0.2)	0	3 (0.6)	0	0	0
Corynebacterium Infection	0	0	3 (0.6)	1 (0.2)	0	0

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Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Corynebacterium Sepsis	2 (0.3)	1 (0.2)	0	0	1 (1.7)	0
Cystitis	10 (1.7)	2 (0 3)	4 (0.7)	0	0	0
Cystitis Escherichia	0	0	1 (0.2)	0	0	0
Cystitis Klebsiella	1 (0.2)	1 (0 2)	0	0	0	0
Cytomegalovirus Colitis	5 (0.8)	1 (0 2)	2 (0.4)	2 (0.4)	0	0
Cytomegalovirus Enteritis	1 (0.2)	0	0	0	0	0
Cytomegalovirus Enterocolitis	0	0	1 (0.2)	0	0	0
Cytomegalovirus Gastritis	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Cytomegalovirus Gastroenteritis	1 (0.2)	1 (0 2)	2 (0.4)	2 (0.4)	0	0
Cytomegalovirus Hepatitis	0	0	2 (0.4)	0	0	0
Cytomegalovirus Infection	40 (6.6)	11 (1.8)	29 (5.4)	11 (2.0)	0	0
Cytomegalovirus Viraemia	12 (2.0)	3 (0 5)	7 (1.3)	1 (0.2)	0	0
Device Related Infection	29 (4.8)	11 (1.8)	33 (6.1)	10 (1.9)	3 (5.2)	2 (3.4)
Device Related Sepsis	4 (0.7)	2 (0.3)	3 (0.6)	1 (0.2)	1 (1.7)	1 (1.7)
Ear Infection	4 (0.7)	1 (0 2)	1 (0.2)	0	0	0
Emphysematous Cystitis	1 (0.2)	1 (0 2)	0	0	0	0
Encephalitis	2 (0.3)	2 (0 3)	1 (0.2)	1 (0.2)	0	0
Encephalitis Viral	0	0	1 (0.2)	1 (0.2)	0	0
Enterobacter Bacteraemia	4 (0.7)	1 (0 2)	1 (0.2)	0	0	0
Enterobacter Infection	4 (0.7)	1 (0 2)	3 (0.6)	0	0	0
Enterobacter Sepsis	2 (0.3)	1 (0.2)	1 (0.2)	0	0	0
Enterococcal Bacteraemia	8 (1.3)	2 (0 3)	3 (0.6)	0	3 (5.2)	3 (5.2)
Enterococcal Infection	3 (0.5)	1 (0 2)	10 (1.9)	4 (0.7)	0	0
Enterococcal Sepsis	0	0	2 (0.4)	1 (0.2)	0	0
Enterovirus Infection	1 (0.2)	0	1 (0.2)	0	0	0
Epididymitis	1 (0.2)	0	1 (0.2)	0	0	0
Epiglottitis	1 (0.2)	0	0	0	0	0
Epstein-Barr Virus Infection	4 (0.7)	0	4 (0.7)	4 (0.7)	0	0
Erysipelas	0	0	1 (0.2)	1 (0.2)	1 (1.7)	1 (1.7)
Escherichia Bacteraemia	11 (1.8)	3 (0.5)	5 (0.9)	1 (0.2)	0	0
Escherichia Infection	2 (0.3)	0	2 (0.4)	1 (0.2)	1 (1.7)	0
Escherichia Sepsis	2 (0.3)	1 (0.2)	2 (0.4)	2 (0.4)	0	0
Escherichia Urinary Tract Infection	3 (0.5)	0	2 (0.4)	1 (0.2)	0	0
Eye Infection	2 (0.3)	0	0	0	1 (1.7)	0
Eye Infection Staphylococcal	0	0	1 (0.2)	0	0	0
Eyelid Infection	0	0	1 (0.2)	0	0	0
Febrile Infection	0	0	1 (0.2)	0	0	0
Folliculitis	11 (1.8)	0	13 (2.4)	0	3 (5.2)	0
Fungaemia	0	0	1 (0.2)	1 (0.2)	0	0
Fungal Infection	13 (2.1)	4 (0.7)	17 (3.2)	5 (0.9)	3 (5.2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Fungal Oesophagitis	1 (0.2)	0	0	0	0	0
Fungal Rhinitis	0	0	1 (0.2)	1 (0.2)	0	0
Fungal Sepsis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Fungal Skin Infection	2 (0.3)	0	2 (0.4)	0	0	0
Furuncle	0	0	1 (0.2)	0	0	0
Fusobacterium Infection	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Gangrene	0	0	2 (0.4)	1 (0.2)	0	0
Gastroenteritis	2 (0.3)	1 (0 2)	2 (0.4)	2 (0.4)	0	0
Gastroenteritis Cryptosporidial	1 (0.2)	0	0	0	0	0
Gastroenteritis Pseudomonas	1 (0.2)	0	0	0	0	0
Gastroenteritis Rotavirus	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Gastroenteritis Viral	1 (0.2)	0	2 (0.4)	0	0	0
Gastrointestinal Candidiasis	0	0	1 (0.2)	0	0	0
Gastrointestinal Infection	1 (0.2)	1 (0 2)	0	0	0	0
Genital Herpes	5 (0.8)	0	1 (0.2)	0	0	0
Genital Herpes Simplex	1 (0.2)	0	1 (0.2)	0	0	0
Genital Infection Bacterial	1 (0.2)	0	0	0	0	0
Giardiasis	1 (0.2)	0	0	0	0	0
Gingivitis	4 (0.7)	0	6 (1.1)	0	1 (1.7)	0
Haemophilus Infection	2 (0.3)	0	2 (0.4)	0	0	0
Hepatitis B	1 (0.2)	0	0	0	0	0
Herpes Dermatitis	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Herpes Oesophagitis	0	0	1 (0.2)	0	1 (1.7)	0
Herpes Pharyngitis	0	0	1 (0.2)	1 (0.2)	0	0
Herpes Simplex	14 (2.3)	3 (0.5)	16 (3.0)	1 (0.2)	0	0
Herpes Virus Infection	16 (2.6)	0	8 (1.5)	1 (0.2)	3 (5.2)	0
Herpes Zoster	21 (3.5)	3 (0.5)	10 (1.9)	1 (0.2)	1 (1.7)	0
Herpes Zoster Disseminated	1 (0.2)	0	1 (0.2)	0	0	0
Hookworm Infection	0	0	1 (0.2)	0	0	0
Hordeolum	0	0	1 (0.2)	0	0	0
Human Herpesvirus 6 Infection	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Impetigo	0	0	1 (0.2)	0	0	0
Infected Skin Ulcer	1 (0.2)	0	0	0	0	0
Infection	8 (1.3)	1 (0 2)	3 (0.6)	1 (0.2)	1 (1.7)	0
Infectious Disease Carrier	1 (0.2)	0	2 (0.4)	0	0	0
Influenza	5 (0.8)	0	4 (0.7)	1 (0.2)	0	0
Infusion Site Infection	0	0	1 (0.2)	1 (0.2)	0	0
Klebsiella Bacteraemia	4 (0.7)	2 (0 3)	6 (1.1)	4 (0.7)	1 (1.7)	1 (1.7)
Klebsiella Infection	2 (0.3)	0	6 (1.1)	2 (0.4)	0	0
Klebsiella Sepsis	1 (0.2)	1 (0.2)	0	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Lactobacillus Infection	0	0	1 (0.2)	0	0	0
Laryngitis	3 (0.5)	0	1 (0.2)	0	0	0
Leptotrichia Infection	0	0	1 (0.2)	1 (0.2)	0	0
Lip Infection	0	0	1 (0.2)	0	0	0
Liver Abscess	0	0	1 (0.2)	1 (0.2)	0	0
Localised Infection	3 (0.5)	1 (0 2)	4 (0.7)	1 (0.2)	0	0
Lower Respiratory Tract Infection	10 (1.7)	3 (0 5)	7 (1.3)	2 (0.4)	0	0
Lower Respiratory Tract Infection Fungal	0	0	1 (0.2)	0	0	0
Lung Abscess	1 (0.2)	1 (0.2)	0	0	0	0
Lung Infection	0	0	0	0	1 (1.7)	0
Lymphangitis	1 (0.2)	0	1 (0.2)	0	0	0
Mastitis	1 (0.2)	0	0	0	0	0
Mastoiditis	4 (0.7)	1 (0 2)	1 (0.2)	0	0	0
Meningitis Listeria	0	0	1 (0.2)	1 (0.2)	0	0
Meningococcal Infection	0	0	1 (0.2)	1 (0.2)	0	0
Micrococcus Infection	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Mycobacterial Infection	0	0	1 (0.2)	1 (0.2)	0	0
Mycobacterium Avium Complex Infection	0	0	1 (0.2)	1 (0.2)	0	0
Myelitis	1 (0.2)	0	0	0	0	0
Nail Infection	1 (0.2)	0	0	0	0	0
Nasopharyngitis	14 (2.3)	0	18 (3.3)	0	3 (5.2)	0
Neisseria Infection	0	0	1 (0.2)	0	0	0
Neutropenic Sepsis	6 (1.0)	2 (0.3)	1 (0.2)	1 (0.2)	5 (8.6)	3 (5.2)
Nocardia Sepsis	0	0	1 (0.2)	0	0	0
Nocardiosis	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Oesophageal Candidiasis	0	0	2 (0.4)	2 (0.4)	0	0
Onychomycosis	1 (0.2)	0	0	0	1 (1.7)	0
Ophthalmic Herpes Simplex	0	0	1 (0.2)	0	0	0
Oral Candidiasis	17 (2.8)	0	18 (3.3)	0	2 (3.4)	1 (1.7)
Oral Fungal Infection	0	0	0	0	1 (1.7)	0
Oral Herpes	56 (9.3)	3 (0.5)	33 (6.1)	2 (0.4)	8 (13.8)	0
Oral Infection	0	0	1 (0.2)	0	1 (1.7)	0
Oropharyngeal Candidiasis	0	0	3 (0.6)	0	1 (1.7)	1 (1.7)
Osteomyelitis	0	0	1 (0.2)	0	0	0
Otitis Externa	0	0	2 (0.4)	0	0	0
Otitis Media	2 (0.3)	0	4 (0.7)	0	0	0
Parainfluenzae Virus Infection	1 (0.2)	0	4 (0.7)	0	0	0
Paronychia	1 (0.2)	0	1 (0.2)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Parotitis	1 (0.2)	0	1 (0.2)	0	1 (1.7)	0
Pericoronitis	1 (0.2)	0	0	0	0	0
Perineal Abscess	1 (0.2)	0	0	0	0	0
Periodontitis	2 (0.3)	0	1 (0.2)	0	1 (1.7)	0
Periorbital Cellulitis	0	0	0	0	1 (1.7)	0
Perirectal Abscess	2 (0.3)	0	1 (0.2)	0	0	0
Peritonitis	0	0	1 (0.2)	1 (0.2)	0	0
Peritonitis Bacterial	0	0	1 (0.2)	1 (0.2)	0	0
Pharyngitis	10 (1.7)	1 (0 2)	8 (1.5)	1 (0.2)	1 (1.7)	0
Pharyngitis Bacterial	1 (0.2)	0	0	0	0	0
Pilonidal Cyst	1 (0.2)	0	0	0	0	0
Pneumococcal Bacteraemia	1 (0.2)	0	0	0	1 (1.7)	0
Pneumocystis Jirovecii Infection	1 (0.2)	0	1 (0.2)	0	0	0
Pneumocystis Jirovecii Pneumonia	2 (0.3)	1 (0 2)	2 (0.4)	1 (0.2)	1 (1.7)	0
Pneumonia	55 (9.1)	26 (4.3)	53 (9.8)	24 (4.5)	7 (12.1)	3 (5.2)
Pneumonia Bacterial	7 (1.2)	3 (0 5)	0	0	0	0
Pneumonia Cytomegaloviral	6 (1.0)	3 (0 5)	0	0	0	0
Pneumonia Fungal	4 (0.7)	4 (0.7)	6 (1.1)	2 (0.4)	1 (1.7)	1 (1.7)
Pneumonia Klebsiella	4 (0.7)	2 (0 3)	5 (0.9)	4 (0.7)	0	0
Pneumonia Necrotising	0	0	1 (0.2)	1 (0.2)	0	0
Pneumonia Pseudomonal	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	0	0
Pneumonia Staphylococcal	2 (0.3)	2 (0 3)	2 (0.4)	1 (0.2)	0	0
Pneumonia Streptococcal	0	0	1 (0.2)	1 (0.2)	0	0
Pneumonia Viral	1 (0.2)	1 (0 2)	0	0	0	0
Polyomavirus-Associated Nephropathy	1 (0.2)	0	2 (0.4)	0	0	0
Progressive Multifocal Leukoencephalopathy	0	0	1 (0.2)	0	0	0
Pseudomembranous Colitis	2 (0.3)	2 (0 3)	0	0	1 (1.7)	0
Pseudomonal Bacteraemia	2 (0.3)	2 (0 3)	3 (0.6)	3 (0.6)	0	0
Pseudomonal Sepsis	3 (0.5)	3 (0.5)	2 (0.4)	2 (0.4)	0	0
Pseudomonas Infection	9 (1.5)	2 (0.3)	6 (1.1)	4 (0.7)	0	0
Pulmonary Mycosis	3 (0.5)	3 (0 5)	5 (0.9)	3 (0.6)	0	0
Pulmonary Tuberculosis	1 (0.2)	0	0	0	0	0
Purulent Discharge	1 (0.2)	0	0	0	0	0
Pyoderma	1 (0.2)	0	0	0	0	0
Pyuria	1 (0.2)	0	0	0	0	0
Rash Pustular	2 (0.3)	0	3 (0.6)	0	0	0
Relapsing Fever	0	0	1 (0.2)	1 (0.2)	0	0
Respiratory Moniliasis	0	0	1 (0.2)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Respiratory Syncytial Virus Infection	6 (1.0)	0	4 (0.7)	1 (0.2)	0	0
Respiratory Tract Infection	2 (0.3)	0	1 (0.2)	0	0	0
Rhinitis	10 (1.7)	0	10 (1.9)	0	1 (1.7)	0
Rhinovirus Infection	0	0	0	0	1 (1.7)	1 (1.7)
Rotavirus Infection	3 (0.5)	0	2 (0.4)	0	0	0
Salmonellosis	1 (0.2)	0	0	0	0	0
Scedosporium Infection	0	0	1 (0.2)	1 (0.2)	0	0
Sepsis	19 (3.1)	14 (2.3)	23 (4.3)	15 (2.8)	3 (5.2)	3 (5.2)
Sepsis Syndrome	1 (0.2)	1 (0.2)	0	0	0	0
Septic Embolus	1 (0.2)	1 (0 2)	0	0	0	0
Septic Rash	1 (0.2)	0	0	0	0	0
Septic Shock	16 (2.6)	16 (2.6)	16 (3.0)	14 (2.6)	6 (10.3)	6 (10.3)
Serratia Infection	3 (0.5)	0	0	0	0	0
Sialoadenitis	1 (0.2)	0	0	0	0	0
Sinusitis	24 (4.0)	4 (0.7)	25 (4.6)	1 (0.2)	2 (3.4)	0
Sinusitis Bacterial	2 (0.3)	1 (0 2)	0	0	0	0
Sinusitis Fungal	0	0	0	0	1 (1.7)	1 (1.7)
Skin Bacterial Infection	1 (0.2)	0	1 (0.2)	0	0	0
Skin Candida	0	0	1 (0.2)	0	0	0
Skin Infection	0	0	4 (0.7)	0	0	0
Soft Tissue Infection	0	0	0	0	1 (1.7)	0
Sputum Purulent	0	0	1 (0.2)	0	0	0
Staphylococcal Abscess	0	0	1 (0.2)	0	0	0
Staphylococcal Bacteraemia	25 (4.1)	7 (1 2)	28 (5.2)	5 (0.9)	3 (5.2)	1 (1.7)
Staphylococcal Infection	26 (4.3)	2 (0 3)	20 (3.7)	1 (0.2)	2 (3.4)	0
Staphylococcal Sepsis	7 (1.2)	2 (0.3)	5 (0.9)	3 (0.6)	1 (1.7)	0
Staphylococcal Skin Infection	1 (0.2)	0	1 (0.2)	0	0	0
Stenotrophomonas Infection	1 (0.2)	0	0	0	0	0
Streptococcal Bacteraemia	6 (1.0)	1 (0 2)	11 (2.0)	2 (0.4)	1 (1.7)	1 (1.7)
Streptococcal Infection	4 (0.7)	1 (0 2)	5 (0.9)	2 (0.4)	0	0
Streptococcal Sepsis	3 (0.5)	3 (0.5)	1 (0.2)	0	0	0
Strongyloidiasis	0	0	1 (0.2)	0	0	0
Subcutaneous Abscess	3 (0.5)	0	2 (0.4)	0	0	0
Superinfection	1 (0.2)	1 (0 2)	0	0	0	0
Systemic Candida	5 (0.8)	4 (0.7)	2 (0.4)	2 (0.4)	0	0
Systemic Mycosis	1 (0.2)	1 (0.2)	4 (0.7)	3 (0.6)	1 (1.7)	0
Tinea Infection	0	0	1 (0.2)	0	0	0
Tonsillitis	0	0	3 (0.6)	0	2 (3.4)	0
Tooth Abscess	4 (0.7)	0	1 (0.2)	0	1 (1.7)	0
Tooth Infection	2 (0.3)	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Toxoplasmosis	0	0	1 (0.2)	0	0	0
Tracheobronchitis	5 (0.8)	1 (0 2)	4 (0.7)	1 (0.2)	0	0
Tracheobronchitis Viral	0	0	1 (0.2)	0	0	0
Trichomoniasis	1 (0.2)	0	0	0	0	0
Tuberculosis	0	0	1 (0.2)	0	0	0
Upper Respiratory Tract Infection	29 (4.8)	3 (0.5)	35 (6.5)	2 (0.4)	0	0
Urethritis	0	0	1 (0.2)	0	0	0
Urinary Tract Infection	25 (4.1)	3 (0 5)	26 (4.8)	2 (0.4)	4 (6.9)	0
Urinary Tract Infection Enterococcal	0	0	1 (0.2)	0	0	0
Urinary Tract Infection Fungal	1 (0.2)	0	0	0	0	0
Urinary Tract Infection Pseudomonal	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Urinary Tract Infection Staphylococcal	1 (0.2)	0	0	0	0	0
Urinary Tract Infection Viral	0	0	1 (0.2)	1 (0.2)	0	0
Varicella	1 (0.2)	0	0	0	0	0
Varicella Zoster Pneumonia	1 (0.2)	1 (0 2)	0	0	0	0
Varicella Zoster Virus Infection	3 (0.5)	2 (0.3)	0	0	0	0
Viral Haemorrhagic Cystitis	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Viral Infection	2 (0.3)	1 (0 2)	5 (0.9)	2 (0.4)	0	0
Vulval Abscess	0	0	1 (0.2)	0	0	0
Vulvitis	1 (0.2)	0	0	0	1 (1.7)	0
Vulvovaginal Candidiasis	0	0	4 (0.7)	0	0	0
Vulvovaginal Mycotic Infection	1 (0.2)	0	0	0	0	0
Vulvovaginitis	1 (0.2)	0	0	0	0	0
Wound Infection	0	0	0	0	1 (1.7)	0
Injury, Poisoning And Procedural Complications	**138 (22.8)**	**17 (2.8)**	**123 (22.8)**	**22 (4.1)**	**21 (36.2)**	**1 (1.7)**
Accidental Overdose	0	0	1 (0.2)	1 (0.2)	0	0
Allergic Transfusion Reaction	3 (0.5)	0	3 (0.6)	0	0	0
Anal Injury	2 (0.3)	0	0	0	0	0
Animal Bite	0	0	0	0	1 (1.7)	0
Arthropod Bite	1 (0.2)	0	0	0	0	0
Back Injury	1 (0.2)	1 (0 2)	0	0	0	0
Brain Herniation	0	0	0	0	1 (1.7)	1 (1.7)
Chemical Eye Injury	0	0	1 (0.2)	0	0	0
Complications Of Transplant Surgery	1 (0.2)	1 (0 2)	0	0	0	0
Compression Fracture	1 (0.2)	1 (0.2)	0	0	0	0
Contusion	16 (2.6)	0	18 (3.3)	1 (0.2)	1 (1.7)	0
Eschar	2 (0.3)	0	2 (0.4)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Excoriation	3 (0.5)	0	2 (0.4)	0	0	0
Eye Burns	1 (0.2)	0	1 (0.2)	0	0	0
Eye Injury	0	0	1 (0.2)	0	0	0
Fall	20 (3.3)	2 (0 3)	19 (3.5)	3 (0.6)	5 (8.6)	0
Femoral Neck Fracture	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Foreign Body	0	0	1 (0.2)	0	0	0
Gastrointestinal Stoma Complication	0	0	1 (0.2)	0	0	0
Haematuria Traumatic	0	0	1 (0.2)	0	0	0
Haemodilution	0	0	1 (0.2)	0	0	0
Hand Fracture	1 (0.2)	0	0	0	0	0
Head Injury	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Hip Fracture	1 (0.2)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Incision Site Erythema	0	0	0	0	1 (1.7)	0
Incision Site Haemorrhage	1 (0.2)	0	1 (0.2)	0	0	0
Incision Site Pain	2 (0.3)	0	1 (0.2)	0	0	0
Inflammation Of Wound	1 (0.2)	0	1 (0.2)	0	1 (1.7)	0
Infusion Related Reaction	7 (1.2)	0	11 (2.0)	0	0	0
Injury	0	0	1 (0.2)	0	0	0
Injury Corneal	0	0	1 (0.2)	0	0	0
Joint Injury	1 (0.2)	0	1 (0.2)	0	0	0
Keratorhexis	0	0	1 (0.2)	0	0	0
Laceration	9 (1.5)	0	8 (1.5)	0	0	0
Ligament Sprain	1 (0.2)	0	1 (0.2)	0	0	0
Lip Injury	1 (0.2)	0	0	0	0	0
Lumbar Vertebral Fracture	1 (0.2)	1 (0.2)	0	0	0	0
Mouth Injury	2 (0.3)	0	1 (0.2)	0	0	0
Muscle Rupture	0	0	1 (0.2)	0	0	0
Muscle Strain	2 (0.3)	0	1 (0.2)	0	0	0
Overdose	0	0	1 (0.2)	1 (0.2)	0	0
Periorbital Haematoma	0	0	1 (0.2)	0	0	0
Pneumothorax Traumatic	0	0	1 (0.2)	0	0	0
Post Lumbar Puncture Syndrome	2 (0.3)	0	0	0	0	0
Post Procedural Complication	2 (0.3)	0	0	0	1 (1.7)	0
Post Procedural Discomfort	0	0	1 (0.2)	0	0	0
Post Procedural Haematoma	1 (0.2)	0	4 (0.7)	0	0	0
Post Procedural Haemorrhage	3 (0.5)	1 (0.2)	6 (1.1)	2 (0.4)	0	0
Post Procedural Oedema	1 (0.2)	0	0	0	0	0
Post-Traumatic Pain	1 (0.2)	0	0	0	0	0
Postoperative Fever	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Procedural Hypertension	1 (0.2)	0	0	0	0	0

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Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Procedural Pain	18 (3.0)	0	16 (3.0)	0	0	0
Rib Fracture	1 (0.2)	0	0	0	0	0
Road Traffic Accident	0	0	1 (0.2)	0	0	0
Scratch	1 (0.2)	0	2 (0.4)	0	0	0
Sedation Complication	1 (0.2)	1 (0 2)	0	0	0	0
Skin Abrasion	5 (0.8)	0	4 (0.7)	0	0	0
Skin Injury	2 (0.3)	0	0	0	0	0
Spinal Fracture	1 (0.2)	1 (0 2)	0	0	0	0
Stoma Site Haemorrhage	0	0	1 (0.2)	0	0	0
Stoma Site Pain	0	0	1 (0.2)	0	0	0
Subarachnoid Haemorrhage	2 (0.3)	2 (0.3)	0	0	1 (1.7)	0
Subcutaneous Haematoma	0	0	0	0	1 (1.7)	0
Subdural Haematoma	2 (0.3)	1 (0 2)	3 (0.6)	3 (0.6)	0	0
Thermal Burn	1 (0.2)	0	2 (0.4)	0	0	0
Tooth Fracture	1 (0.2)	0	1 (0.2)	0	1 (1.7)	0
Toxicity To Various Agents	8 (1.3)	2 (0.3)	7 (1.3)	2 (0.4)	0	0
Transfusion Reaction	34 (5.6)	1 (0 2)	21 (3.9)	2 (0.4)	10 (17.2)	0
Transplant Failure	2 (0.3)	2 (0 3)	3 (0.6)	3 (0.6)	0	0
Traumatic Haematoma	1 (0.2)	0	1 (0.2)	0	0	0
Vaginal Laceration	0	0	1 (0.2)	0	0	0
Vascular Injury	0	0	1 (0.2)	0	0	0
Wound	3 (0.5)	0	10 (1.9)	0	0	0
Wound Complication	2 (0.3)	0	0	0	0	0
Wound Haemorrhage	1 (0.2)	0	0	0	0	0
Wound Secretion	0	0	1 (0.2)	0	0	0
Investigations	**328 (54.2)**	**99 (16.4)**	**287 (53.2)**	**89 (16.5)**	**33 (56.9)**	**5 (8.6)**
Activated Partial Thromboplastin Time Prolonged	0	0	3 (0.6)	1 (0.2)	0	0
Activated Partial Thromboplastin Time Shortened	0	0	1 (0.2)	0	0	0
Alanine Aminotransferase Abnormal	1 (0.2)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Alanine Aminotransferase Decreased	1 (0.2)	0	0	0	0	0
Alanine Aminotransferase Increased	37 (6.1)	12 (2.0)	26 (4.8)	14 (2.6)	3 (5.2)	1 (1.7)
Ammonia Increased	1 (0.2)	1 (0 2)	0	0	0	0
Amylase Increased	0	0	1 (0.2)	0	0	0
Antithrombin III Decreased	1 (0.2)	0	0	0	0	0
Aspartate Aminotransferase Abnormal	1 (0.2)	0	1 (0.2)	0	0	0
Aspartate Aminotransferase Increased	19 (3.1)	3 (0.5)	17 (3.2)	8 (1.5)	3 (5.2)	0

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Aspergillus Test Positive	0	0	2 (0.4)	0	0	0
Aspiration Bronchial	1 (0.2)	0	0	0	0	0
Aspiration Tracheal	0	0	1 (0.2)	0	0	0
Aspiration Tracheal Abnormal	0	0	1 (0.2)	0	0	0
Atrial Pressure Increased	0	0	1 (0.2)	0	0	0
Bacterial Test Positive	12 (2.0)	4 (0.7)	18 (3.3)	6 (1.1)	0	0
Basophil Count Increased	1 (0.2)	1 (0 2)	0	0	0	0
Bilirubin Conjugated Increased	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Blast Cells Present	1 (0.2)	1 (0 2)	0	0	0	0
Bleeding Time Prolonged	3 (0.5)	2 (0 3)	1 (0.2)	0	0	0
Blood Albumin Abnormal	1 (0.2)	1 (0 2)	0	0	0	0
Blood Albumin Decreased	6 (1.0)	0	6 (1.1)	0	1 (1.7)	0
Blood Albumin Increased	0	0	2 (0.4)	0	0	0
Blood Alkaline Phosphatase Decreased	0	0	0	0	1 (1.7)	0
Blood Alkaline Phosphatase Increased	16 (2.6)	5 (0.8)	19 (3.5)	0	1 (1.7)	0
Blood Bicarbonate Decreased	3 (0.5)	1 (0.2)	5 (0.9)	1 (0.2)	1 (1.7)	0
Blood Bilirubin Abnormal	1 (0.2)	0	0	0	0	0
Blood Bilirubin Increased	29 (4.8)	7 (1 2)	26 (4.8)	14 (2.6)	4 (6.9)	2 (3.4)
Blood Calcium Decreased	2 (0.3)	0	7 (1.3)	1 (0.2)	0	0
Blood Chloride Increased	1 (0.2)	0	0	0	0	0
Blood Cholesterol Increased	5 (0.8)	1 (0 2)	1 (0.2)	0	0	0
Blood Creatine Decreased	0	0	1 (0.2)	0	0	0
Blood Creatine Increased	2 (0.3)	0	0	0	0	0
Blood Creatine Phosphokinase Increased	1 (0.2)	0	0	0	0	0
Blood Creatinine Decreased	0	0	1 (0.2)	0	0	0
Blood Creatinine Increased	34 (5.6)	2 (0 3)	48 (8.9)	4 (0.7)	2 (3.4)	0
Blood Culture Positive	17 (2.8)	1 (0 2)	9 (1.7)	4 (0.7)	1 (1.7)	0
Blood Electrolytes Abnormal	0	0	1 (0.2)	0	0	0
Blood Gastrin Increased	0	0	1 (0.2)	0	0	0
Blood Glucose Increased	5 (0.8)	0	6 (1.1)	1 (0.2)	0	0
Blood Immunoglobulin G Decreased	2 (0.3)	0	1 (0.2)	0	0	0
Blood Lactate Dehydrogenase	0	0	1 (0.2)	1 (0.2)	0	0
Blood Lactate Dehydrogenase Increased	18 (3.0)	2 (0.3)	17 (3.2)	8 (1.5)	0	0
Blood Magnesium Decreased	11 (1.8)	1 (0.2)	8 (1.5)	0	0	0
Blood Magnesium Increased	1 (0.2)	0	0	0	0	0
Blood Phosphorus Decreased	4 (0.7)	0	3 (0.6)	0	0	0

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Blood Phosphorus Increased	1 (0.2)	0	2 (0.4)	0	0	0
Blood Potassium	1 (0.2)	0	0	0	0	0
Blood Potassium Abnormal	0	0	0	0	1 (1.7)	0
Blood Potassium Decreased	8 (1.3)	1 (0.2)	8 (1.5)	0	1 (1.7)	0
Blood Potassium Increased	0	0	2 (0.4)	0	0	0
Blood Pressure Decreased	0	0	1 (0.2)	1 (0.2)	0	0
Blood Pressure Diastolic Increased	1 (0.2)	0	0	0	0	0
Blood Pressure Increased	6 (1.0)	1 (0.2)	6 (1.1)	1 (0.2)	0	0
Blood Pressure Orthostatic	2 (0.3)	0	0	0	0	0
Blood Sodium Decreased	0	0	1 (0.2)	0	0	0
Blood Testosterone Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Blood Thyroid Stimulating Hormone Decreased	1 (0.2)	0	0	0	0	0
Blood Triglycerides Increased	2 (0.3)	0	3 (0.6)	0	0	0
Blood Urea Decreased	0	0	1 (0.2)	0	0	0
Blood Urea Increased	5 (0.8)	2 (0 3)	13 (2.4)	2 (0.4)	0	0
Blood Uric Acid Decreased	0	0	1 (0.2)	0	0	0
Blood Uric Acid Increased	5 (0.8)	2 (0 3)	5 (0.9)	0	0	0
Blood Urine Present	3 (0.5)	0	1 (0.2)	0	0	0
Body Temperature	1 (0.2)	1 (0 2)	0	0	0	0
Body Temperature Increased	4 (0.7)	0	0	0	0	0
Breath Sounds Abnormal	18 (3.0)	1 (0.2)	11 (2.0)	1 (0.2)	0	0
Bronchoscopy	0	0	1 (0.2)	1 (0.2)	0	0
C-Reactive Protein Abnormal	1 (0.2)	1 (0 2)	0	0	0	0
C-Reactive Protein Increased	4 (0.7)	0	3 (0.6)	1 (0.2)	2 (3.4)	1 (1.7)
Carbon Dioxide Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Carbon Monoxide Diffusing Capacity Decreased	0	0	1 (0.2)	0	0	0
Cardiac Murmur	14 (2.3)	0	7 (1.3)	0	0	0
Central Venous Pressure Decreased	1 (0.2)	1 (0.2)	0	0	0	0
Chest X-Ray Abnormal	6 (1.0)	0	6 (1.1)	1 (0.2)	0	0
Clostridium Test	1 (0.2)	0	1 (0.2)	0	0	0
Clostridium Test Positive	7 (1.2)	1 (0 2)	6 (1.1)	0	0	0
Coagulation Factor Decreased	1 (0.2)	0	0	0	0	0
Coagulation Factor XIII Level Decreased	0	0	1 (0.2)	0	0	0
Coagulation Test Abnormal	2 (0.3)	0	2 (0.4)	1 (0.2)	0	0
Coagulation Time Prolonged	1 (0.2)	0	1 (0.2)	0	0	0
Coagulation Time Shortened	1 (0.2)	0	1 (0.2)	0	0	0
Colour Vision Tests Abnormal	0	0	1 (0.2)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Computerised Tomogram Abnormal	1 (0.2)	0	4 (0.7)	1 (0.2)	1 (1.7)	0
Creatinine Renal Clearance Decreased	2 (0.3)	0	6 (1.1)	0	0	0
Culture	1 (0.2)	0	0	0	0	0
Culture Positive	1 (0.2)	0	0	0	0	0
Culture Stool Positive	1 (0.2)	0	1 (0.2)	0	0	0
Culture Urine Positive	2 (0.3)	0	1 (0.2)	0	0	0
Culture Wound Positive	0	0	1 (0.2)	0	0	0
Cytomegalovirus Test	5 (0.8)	1 (0 2)	6 (1.1)	2 (0.4)	0	0
Cytomegalovirus Test Positive	27 (4.5)	4 (0.7)	22 (4.1)	2 (0.4)	0	0
Drug Level Changed	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Drug Level Increased	5 (0.8)	2 (0.3)	3 (0.6)	2 (0.4)	0	0
Echocardiogram Abnormal	1 (0.2)	0	0	0	0	0
Ejection Fraction Decreased	2 (0.3)	1 (0 2)	0	0	0	0
Electrocardiogram Abnormal	3 (0.5)	1 (0 2)	2 (0.4)	0	0	0
Electrocardiogram Qt Interval	0	0	0	0	1 (1.7)	0
Electrocardiogram Qt Prolonged	24 (4.0)	2 (0.3)	19 (3.5)	2 (0.4)	5 (8.6)	0
Electrocardiogram Repolarisation Abnormality	1 (0.2)	0	0	0	0	0
Electrocardiogram St Segment Abnormal	1 (0.2)	0	0	0	0	0
Electrocardiogram St-T Change	1 (0.2)	0	0	0	0	0
Electrocardiogram St-T Segment Abnormal	1 (0.2)	0	0	0	0	0
Electrocardiogram T Wave Abnormal	4 (0.7)	1 (0.2)	0	0	0	0
Electrocardiogram T Wave Inversion	1 (0.2)	0	0	0	0	0
Electroencephalogram Abnormal	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Eosinophil Count Increased	1 (0.2)	0	0	0	0	0
Fibrinolysis	0	0	1 (0.2)	0	0	0
Fungal Test	0	0	0	0	1 (1.7)	0
Fungal Test Positive	3 (0.5)	0	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	1 (0.2)	1 (0.2)	0	0
Gamma-Glutamyltransferase Increased	41 (6.8)	20 (3.3)	38 (7.1)	22 (4.1)	4 (6.9)	0
Gastric Ph Decreased	1 (0.2)	0	1 (0.2)	0	0	0
General Physical Condition	1 (0.2)	0	0	0	0	0
Glucose Urine	1 (0.2)	0	0	0	0	0
Haematocrit Decreased	0	0	2 (0.4)	1 (0.2)	0	0
Haemoglobin Decreased	8 (1.3)	2 (0 3)	2 (0.4)	1 (0.2)	1 (1.7)	1 (1.7)

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Heart Rate Increased	0	0	2 (0.4)	0	0	0
Heart Rate Irregular	5 (0.8)	0	3 (0.6)	0	0	0
Heart Sounds Abnormal	1 (0.2)	1 (0.2)	0	0	0	0
Hepatic Enzyme Abnormal	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)	0	0
Hepatic Enzyme Increased	9 (1.5)	4 (0.7)	12 (2.2)	3 (0.6)	0	0
Herpes Simplex Test Positive	1 (0.2)	0	0	0	0	0
High Density Lipoprotein Increased	1 (0.2)	0	0	0	0	0
Immunoglobulins Decreased	1 (0.2)	0	0	0	0	0
Immunosuppressant Drug Level Decreased	0	0	1 (0.2)	0	0	0
International Normalised Ratio Abnormal	2 (0.3)	0	0	0	0	0
International Normalised Ratio Increased	2 (0.3)	0	2 (0.4)	0	0	0
Liver Function Test Abnormal	2 (0.3)	1 (0 2)	3 (0.6)	2 (0.4)	0	0
Liver Function Test Increased	18 (3.0)	6 (1.0)	16 (3.0)	6 (1.1)	1 (1.7)	0
Lymphocyte Count Decreased	0	0	1 (0.2)	1 (0.2)	0	0
Lymphocyte Count Increased	0	0	1 (0.2)	1 (0.2)	0	0
Microbiology Test Normal	1 (0.2)	0	0	0	0	0
Neurological Examination Abnormal	0	0	1 (0.2)	0	0	0
Neutrophil Count Abnormal	2 (0.3)	1 (0 2)	0	0	0	0
Neutrophil Count Decreased	3 (0.5)	1 (0 2)	1 (0.2)	1 (0.2)	1 (1.7)	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	1 (0.2)	0	0	0
Nuclear Magnetic Resonance Imaging Brain Abnormal	1 (0.2)	0	0	0	0	0
Nutritional Condition Abnormal	0	0	2 (0.4)	1 (0.2)	0	0
Occult Blood Positive	7 (1.2)	1 (0 2)	7 (1.3)	0	1 (1.7)	0
Oxygen Consumption Decreased	0	0	1 (0.2)	0	0	0
Oxygen Saturation Decreased	9 (1.5)	5 (0.8)	9 (1.7)	2 (0.4)	0	0
Parvovirus B19 Test Positive	1 (0.2)	0	0	0	0	0
Pedal Pulse Abnormal	0	0	1 (0.2)	0	0	0
Platelet Count Decreased	9 (1.5)	3 (0.5)	6 (1.1)	1 (0.2)	1 (1.7)	0
Po2 Decreased	1 (0.2)	0	0	0	0	0
Protein Total Decreased	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (1.7)	0
Protein Total Increased	0	0	1 (0.2)	0	0	0
Prothrombin Time Prolonged	5 (0.8)	0	12 (2.2)	1 (0.2)	3 (5.2)	0
Prothrombin Time Ratio Decreased	0	0	1 (0.2)	0	0	0
Prothrombin Time Shortened	3 (0.5)	0	2 (0.4)	0	1 (1.7)	0
Pulmonary Function Test Decreased	1 (0.2)	0	1 (0.2)	0	0	0

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Pulse Absent	0	0	1 (0.2)	1 (0.2)	0	0
Qrs Axis Abnormal	0	0	1 (0.2)	0	0	0
Red Blood Cell Count Decreased	1 (0.2)	1 (0.2)	0	0	0	0
Red Blood Cell Schistocytes Present	0	0	1 (0.2)	0	0	0
Respiratory Rate Increased	1 (0.2)	1 (0.2)	2 (0.4)	0	0	0
Romberg Test Positive	0	0	1 (0.2)	0	0	0
Rotavirus Test Positive	0	0	1 (0.2)	0	0	0
Salmonella Test Positive	1 (0.2)	1 (0 2)	0	0	0	0
Scan Bone Marrow Abnormal	1 (0.2)	0	0	0	0	0
Serum Ferritin Increased	1 (0.2)	1 (0.2)	0	0	0	0
Sputum Abnormal	1 (0.2)	0	0	0	0	0
Sputum Culture Positive	0	0	1 (0.2)	0	0	0
Thrombin Time Prolonged	1 (0.2)	0	0	0	0	0
Thyroid Function Test Abnormal	0	0	1 (0.2)	0	0	0
Total Lung Capacity Decreased	1 (0.2)	0	0	0	0	0
Toxoplasma Serology Positive	1 (0.2)	0	0	0	0	0
Transaminases Increased	13 (2.1)	9 (1.5)	14 (2.6)	5 (0.9)	0	0
Troponin I Increased	0	0	1 (0.2)	1 (0.2)	0	0
Troponin Increased	1 (0.2)	1 (0 2)	2 (0.4)	0	0	0
Urine Output Decreased	3 (0.5)	1 (0.2)	1 (0.2)	0	0	0
Urine Output Increased	1 (0.2)	0	0	0	0	0
Viral Test Positive	1 (0.2)	0	1 (0.2)	0	0	0
Vitamin K Decreased	1 (0.2)	0	0	0	0	0
Volume Blood Decreased	0	0	0	0	1 (1.7)	0
Weight Decreased	41 (6.8)	7 (1 2)	50 (9.3)	5 (0.9)	4 (6.9)	0
Weight Increased	12 (2.0)	0	9 (1.7)	1 (0.2)	5 (8.6)	0
White Blood Cell Count Abnormal	1 (0.2)	1 (0 2)	0	0	0	0
White Blood Cell Count Decreased	1 (0.2)	0	3 (0.6)	0	1 (1.7)	0
White Blood Cell Count Increased	2 (0.3)	0	0	0	0	0
X-Ray Abnormal	1 (0.2)	0	0	0	0	0
Metabolism And Nutrition Disorders	**354 (58.5)**	**92 (15 2)**	**314 (58.3)**	**69 (12.8)**	**45 (77.6)**	**10 (17.2)**
Acidosis	11 (1.8)	6 (1.0)	6 (1.1)	1 (0.2)	2 (3.4)	2 (3.4)
Appetite Disorder	1 (0.2)	0	1 (0.2)	0	0	0
Cachexia	2 (0.3)	1 (0 2)	0	0	0	0
Calcium Deficiency	0	0	1 (0.2)	0	0	0
Decreased Appetite	88 (14.5)	7 (1.2)	87 (16.1)	11 (2.0)	17 (29.3)	0
Dehydration	26 (4.3)	7 (1 2)	27 (5.0)	4 (0.7)	2 (3.4)	0
Diabetes Mellitus	17 (2.8)	4 (0.7)	7 (1.3)	2 (0.4)	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	1 (1.7)	0

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	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Electrolyte Depletion	1 (0.2)	1 (0 2)	0	0	0	0
Electrolyte Imbalance	6 (1.0)	2 (0 3)	3 (0.6)	1 (0.2)	4 (6.9)	0
Enzyme Abnormality	0	0	1 (0.2)	0	0	0
Failure To Thrive	1 (0.2)	1 (0 2)	4 (0.7)	0	0	0
Feeding Disorder	0	0	1 (0.2)	1 (0.2)	0	0
Fluid Imbalance	0	0	1 (0.2)	0	0	0
Fluid Overload	27 (4.5)	0	17 (3.2)	5 (0.9)	2 (3.4)	1 (1.7)
Fluid Retention	18 (3.0)	1 (0 2)	24 (4.5)	3 (0.6)	3 (5.2)	0
Food Aversion	1 (0.2)	0	0	0	0	0
Food Craving	1 (0.2)	0	0	0	0	0
Food Intolerance	1 (0.2)	0	0	0	0	0
Glucose Tolerance Impaired	0	0	1 (0.2)	0	0	0
Gout	3 (0.5)	1 (0 2)	4 (0.7)	0	0	0
Haemochromatosis	0	0	1 (0.2)	0	0	0
Haemosiderosis	0	0	1 (0.2)	0	0	0
Hypercalcaemia	3 (0.5)	0	3 (0.6)	0	0	0
Hyperchloraemia	1 (0.2)	0	0	0	0	0
Hypercholesterolaemia	4 (0.7)	1 (0 2)	0	0	0	0
Hypercreatininaemia	1 (0.2)	0	0	0	0	0
Hyperferritinaemia	0	0	1 (0.2)	0	0	0
Hyperglycaemia	66 (10.9)	17 (2.8)	71 (13.2)	17 (3.2)	2 (3.4)	0
Hyperhomocysteinaemia	1 (0.2)	0	0	0	0	0
Hyperinsulinaemic Hypoglycaemia	1 (0.2)	1 (0 2)	0	0	0	0
Hyperkalaemia	15 (2.5)	4 (0.7)	23 (4.3)	5 (0.9)	2 (3.4)	0
Hyperlipidaemia	0	0	1 (0.2)	0	0	0
Hypermagnesaemia	6 (1.0)	2 (0 3)	3 (0.6)	0	3 (5.2)	0
Hypernatraemia	6 (1.0)	1 (0 2)	4 (0.7)	0	2 (3.4)	1 (1.7)
Hyperosmolar State	1 (0.2)	0	0	0	0	0
Hyperphagia	1 (0.2)	0	0	0	0	0
Hyperphosphataemia	6 (1.0)	0	8 (1.5)	1 (0.2)	0	0
Hypertriglyceridaemia	2 (0.3)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Hyperuricaemia	4 (0.7)	1 (0 2)	10 (1.9)	0	0	0
Hypervolaemia	1 (0.2)	0	3 (0.6)	0	0	0
Hypoalbuminaemia	28 (4.6)	5 (0.8)	18 (3.3)	2 (0.4)	2 (3.4)	1 (1.7)
Hypocalcaemia	53 (8.8)	8 (1 3)	46 (8.5)	2 (0.4)	5 (8.6)	1 (1.7)
Hypochloraemia	0	0	1 (0.2)	0	0	0
Hypoglycaemia	10 (1.7)	4 (0.7)	9 (1.7)	0	0	0
Hypokalaemia	172 (28.4)	27 (4.5)	136 (25.2)	18 (3.3)	29 (50.0)	5 (8.6)
Hypomagnesaemia	98 (16.2)	8 (1 3)	75 (13.9)	3 (0.6)	11 (19.0)	0
Hyponatraemia	30 (5.0)	4 (0.7)	29 (5.4)	4 (0.7)	3 (5.2)	1 (1.7)

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Hypophagia	10 (1.7)	3 (0 5)	11 (2.0)	0	0	0
Hypophosphataemia	47 (7.8)	7 (1 2)	37 (6.9)	3 (0.6)	6 (10.3)	1 (1.7)
Hypoproteinaemia	5 (0.8)	1 (0 2)	3 (0.6)	0	1 (1.7)	0
Hypovitaminosis	2 (0.3)	0	0	0	0	0
Hypovolaemia	3 (0.5)	0	4 (0.7)	2 (0.4)	0	0
Lactose Intolerance	0	0	1 (0.2)	0	0	0
Magnesium Deficiency	1 (0.2)	0	1 (0.2)	0	0	0
Malnutrition	5 (0.8)	4 (0.7)	15 (2.8)	4 (0.7)	0	0
Metabolic Acidosis	10 (1.7)	5 (0.8)	6 (1.1)	4 (0.7)	2 (3.4)	2 (3.4)
Metabolic Alkalosis	0	0	2 (0.4)	1 (0.2)	0	0
Obesity	0	0	2 (0.4)	0	0	0
Phosphorus Metabolism Disorder	1 (0.2)	0	0	0	0	0
Polydipsia	3 (0.5)	0	0	0	0	0
Vitamin B12 Deficiency	1 (0.2)	0	0	0	0	0
Vitamin B6 Deficiency	0	0	1 (0.2)	0	0	0
Vitamin C Deficiency	0	0	1 (0.2)	0	0	0
Vitamin K Deficiency	1 (0.2)	0	2 (0.4)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**249 (41.2)**	**33 (5.5)**	**246 (45.6)**	**22 (4.1)**	**20 (34.5)**	**2 (3.4)**
Arthralgia	58 (9.6)	5 (0.8)	56 (10.4)	4 (0.7)	3 (5.2)	0
Arthritis	4 (0.7)	0	1 (0.2)	0	1 (1.7)	0
Axillary Mass	1 (0.2)	0	0	0	0	0
Back Pain	61 (10.1)	8 (1 3)	66 (12.2)	4 (0.7)	4 (6.9)	1 (1.7)
Bone Pain	26 (4.3)	6 (1.0)	11 (2.0)	2 (0.4)	3 (5.2)	0
Bursitis	1 (0.2)	0	1 (0.2)	0	0	0
Chondritis	1 (0.2)	0	0	0	0	0
Clubbing	0	0	1 (0.2)	0	0	0
Coccydynia	2 (0.3)	0	0	0	0	0
Flank Pain	9 (1.5)	2 (0 3)	7 (1.3)	1 (0.2)	1 (1.7)	0
Groin Pain	2 (0.3)	0	3 (0.6)	0	1 (1.7)	0
Haemarthrosis	2 (0.3)	0	1 (0.2)	0	0	0
Inguinal Mass	2 (0.3)	0	0	0	0	0
Intervertebral Disc Degeneration	0	0	1 (0.2)	1 (0.2)	0	0
Intervertebral Disc Protrusion	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Joint Contracture	1 (0.2)	0	0	0	0	0
Joint Effusion	3 (0.5)	0	0	0	0	0
Joint Stiffness	2 (0.3)	0	2 (0.4)	0	0	0
Joint Swelling	9 (1.5)	0	6 (1.1)	0	0	0
Kyphoscoliosis	1 (0.2)	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Limb Discomfort	1 (0.2)	0	2 (0.4)	0	0	0
Mobility Decreased	1 (0.2)	0	0	0	0	0
Muscle Atrophy	4 (0.7)	0	1 (0.2)	0	0	0
Muscle Contracture	1 (0.2)	1 (0 2)	0	0	0	0
Muscle Fatigue	1 (0.2)	0	1 (0.2)	0	0	0
Muscle Spasms	31 (5.1)	2 (0.3)	38 (7.1)	1 (0.2)	0	0
Muscle Swelling	0	0	1 (0.2)	0	1 (1.7)	0
Muscle Tightness	1 (0.2)	0	0	0	0	0
Muscle Twitching	4 (0.7)	0	3 (0.6)	0	0	0
Muscular Weakness	28 (4.6)	5 (0.8)	28 (5.2)	3 (0.6)	1 (1.7)	1 (1.7)
Musculoskeletal Chest Pain	12 (2.0)	0	12 (2.2)	0	0	0
Musculoskeletal Discomfort	4 (0.7)	0	3 (0.6)	0	0	0
Musculoskeletal Pain	16 (2.6)	0	20 (3.7)	2 (0.4)	4 (6.9)	0
Musculoskeletal Stiffness	5 (0.8)	0	10 (1.9)	1 (0.2)	1 (1.7)	0
Myalgia	31 (5.1)	3 (0 5)	33 (6.1)	3 (0.6)	1 (1.7)	0
Myopathy	20 (3.3)	8 (1 3)	11 (2.0)	1 (0.2)	0	0
Myositis	1 (0.2)	0	0	0	0	0
Neck Mass	1 (0.2)	0	2 (0.4)	0	0	0
Neck Pain	9 (1.5)	1 (0 2)	20 (3.7)	1 (0.2)	1 (1.7)	0
Nuchal Rigidity	0	0	1 (0.2)	0	0	0
Osteoarthritis	0	0	1 (0.2)	0	0	0
Osteolysis	0	0	1 (0.2)	0	0	0
Osteonecrosis	2 (0.3)	0	3 (0.6)	1 (0.2)	0	0
Osteopenia	2 (0.3)	0	0	0	0	0
Osteoporosis	0	0	2 (0.4)	0	0	0
Pain In Extremity	58 (9.6)	3 (0 5)	48 (8.9)	2 (0.4)	5 (8.6)	1 (1.7)
Pain In Jaw	6 (1.0)	0	2 (0.4)	0	1 (1.7)	0
Pathological Fracture	0	0	1 (0.2)	1 (0.2)	0	0
Plantar Fasciitis	1 (0.2)	0	0	0	0	0
Polychondritis	0	0	0	0	1 (1.7)	0
Scoliosis	1 (0.2)	0	0	0	0	0
Sjogren's Syndrome	3 (0.5)	0	1 (0.2)	0	0	0
Soft Tissue Disorder	0	0	3 (0.6)	0	0	0
Spinal Osteoarthritis	3 (0.5)	0	0	0	0	0
Spinal Pain	0	0	1 (0.2)	0	0	0
Temporomandibular Joint Syndrome	1 (0.2)	0	0	0	0	0
Tendon Pain	0	0	1 (0.2)	0	0	0
Tendonitis	3 (0.5)	0	0	0	2 (3.4)	0
Tenosynovitis	1 (0.2)	0	0	0	0	0
Torticollis	1 (0.2)	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**61 (10.1)**	**44 (7.3)**	**57 (10.6)**	**39 (7.2)**	**3 (5.2)**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	6 (1.1)	5 (0.9)	0	0
Acute Myeloid Leukaemia	13 (2.1)	13 (2.1)	9 (1.7)	9 (1.7)	1 (1.7)	0
Acute Myeloid Leukaemia Recurrent	12 (2.0)	12 (2.0)	6 (1.1)	6 (1.1)	0	0
Adenoma Benign	0	0	1 (0.2)	0	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	1 (0.2)	1 (0.2)	0	0
Angiomyolipoma	0	0	1 (0.2)	0	0	0
Anogenital Warts	1 (0.2)	0	0	0	0	0
B-Cell Lymphoma	0	0	1 (0.2)	1 (0.2)	0	0
Basal Cell Carcinoma	0	0	1 (0.2)	0	0	0
Bowen's Disease	1 (0.2)	0	0	0	0	0
Breast Neoplasm	1 (0.2)	0	0	0	0	0
Chloroma	1 (0.2)	0	0	0	0	0
Chronic Lymphocytic Leukaemia Recurrent	0	0	1 (0.2)	0	0	0
Chronic Myeloid Leukaemia	1 (0.2)	1 (0 2)	0	0	0	0
Colon Adenoma	1 (0.2)	0	0	0	0	0
Haemangioma Of Liver	1 (0.2)	0	2 (0.4)	0	0	0
Hodgkin's Disease	0	0	1 (0.2)	1 (0.2)	0	0
Hodgkin's Disease Recurrent	0	0	1 (0.2)	1 (0.2)	0	0
Leukaemia	4 (0.7)	2 (0 3)	3 (0.6)	2 (0.4)	0	0
Leukaemia Cutis	0	0	0	0	1 (1.7)	0
Leukaemia Recurrent	6 (1.0)	5 (0.8)	5 (0.9)	3 (0.6)	0	0
Lipoma	2 (0.3)	0	0	0	0	0
Lymphoma	6 (1.0)	5 (0.8)	2 (0.4)	2 (0.4)	0	0
Malignant Melanoma	0	0	1 (0.2)	0	0	0
Melanocytic Naevus	0	0	1 (0.2)	0	0	0
Meningioma	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Metastases To Kidney	0	0	1 (0.2)	1 (0.2)	0	0
Metastases To Liver	0	0	1 (0.2)	1 (0.2)	0	0
Metastatic Neoplasm	1 (0.2)	1 (0 2)	0	0	0	0
Myelodysplastic Syndrome	1 (0.2)	1 (0 2)	2 (0.4)	0	0	0
Nasal Neoplasm	1 (0.2)	0	0	0	0	0
Neoplasm Malignant	1 (0.2)	1 (0 2)	3 (0.6)	3 (0.6)	0	0
Neuroma	1 (0.2)	0	0	0	0	0
Non-Hodgkin's Lymphoma	1 (0.2)	1 (0 2)	4 (0.7)	3 (0.6)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Non-Hodgkin's Lymphoma Recurrent	0	0	2 (0.4)	2 (0.4)	0	0
Plasma Cell Myeloma	0	0	1 (0.2)	1 (0.2)	0	0
Post Transplant Lymphoproliferative Disorder	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Pyogenic Granuloma	0	0	1 (0.2)	0	0	0
Renal Cancer	1 (0.2)	1 (0 2)	0	0	0	0
Renal Neoplasm	1 (0.2)	0	0	0	0	0
Seborrhoeic Keratosis	0	0	1 (0.2)	0	0	0
Skin Papilloma	1 (0.2)	0	0	0	0	0
Squamous Cell Carcinoma	2 (0.3)	0	1 (0.2)	1 (0.2)	0	0
Thyroid Adenoma	1 (0.2)	0	0	0	0	0
Tumour Associated Fever	0	0	0	0	1 (1.7)	0
Tumour Pain	2 (0.3)	1 (0 2)	0	0	0	0
Uterine Leiomyoma	2 (0.3)	1 (0 2)	0	0	0	0
Vaginal Neoplasm	1 (0.2)	0	0	0	0	0
Nervous System Disorders	**295 (48.8)**	**64 (10.6)**	**286 (53.1)**	**55 (10.2)**	**31 (53.4)**	**4 (6.9)**
Ageusia	1 (0.2)	0	2 (0.4)	0	0	0
Akathisia	0	0	1 (0.2)	0	0	0
Akinesia	0	0	1 (0.2)	0	0	0
Amnesia	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Aphasia	1 (0.2)	0	1 (0.2)	0	0	0
Areflexia	2 (0.3)	0	0	0	0	0
Asterixis	1 (0.2)	0	0	0	0	0
Ataxia	2 (0.3)	1 (0 2)	2 (0.4)	0	0	0
Athetosis	0	0	1 (0.2)	0	0	0
Balance Disorder	5 (0.8)	0	4 (0.7)	1 (0.2)	0	0
Brachial Plexopathy	0	0	1 (0.2)	0	0	0
Brain Compression	0	0	0	0	1 (1.7)	1 (1.7)
Brain Oedema	4 (0.7)	3 (0 5)	2 (0.4)	2 (0.4)	0	0
Burning Sensation	8 (1.3)	0	2 (0.4)	0	0	0
Central Nervous System Lesion	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Cerebellar Haemorrhage	2 (0.3)	2 (0 3)	0	0	1 (1.7)	1 (1.7)
Cerebral Haemorrhage	5 (0.8)	5 (0.8)	5 (0.9)	5 (0.9)	0	0
Cerebral Hypoperfusion	0	0	1 (0.2)	1 (0.2)	0	0
Cerebral Infarction	1 (0.2)	1 (0 2)	3 (0.6)	2 (0.4)	0	0
Cerebrovascular Accident	2 (0.3)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Clonus	1 (0.2)	0	0	0	0	0
Cluster Headache	1 (0.2)	0	0	0	0	0
Cognitive Disorder	3 (0.5)	2 (0 3)	1 (0.2)	0	0	0

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All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Coma	3 (0.5)	3 (0 5)	5 (0.9)	5 (0.9)	0	0
Demyelination	4 (0.7)	1 (0 2)	0	0	0	0
Depressed Level Of Consciousness	3 (0.5)	3 (0.5)	3 (0.6)	2 (0.4)	1 (1.7)	0
Disturbance In Attention	0	0	6 (1.1)	0	0	0
Dizziness	61 (10.1)	2 (0 3)	52 (9.6)	2 (0.4)	5 (8.6)	0
Dizziness Postural	4 (0.7)	0	3 (0.6)	0	0	0
Dysaesthesia	1 (0.2)	0	0	0	0	0
Dysarthria	2 (0.3)	0	3 (0.6)	0	1 (1.7)	0
Dysgeusia	9 (1.5)	0	9 (1.7)	0	0	0
Encephalopathy	5 (0.8)	4 (0.7)	3 (0.6)	2 (0.4)	0	0
Epilepsy	0	0	1 (0.2)	0	0	0
Extrapyramidal Disorder	2 (0.3)	0	0	0	0	0
Facial Paralysis	1 (0.2)	0	2 (0.4)	0	0	0
Facial Paresis	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Generalised Tonic-Clonic Seizure	0	0	2 (0.4)	2 (0.4)	0	0
Guillain-Barre Syndrome	0	0	1 (0.2)	1 (0.2)	0	0
Haemorrhage Intracranial	2 (0.3)	2 (0 3)	6 (1.1)	5 (0.9)	0	0
Haemorrhagic Stroke	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Head Discomfort	1 (0.2)	0	0	0	0	0
Headache	171 (28.3)	15 (2.5)	139 (25.8)	12 (2.2)	22 (37.9)	2 (3.4)
Hemiparesis	0	0	7 (1.3)	4 (0.7)	0	0
Hemiplegia	1 (0.2)	1 (0 2)	3 (0.6)	2 (0.4)	0	0
Hydrocephalus	0	0	0	0	1 (1.7)	1 (1.7)
Hyperreflexia	0	0	2 (0.4)	0	0	0
Hypertonia	0	0	3 (0.6)	0	0	0
Hypoaesthesia	6 (1.0)	0	13 (2.4)	0	3 (5.2)	0
Hypogeusia	2 (0.3)	0	3 (0.6)	0	0	0
Hypoglycaemic Coma	1 (0.2)	1 (0 2)	0	0	0	0
Hypokinesia	0	0	1 (0.2)	1 (0.2)	0	0
Hyporeflexia	3 (0.5)	1 (0 2)	2 (0.4)	0	0	0
Hypotonia	1 (0.2)	0	3 (0.6)	0	0	0
Incoherent	0	0	1 (0.2)	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	1 (1.7)	1 (1.7)
Intention Tremor	0	0	1 (0.2)	0	0	0
Intercostal Neuralgia	0	0	1 (0.2)	0	0	0
Intracranial Aneurysm	0	0	1 (0.2)	0	0	0
Lethargy	19 (3.1)	3 (0 5)	22 (4.1)	0	3 (5.2)	1 (1.7)
Leukoencephalopathy	2 (0.3)	1 (0 2)	0	0	0	0
Loss Of Consciousness	4 (0.7)	4 (0.7)	5 (0.9)	5 (0.9)	1 (1.7)	1 (1.7)

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All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Memory Impairment	3 (0.5)	0	3 (0.6)	0	0	0
Meningism	1 (0.2)	1 (0 2)	0	0	0	0
Mental Impairment	0	0	1 (0.2)	0	0	0
Metabolic Encephalopathy	3 (0.5)	1 (0 2)	0	0	0	0
Migraine	1 (0.2)	1 (0 2)	2 (0.4)	0	0	0
Myoclonus	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Nerve Compression	1 (0.2)	0	0	0	0	0
Nervous System Disorder	2 (0.3)	1 (0.2)	0	0	0	0
Neuralgia	1 (0.2)	0	1 (0.2)	0	0	0
Neurological Symptom	1 (0.2)	0	0	0	0	0
Neuropathy Peripheral	9 (1.5)	1 (0 2)	12 (2.2)	1 (0.2)	0	0
Neurotoxicity	0	0	2 (0.4)	1 (0.2)	0	0
Nystagmus	0	0	2 (0.4)	0	1 (1.7)	1 (1.7)
Paraesthesia	17 (2.8)	0	21 (3.9)	0	1 (1.7)	0
Paralysis	2 (0.3)	1 (0 2)	0	0	0	0
Paresis	0	0	1 (0.2)	1 (0.2)	0	0
Parosmia	1 (0.2)	0	0	0	0	0
Peripheral Sensory Neuropathy	0	0	1 (0.2)	0	1 (1.7)	0
Peroneal Nerve Palsy	2 (0.3)	1 (0.2)	1 (0.2)	0	0	0
Polyneuropathy	1 (0.2)	0	3 (0.6)	0	0	0
Poor Quality Sleep	1 (0.2)	0	1 (0.2)	0	0	0
Post Herpetic Neuralgia	2 (0.3)	2 (0 3)	3 (0.6)	1 (0.2)	0	0
Presyncope	3 (0.5)	0	0	0	2 (3.4)	0
Psychomotor Hyperactivity	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Reflexes Abnormal	1 (0.2)	0	1 (0.2)	0	0	0
Sciatica	1 (0.2)	0	2 (0.4)	0	0	0
Sedation	1 (0.2)	0	0	0	0	0
Seizure	9 (1.5)	9 (1 5)	7 (1.3)	5 (0.9)	0	0
Sensory Disturbance	1 (0.2)	0	0	0	0	0
Sensory Loss	4 (0.7)	1 (0.2)	2 (0.4)	0	0	0
Sinus Headache	3 (0.5)	0	0	0	0	0
Somnolence	17 (2.8)	2 (0 3)	12 (2.2)	3 (0.6)	0	0
Speech Disorder	1 (0.2)	0	2 (0.4)	0	0	0
Stupor	2 (0.3)	2 (0 3)	2 (0.4)	2 (0.4)	0	0
Syncope	16 (2.6)	9 (1 5)	5 (0.9)	2 (0.4)	1 (1.7)	1 (1.7)
Tension Headache	0	0	2 (0.4)	0	1 (1.7)	0
Tonic Convulsion	1 (0.2)	1 (0 2)	0	0	0	0
Toxic Neuropathy	1 (0.2)	0	0	0	0	0
Transient Ischaemic Attack	1 (0.2)	1 (0.2)	0	0	0	0
Tremor	48 (7.9)	0	44 (8.2)	2 (0.4)	2 (3.4)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Trigeminal Neuralgia	0	0	1 (0.2)	1 (0.2)	0	0
Unresponsive To Stimuli	1 (0.2)	1 (0.2)	3 (0.6)	3 (0.6)	0	0
Visual Field Defect	2 (0.3)	0	1 (0.2)	1 (0.2)	0	0
Pregnancy, Puerperium And Perinatal Conditions	**1 (0.2)**	**0**	**0**	**0**	**0**	**0**
Pregnancy	1 (0.2)	0	0	0	0	0
Product Issues	**16 (2.6)**	**0**	**14 (2.6)**	**1 (0.2)**	**0**	**0**
Device Breakage	0	0	1 (0.2)	1 (0.2)	0	0
Device Leakage	3 (0.5)	0	1 (0.2)	0	0	0
Device Occlusion	10 (1.7)	0	7 (1.3)	0	0	0
Thrombosis In Device	3 (0.5)	0	5 (0.9)	0	0	0
Psychiatric Disorders	**220 (36.4)**	**24 (4.0)**	**200 (37.1)**	**20 (3.7)**	**27 (46.6)**	**1 (1.7)**
Abnormal Behaviour	0	0	1 (0.2)	1 (0.2)	0	0
Abnormal Dreams	0	0	1 (0.2)	0	0	0
Adjustment Disorder With Depressed Mood	1 (0.2)	0	1 (0.2)	0	0	0
Affect Lability	4 (0.7)	0	2 (0.4)	0	0	0
Affective Disorder	2 (0.3)	0	0	0	0	0
Aggression	1 (0.2)	0	0	0	0	0
Agitated Depression	1 (0.2)	0	0	0	0	0
Agitation	16 (2.6)	1 (0 2)	14 (2.6)	2 (0.4)	0	0
Anger	1 (0.2)	0	2 (0.4)	0	0	0
Anxiety	53 (8.8)	1 (0 2)	56 (10.4)	4 (0.7)	9 (15.5)	0
Aversion	0	0	0	0	1 (1.7)	0
Claustrophobia	0	0	1 (0.2)	0	0	0
Confusional State	29 (4.8)	6 (1.0)	28 (5.2)	4 (0.7)	3 (5.2)	1 (1.7)
Delirium	5 (0.8)	1 (0 2)	2 (0.4)	0	0	0
Depressed Mood	5 (0.8)	0	4 (0.7)	0	1 (1.7)	0
Depression	51 (8.4)	5 (0.8)	45 (8.3)	5 (0.9)	3 (5.2)	0
Depression Suicidal	0	0	1 (0.2)	1 (0.2)	0	0
Disorientation	3 (0.5)	0	3 (0.6)	1 (0.2)	0	0
Disturbance In Social Behaviour	1 (0.2)	0	0	0	0	0
Eating Disorder	0	0	2 (0.4)	1 (0.2)	0	0
Emotional Disorder	0	0	1 (0.2)	0	0	0
Emotional Distress	1 (0.2)	0	1 (0.2)	0	0	0
Euphoric Mood	2 (0.3)	0	0	0	0	0
Fear	0	0	1 (0.2)	1 (0.2)	0	0

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All and Severe/Life Threatening
Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Feeling Of Despair	1 (0.2)	0	0	0	0	0
Flat Affect	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Frustration Tolerance Decreased	1 (0.2)	0	0	0	0	0
Generalised Anxiety Disorder	1 (0.2)	0	1 (0.2)	0	0	0
Hallucination	6 (1.0)	1 (0 2)	5 (0.9)	2 (0.4)	1 (1.7)	0
Hallucination, Visual	2 (0.3)	1 (0 2)	1 (0.2)	0	2 (3.4)	0
Hypomania	1 (0.2)	1 (0 2)	0	0	0	0
Insomnia	101 (16.7)	1 (0.2)	94 (17.4)	1 (0.2)	12 (20.7)	0
Irritability	2 (0.3)	0	2 (0.4)	0	0	0
Mania	0	0	2 (0.4)	0	0	0
Mental Disorder	0	0	1 (0.2)	0	0	0
Mental Status Changes	10 (1.7)	5 (0.8)	11 (2.0)	5 (0.9)	0	0
Mood Altered	6 (1.0)	0	3 (0.6)	1 (0.2)	0	0
Mood Swings	0	0	3 (0.6)	0	0	0
Nervousness	2 (0.3)	0	0	0	1 (1.7)	0
Nightmare	3 (0.5)	0	2 (0.4)	0	0	0
Obsessive-Compulsive Disorder	1 (0.2)	0	0	0	0	0
Paranoia	0	0	2 (0.4)	0	0	0
Phonophobia	0	0	1 (0.2)	0	0	0
Posturing	0	0	1 (0.2)	0	0	0
Psychotic Disorder	2 (0.3)	0	1 (0.2)	0	0	0
Restlessness	5 (0.8)	0	2 (0.4)	0	3 (5.2)	0
Sleep Disorder	3 (0.5)	0	4 (0.7)	0	0	0
Sleep Disorder Due To General Medical Condition, Insomnia Type	1 (0.2)	0	0	0	0	0
Stress	2 (0.3)	1 (0 2)	3 (0.6)	1 (0.2)	0	0
Substance-Induced Psychotic Disorder	0	0	1 (0.2)	0	0	0
Suicidal Ideation	2 (0.3)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Tachyphrenia	0	0	1 (0.2)	0	0	0
Tearfulness	0	0	1 (0.2)	0	0	0
Renal And Urinary Disorders	**168 (27.8)**	**43 (7.1)**	**155 (28.8)**	**43 (8.0)**	**15 (25.9)**	**1 (1.7)**
Acute Kidney Injury	14 (2.3)	9 (1 5)	12 (2.2)	8 (1.5)	2 (3.4)	1 (1.7)
Acute Prerenal Failure	1 (0.2)	0	0	0	0	0
Anuria	4 (0.7)	3 (0 5)	1 (0.2)	0	0	0
Azotaemia	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Bilirubinuria	0	0	1 (0.2)	0	0	0
Bladder Dilatation	0	0	1 (0.2)	0	0	0
Bladder Pain	2 (0.3)	0	2 (0.4)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Bladder Spasm	5 (0.8)	2 (0 3)	3 (0.6)	0	0	0
Choluria	1 (0.2)	1 (0 2)	0	0	0	0
Chromaturia	2 (0.3)	0	3 (0.6)	0	0	0
Chronic Kidney Disease	1 (0.2)	0	1 (0.2)	0	0	0
Costovertebral Angle Tenderness	1 (0.2)	0	0	0	0	0
Cystitis Haemorrhagic	11 (1.8)	3 (0 5)	11 (2.0)	3 (0.6)	0	0
Dysuria	36 (6.0)	2 (0 3)	29 (5.4)	3 (0.6)	1 (1.7)	0
Glycosuria	1 (0.2)	0	1 (0.2)	0	0	0
Haematuria	39 (6.4)	8 (1 3)	38 (7.1)	7 (1.3)	7 (12.1)	0
Hydronephrosis	2 (0.3)	2 (0 3)	0	0	1 (1.7)	0
Incontinence	1 (0.2)	0	0	0	0	0
Kidney Enlargement	0	0	1 (0.2)	0	0	0
Micturition Disorder	1 (0.2)	0	0	0	0	0
Micturition Frequency Decreased	1 (0.2)	0	0	0	0	0
Micturition Urgency	4 (0.7)	0	2 (0.4)	0	0	0
Nephrolithiasis	4 (0.7)	0	0	0	0	0
Nephropathy	0	0	1 (0.2)	0	0	0
Nocturia	3 (0.5)	0	5 (0.9)	0	0	0
Obstructive Nephropathy	0	0	1 (0.2)	1 (0.2)	0	0
Oliguria	10 (1.7)	5 (0.8)	3 (0.6)	1 (0.2)	1 (1.7)	0
Pollakiuria	17 (2.8)	0	12 (2.2)	0	0	0
Polyuria	8 (1.3)	1 (0 2)	1 (0.2)	0	0	0
Proteinuria	1 (0.2)	0	1 (0.2)	0	0	0
Renal Cyst	1 (0.2)	0	2 (0.4)	0	1 (1.7)	0
Renal Disorder	2 (0.3)	0	0	0	0	0
Renal Failure	40 (6.6)	17 (2.8)	63 (11.7)	22 (4.1)	2 (3.4)	0
Renal Haematoma	1 (0.2)	1 (0 2)	0	0	0	0
Renal Hypertension	0	0	1 (0.2)	0	0	0
Renal Impairment	12 (2.0)	3 (0 5)	16 (3.0)	3 (0.6)	1 (1.7)	0
Renal Mass	0	0	0	0	1 (1.7)	0
Renal Pain	1 (0.2)	0	0	0	0	0
Renal Tubular Necrosis	0	0	3 (0.6)	2 (0.4)	0	0
Renal Vein Thrombosis	1 (0.2)	0	0	0	0	0
Stress Urinary Incontinence	2 (0.3)	0	0	0	0	0
Tubulointerstitial Nephritis	0	0	2 (0.4)	1 (0.2)	0	0
Urethral Discharge	0	0	1 (0.2)	1 (0.2)	0	0
Urethral Haemorrhage	1 (0.2)	0	0	0	0	0
Urinary Hesitation	1 (0.2)	0	2 (0.4)	0	0	0
Urinary Incontinence	12 (2.0)	1 (0 2)	11 (2.0)	2 (0.4)	0	0
Urinary Retention	8 (1.3)	1 (0 2)	9 (1.7)	0	2 (3.4)	0

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All Randomized Subjects
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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Urine Abnormality	1 (0.2)	0	0	0	0	0
Urine Odour Abnormal	1 (0.2)	0	0	0	0	0
Urogenital Disorder	1 (0.2)	0	0	0	0	0
Reproductive System And Breast Disorders	**62 (10.2)**	**12 (2.0)**	**59 (10.9)**	**8 (1.5)**	**8 (13.8)**	**0**
Adnexa Uteri Cyst	1 (0.2)	0	0	0	0	0
Balanoposthitis	1 (0.2)	0	1 (0.2)	0	1 (1.7)	0
Bartholin's Cyst	1 (0.2)	0	0	0	0	0
Benign Prostatic Hyperplasia	2 (0.3)	0	0	0	0	0
Breast Mass	1 (0.2)	0	0	0	0	0
Breast Pain	1 (0.2)	0	1 (0.2)	0	0	0
Dysfunctional Uterine Bleeding	1 (0.2)	0	0	0	0	0
Dysmenorrhoea	2 (0.3)	0	4 (0.7)	0	0	0
Dyspareunia	1 (0.2)	0	0	0	0	0
Epididymal Disorder	1 (0.2)	0	0	0	0	0
Erectile Dysfunction	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Genital Erosion	0	0	1 (0.2)	0	0	0
Genital Erythema	0	0	2 (0.4)	0	0	0
Genital Lesion	0	0	2 (0.4)	0	0	0
Genital Swelling	0	0	1 (0.2)	0	2 (3.4)	0
Genital Ulceration	1 (0.2)	0	1 (0.2)	0	0	0
Gynaecomastia	1 (0.2)	0	0	0	0	0
Menopausal Symptoms	2 (0.3)	0	0	0	0	0
Menorrhagia	2 (0.3)	1 (0 2)	5 (0.9)	2 (0.4)	1 (1.7)	0
Menstrual Disorder	2 (0.3)	1 (0 2)	1 (0.2)	0	1 (1.7)	0
Metrorrhagia	5 (0.8)	0	6 (1.1)	0	0	0
Pelvic Discomfort	1 (0.2)	0	1 (0.2)	0	0	0
Pelvic Haematoma	1 (0.2)	0	0	0	0	0
Pelvic Pain	2 (0.3)	0	1 (0.2)	0	0	0
Penile Discharge	0	0	1 (0.2)	0	0	0
Penile Haemorrhage	1 (0.2)	0	1 (0.2)	0	0	0
Penile Necrosis	1 (0.2)	0	0	0	0	0
Penile Oedema	1 (0.2)	0	1 (0.2)	0	0	0
Penile Pain	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Perineal Pain	1 (0.2)	0	0	0	0	0
Postmenopausal Haemorrhage	1 (0.2)	0	0	0	0	0
Prostatism	1 (0.2)	0	0	0	0	0
Prostatitis	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Pruritus Genital	2 (0.3)	0	0	0	0	0

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All Randomized Subjects
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	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Scrotal Oedema	2 (0.3)	1 (0 2)	3 (0.6)	0	0	0
Scrotal Pain	0	0	1 (0.2)	0	0	0
Scrotal Swelling	1 (0.2)	0	1 (0.2)	0	0	0
Sexual Dysfunction	0	0	1 (0.2)	0	0	0
Testicular Pain	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Testicular Swelling	1 (0.2)	0	0	0	0	0
Uterine Disorder	1 (0.2)	0	0	0	0	0
Uterine Haemorrhage	0	0	1 (0.2)	1 (0.2)	0	0
Vaginal Discharge	0	0	2 (0.4)	0	1 (1.7)	0
Vaginal Dysplasia	0	0	1 (0.2)	0	0	0
Vaginal Haemorrhage	24 (4.0)	6 (1.0)	20 (3.7)	3 (0.6)	3 (5.2)	0
Vulval Oedema	1 (0.2)	1 (0 2)	0	0	0	0
Vulval Ulceration	0	0	1 (0.2)	0	0	0
Vulvovaginal Burning Sensation	2 (0.3)	0	0	0	0	0
Vulvovaginal Discomfort	1 (0.2)	0	2 (0.4)	0	0	0
Vulvovaginal Dryness	1 (0.2)	0	0	0	0	0
Vulvovaginal Pain	1 (0.2)	0	0	0	0	0
Vulvovaginal Pruritus	1 (0.2)	0	1 (0.2)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**362 (59.8)**	**101 (16.7)**	**326 (60.5)**	**108 (20.0)**	**44 (75.9)**	**14 (24.1)**
Acute Promyelocytic Leukaemia Differentiation Syndrome	1 (0.2)	0	0	0	1 (1.7)	0
Acute Pulmonary Oedema	2 (0.3)	2 (0.3)	2 (0.4)	2 (0.4)	0	0
Acute Respiratory Distress Syndrome	6 (1.0)	6 (1.0)	7 (1.3)	7 (1.3)	1 (1.7)	1 (1.7)
Acute Respiratory Failure	5 (0.8)	5 (0.8)	1 (0.2)	1 (0.2)	0	0
Apnoea	2 (0.3)	2 (0 3)	0	0	0	0
Asthma	4 (0.7)	0	1 (0.2)	1 (0.2)	0	0
Atelectasis	25 (4.1)	2 (0 3)	12 (2.2)	2 (0.4)	3 (5.2)	0
Bronchial Hyperreactivity	0	0	1 (0.2)	1 (0.2)	0	0
Bronchial Obstruction	0	0	2 (0.4)	2 (0.4)	0	0
Bronchial Wall Thickening	1 (0.2)	0	0	0	0	0
Bronchitis Chronic	0	0	1 (0.2)	0	0	0
Bronchopneumopathy	1 (0.2)	1 (0 2)	0	0	0	0
Bronchospasm	9 (1.5)	0	9 (1.7)	2 (0.4)	0	0
Chronic Obstructive Pulmonary Disease	3 (0.5)	0	2 (0.4)	1 (0.2)	0	0
Cough	156 (25.8)	3 (0 5)	138 (25.6)	3 (0.6)	16 (27.6)	0
Diaphragmalgia	1 (0.2)	0	0	0	0	0
Diaphragmatic Disorder	0	0	1 (0.2)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Diffuse Alveolar Damage	0	0	1 (0.2)	1 (0.2)	0	0
Dry Throat	1 (0.2)	0	2 (0.4)	0	0	0
Dysphonia	6 (1.0)	0	8 (1.5)	0	0	0
Dyspnoea	101 (16.7)	31 (5.1)	106 (19.7)	29 (5.4)	13 (22.4)	4 (6.9)
Dyspnoea Exertional	23 (3.8)	0	18 (3.3)	0	1 (1.7)	0
Dyspnoea Paroxysmal Nocturnal	0	0	1 (0.2)	0	0	0
Emphysema	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Epiglottis Ulcer	1 (0.2)	1 (0 2)	0	0	0	0
Epistaxis	80 (13.2)	9 (1 5)	72 (13.4)	5 (0.9)	12 (20.7)	0
Haemoptysis	22 (3.6)	4 (0.7)	20 (3.7)	3 (0.6)	3 (5.2)	0
Haemothorax	0	0	2 (0.4)	2 (0.4)	0	0
Hiccups	12 (2.0)	0	7 (1.3)	0	1 (1.7)	0
Hydrothorax	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Hypercapnia	1 (0.2)	1 (0 2)	0	0	0	0
Hyperventilation	3 (0.5)	0	0	0	0	0
Hypocapnia	1 (0.2)	0	0	0	0	0
Hypoxia	22 (3.6)	9 (1 5)	34 (6.3)	20 (3.7)	7 (12.1)	7 (12.1)
Increased Bronchial Secretion	4 (0.7)	0	1 (0.2)	0	0	0
Increased Upper Airway Secretion	2 (0.3)	0	4 (0.7)	0	0	0
Increased Viscosity Of Bronchial Secretion	3 (0.5)	0	3 (0.6)	0	0	0
Interstitial Lung Disease	4 (0.7)	4 (0.7)	2 (0.4)	1 (0.2)	0	0
Laryngeal Infiltration	0	0	1 (0.2)	0	0	0
Laryngeal Oedema	1 (0.2)	0	0	0	1 (1.7)	1 (1.7)
Lung Consolidation	2 (0.3)	0	2 (0.4)	1 (0.2)	2 (3.4)	1 (1.7)
Lung Disorder	4 (0.7)	2 (0 3)	1 (0.2)	1 (0.2)	1 (1.7)	0
Lung Infiltration	21 (3.5)	4 (0.7)	23 (4.3)	7 (1.3)	0	0
Nasal Congestion	25 (4.1)	1 (0 2)	21 (3.9)	0	2 (3.4)	0
Nasal Discomfort	3 (0.5)	0	1 (0.2)	0	0	0
Nasal Dryness	1 (0.2)	0	4 (0.7)	0	0	0
Nasal Inflammation	0	0	1 (0.2)	0	0	0
Nasal Necrosis	0	0	1 (0.2)	1 (0.2)	0	0
Nasal Obstruction	2 (0.3)	0	1 (0.2)	0	0	0
Nasal Septum Disorder	1 (0.2)	0	0	0	0	0
Nasal Ulcer	0	0	1 (0.2)	0	0	0
Nocturnal Dyspnoea	1 (0.2)	0	0	0	0	0
Obliterative Bronchiolitis	0	0	2 (0.4)	1 (0.2)	0	0
Obstructive Airways Disorder	0	0	1 (0.2)	0	0	0
Organising Pneumonia	2 (0.3)	2 (0 3)	0	0	0	0
Oropharyngeal Pain	64 (10.6)	0	54 (10.0)	4 (0.7)	11 (19.0)	0

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All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Oropharyngeal Swelling	1 (0.2)	0	0	0	0	0
Orthopnoea	1 (0.2)	0	3 (0.6)	0	0	0
Painful Respiration	2 (0.3)	0	0	0	0	0
Paranasal Sinus Discomfort	3 (0.5)	0	0	0	0	0
Paranasal Sinus Hypersecretion	1 (0.2)	0	0	0	0	0
Pharyngeal Erythema	5 (0.8)	0	2 (0.4)	0	1 (1.7)	0
Pharyngeal Lesion	1 (0.2)	0	0	0	0	0
Pharyngeal Ulceration	0	0	1 (0.2)	0	1 (1.7)	0
Pleural Effusion	47 (7.8)	6 (1.0)	39 (7.2)	6 (1.1)	4 (6.9)	0
Pleural Rub	0	0	1 (0.2)	0	0	0
Pleurisy	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Pleuritic Pain	6 (1.0)	2 (0 3)	7 (1.3)	1 (0.2)	0	0
Pneumomediastinum	0	0	1 (0.2)	0	0	0
Pneumonia Aspiration	3 (0.5)	3 (0 5)	3 (0.6)	3 (0.6)	0	0
Pneumonitis	7 (1.2)	4 (0.7)	4 (0.7)	1 (0.2)	0	0
Pneumothorax	5 (0.8)	3 (0 5)	5 (0.9)	2 (0.4)	1 (1.7)	0
Productive Cough	30 (5.0)	1 (0 2)	33 (6.1)	4 (0.7)	2 (3.4)	0
Prolonged Expiration	1 (0.2)	0	0	0	0	0
Pulmonary Alveolar Haemorrhage	3 (0.5)	3 (0.5)	2 (0.4)	1 (0.2)	1 (1.7)	1 (1.7)
Pulmonary Congestion	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Pulmonary Embolism	7 (1.2)	3 (0 5)	2 (0.4)	2 (0.4)	0	0
Pulmonary Fibrosis	0	0	1 (0.2)	1 (0.2)	0	0
Pulmonary Haemorrhage	7 (1.2)	6 (1.0)	6 (1.1)	4 (0.7)	0	0
Pulmonary Haemosiderosis	0	0	1 (0.2)	1 (0.2)	0	0
Pulmonary Hypertension	3 (0.5)	2 (0 3)	1 (0.2)	0	0	0
Pulmonary Mass	8 (1.3)	3 (0 5)	8 (1.5)	4 (0.7)	0	0
Pulmonary Oedema	16 (2.6)	8 (1.3)	19 (3.5)	9 (1.7)	3 (5.2)	1 (1.7)
Rales	35 (5.8)	1 (0 2)	30 (5.6)	0	5 (8.6)	0
Respiratory Acidosis	2 (0.3)	1 (0 2)	2 (0.4)	1 (0.2)	0	0
Respiratory Alkalosis	0	0	2 (0.4)	0	0	0
Respiratory Arrest	1 (0.2)	1 (0 2)	0	0	0	0
Respiratory Disorder	2 (0.3)	1 (0 2)	1 (0.2)	1 (0.2)	1 (1.7)	1 (1.7)
Respiratory Distress	10 (1.7)	9 (1.5)	7 (1.3)	5 (0.9)	2 (3.4)	2 (3.4)
Respiratory Failure	25 (4.1)	24 (4.0)	37 (6.9)	37 (6.9)	2 (3.4)	2 (3.4)
Respiratory Tract Congestion	4 (0.7)	0	1 (0.2)	0	1 (1.7)	0
Respiratory Tract Haemorrhage	1 (0.2)	1 (0.2)	0	0	0	0
Restrictive Pulmonary Disease	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Rhinalgia	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Rhinitis Allergic	0	0	1 (0.2)	0	0	0
Rhinorrhoea	30 (5.0)	0	22 (4.1)	0	4 (6.9)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Rhonchi	7 (1.2)	0	10 (1.9)	0	0	0
Sinus Congestion	17 (2.8)	0	14 (2.6)	1 (0.2)	0	0
Sinus Disorder	1 (0.2)	1 (0 2)	2 (0.4)	0	0	0
Sinus Pain	4 (0.7)	0	10 (1.9)	0	0	0
Sinus Polyp	2 (0.3)	0	0	0	0	0
Sleep Apnoea Syndrome	0	0	1 (0.2)	0	0	0
Sneezing	2 (0.3)	0	3 (0.6)	0	1 (1.7)	0
Sputum Discoloured	3 (0.5)	0	1 (0.2)	0	0	0
Sputum Increased	1 (0.2)	0	1 (0.2)	0	0	0
Tachypnoea	18 (3.0)	7 (1 2)	15 (2.8)	5 (0.9)	5 (8.6)	0
Throat Irritation	1 (0.2)	0	1 (0.2)	0	0	0
Throat Lesion	1 (0.2)	0	0	0	0	0
Throat Tightness	1 (0.2)	0	1 (0.2)	0	0	0
Tonsillar Disorder	1 (0.2)	1 (0 2)	0	0	0	0
Tonsillar Ulcer	1 (0.2)	0	0	0	0	0
Upper-Airway Cough Syndrome	9 (1.5)	0	4 (0.7)	0	0	0
Vocal Cord Inflammation	1 (0.2)	0	0	0	0	0
Wheezing	19 (3.1)	0	23 (4.3)	1 (0.2)	6 (10.3)	0
Skin And Subcutaneous Tissue Disorders	**308 (50.9)**	**26 (4.3)**	**267 (49.5)**	**17 (3.2)**	**42 (72.4)**	**3 (5.2)**
Acne	2 (0.3)	0	8 (1.5)	0	0	0
Actinic Cheilitis	1 (0.2)	0	0	0	0	0
Acute Febrile Neutrophilic Dermatosis	0	0	1 (0.2)	0	1 (1.7)	0
Alopecia	31 (5.1)	1 (0 2)	24 (4.5)	2 (0.4)	3 (5.2)	0
Alopecia Totalis	1 (0.2)	1 (0 2)	0	0	0	0
Angioedema	1 (0.2)	0	1 (0.2)	0	0	0
Blister	10 (1.7)	2 (0 3)	5 (0.9)	1 (0.2)	0	0
Blood Blister	5 (0.8)	0	2 (0.4)	0	2 (3.4)	0
Cold Sweat	2 (0.3)	1 (0 2)	0	0	0	0
Cutaneous Vasculitis	1 (0.2)	0	0	0	0	0
Decubitus Ulcer	5 (0.8)	0	8 (1.5)	1 (0.2)	0	0
Dermal Cyst	0	0	1 (0.2)	0	0	0
Dermatitis	7 (1.2)	0	5 (0.9)	0	1 (1.7)	0
Dermatitis Acneiform	1 (0.2)	0	0	0	0	0
Dermatitis Allergic	12 (2.0)	0	6 (1.1)	0	0	0
Dermatitis Bullous	0	0	2 (0.4)	0	0	0
Dermatitis Contact	2 (0.3)	0	0	0	1 (1.7)	0
Dermatitis Exfoliative	0	0	1 (0.2)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Drug Eruption	5 (0.8)	0	7 (1.3)	0	2 (3.4)	0
Dry Skin	16 (2.6)	1 (0 2)	13 (2.4)	1 (0.2)	1 (1.7)	0
Ecchymosis	8 (1.3)	0	17 (3.2)	0	3 (5.2)	0
Eczema	4 (0.7)	0	0	0	0	0
Erythema	41 (6.8)	2 (0 3)	32 (5.9)	0	5 (8.6)	0
Erythema Multiforme	0	0	1 (0.2)	0	0	0
Erythema Nodosum	0	0	0	0	1 (1.7)	0
Erythrosis	1 (0.2)	0	0	0	0	0
Exfoliative Rash	0	0	1 (0.2)	1 (0.2)	0	0
Generalised Erythema	1 (0.2)	0	0	0	0	0
Hangnail	1 (0.2)	0	1 (0.2)	0	0	0
Hidradenitis	3 (0.5)	0	0	0	0	0
Hirsutism	2 (0.3)	0	0	0	0	0
Hyperhidrosis	20 (3.3)	0	19 (3.5)	0	3 (5.2)	0
Hypersensitivity Vasculitis	2 (0.3)	1 (0 2)	0	0	0	0
Hypertrichosis	2 (0.3)	0	1 (0.2)	0	0	0
Ingrowing Nail	4 (0.7)	0	1 (0.2)	0	0	0
Leukoplakia	1 (0.2)	0	1 (0.2)	0	0	0
Lichenification	2 (0.3)	0	3 (0.6)	0	0	0
Lichenoid Keratosis	0	0	1 (0.2)	0	0	0
Lipohypertrophy	0	0	1 (0.2)	0	0	0
Livedo Reticularis	0	0	1 (0.2)	0	0	0
Macule	1 (0.2)	0	1 (0.2)	0	0	0
Madarosis	0	0	1 (0.2)	0	0	0
Nail Disorder	1 (0.2)	0	0	0	0	0
Neurodermatitis	1 (0.2)	0	0	0	0	0
Night Sweats	18 (3.0)	2 (0 3)	10 (1.9)	0	1 (1.7)	0
Onychoclasis	1 (0.2)	0	0	0	0	0
Onychomadesis	1 (0.2)	0	1 (0.2)	0	0	0
Pain Of Skin	4 (0.7)	0	6 (1.1)	0	0	0
Palmar Erythema	2 (0.3)	0	2 (0.4)	0	1 (1.7)	0
Palmar-Plantar Erythrodysaesthesia Syndrome	4 (0.7)	1 (0.2)	1 (0.2)	0	0	0
Papule	2 (0.3)	0	3 (0.6)	0	3 (5.2)	0
Penile Ulceration	0	0	1 (0.2)	0	0	0
Petechiae	59 (9.8)	2 (0 3)	52 (9.6)	2 (0.4)	9 (15.5)	0
Photosensitivity Reaction	1 (0.2)	0	2 (0.4)	0	0	0
Pigmentation Disorder	2 (0.3)	0	4 (0.7)	0	0	0
Prurigo	1 (0.2)	0	0	0	0	0
Pruritus	60 (9.9)	2 (0 3)	56 (10.4)	2 (0.4)	9 (15.5)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Pruritus Allergic	0	0	2 (0.4)	0	0	0
Pruritus Generalised	6 (1.0)	0	3 (0.6)	0	1 (1.7)	0
Psoriasis	0	0	1 (0.2)	0	0	0
Purpura	10 (1.7)	0	5 (0.9)	0	2 (3.4)	0
Purpura Senile	1 (0.2)	0	0	0	0	0
Rash	100 (16.5)	5 (0.8)	88 (16.3)	3 (0.6)	23 (39.7)	1 (1.7)
Rash Erythematous	8 (1.3)	1 (0 2)	6 (1.1)	0	1 (1.7)	0
Rash Follicular	2 (0.3)	0	3 (0.6)	0	0	0
Rash Generalised	5 (0.8)	0	5 (0.9)	0	2 (3.4)	2 (3.4)
Rash Macular	5 (0.8)	0	2 (0.4)	0	2 (3.4)	0
Rash Maculo-Papular	14 (2.3)	3 (0 5)	7 (1.3)	0	1 (1.7)	0
Rash Papular	4 (0.7)	0	4 (0.7)	0	0	0
Rash Pruritic	7 (1.2)	0	12 (2.2)	3 (0.6)	0	0
Rash Vesicular	1 (0.2)	0	1 (0.2)	0	0	0
Red Man Syndrome	1 (0.2)	0	0	0	0	0
Rosacea	1 (0.2)	0	0	0	0	0
Scab	2 (0.3)	0	2 (0.4)	0	0	0
Skin Burning Sensation	1 (0.2)	0	1 (0.2)	0	0	0
Skin Discolouration	2 (0.3)	0	2 (0.4)	0	0	0
Skin Disorder	7 (1.2)	1 (0 2)	9 (1.7)	1 (0.2)	1 (1.7)	0
Skin Dystrophy	0	0	1 (0.2)	0	0	0
Skin Exfoliation	8 (1.3)	0	9 (1.7)	1 (0.2)	1 (1.7)	0
Skin Fissures	0	0	1 (0.2)	0	0	0
Skin Haemorrhage	1 (0.2)	0	0	0	0	0
Skin Hyperpigmentation	7 (1.2)	0	4 (0.7)	0	0	0
Skin Hypopigmentation	1 (0.2)	1 (0 2)	0	0	0	0
Skin Irritation	0	0	1 (0.2)	0	0	0
Skin Lesion	20 (3.3)	0	14 (2.6)	2 (0.4)	3 (5.2)	0
Skin Mass	5 (0.8)	0	0	0	0	0
Skin Necrosis	0	0	1 (0.2)	0	0	0
Skin Oedema	1 (0.2)	1 (0 2)	0	0	0	0
Skin Striae	1 (0.2)	0	3 (0.6)	0	0	0
Skin Ulcer	5 (0.8)	0	2 (0.4)	1 (0.2)	0	0
Subcutaneous Emphysema	1 (0.2)	1 (0.2)	0	0	0	0
Swelling Face	7 (1.2)	0	1 (0.2)	0	1 (1.7)	0
Transient Acantholytic Dermatosis	1 (0.2)	0	0	0	0	0
Urticaria	13 (2.1)	0	10 (1.9)	0	1 (1.7)	0
Vascular Skin Disorder	1 (0.2)	0	0	0	0	0
Vitiligo	0	0	1 (0.2)	0	0	0
Xanthomatosis	0	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Social Circumstances	**2 (0.3)**	**1 (0.2)**	**2 (0.4)**	**0**	**0**	**0**
Loss Of Personal Independence In Daily Activities	0	0	1 (0.2)	0	0	0
Menopause	1 (0.2)	0	0	0	0	0
Social Problem	1 (0.2)	1 (0 2)	0	0	0	0
Treatment Noncompliance	0	0	1 (0.2)	0	0	0
Surgical And Medical Procedures	**17 (2.8)**	**3 (0.5)**	**16 (3.0)**	**1 (0.2)**	**3 (5.2)**	**1 (1.7)**
Abscess Drainage	0	0	1 (0.2)	0	0	0
Analgesic Therapy	0	0	1 (0.2)	0	0	0
Artificial Crown Procedure	0	0	1 (0.2)	0	0	0
Astringent Therapy	1 (0.2)	0	0	0	2 (3.4)	0
Blood Stem Cell Harvest	1 (0.2)	0	0	0	0	0
Bone Marrow Transplant	2 (0.3)	2 (0 3)	0	0	0	0
Central Venous Catheter Removal	0	0	1 (0.2)	0	0	0
Central Venous Catheterisation	0	0	1 (0.2)	0	0	0
Chemotherapy	0	0	2 (0.4)	1 (0.2)	0	0
Fluid Replacement	1 (0.2)	0	1 (0.2)	0	0	0
Incisional Drainage	0	0	1 (0.2)	0	0	0
Mitral Valve Replacement	1 (0.2)	0	0	0	0	0
Oesophageal Dilation Procedure	1 (0.2)	0	0	0	0	0
Oxygen Therapy	0	0	1 (0.2)	0	0	0
Parenteral Nutrition	1 (0.2)	0	0	0	0	0
Prophylaxis	0	0	1 (0.2)	0	0	0
Sinus Operation	5 (0.8)	0	3 (0.6)	0	0	0
Stem Cell Transplant	1 (0.2)	1 (0 2)	0	0	0	0
Surgery	0	0	0	0	1 (1.7)	1 (1.7)
Therapeutic Procedure	1 (0.2)	0	0	0	0	0
Tooth Extraction	1 (0.2)	0	1 (0.2)	0	0	0
Wisdom Teeth Removal	1 (0.2)	0	1 (0.2)	0	0	0
Vascular Disorders	**231 (38.2)**	**59 (9.8)**	**216 (40.1)**	**69 (12.8)**	**24 (41.4)**	**7 (12.1)**
Air Embolism	1 (0.2)	0	0	0	0	0
Angiodysplasia	0	0	0	0	1 (1.7)	0
Arteriovenous Fistula	1 (0.2)	0	0	0	0	0
Capillary Leak Syndrome	1 (0.2)	0	0	0	0	0
Circulatory Collapse	2 (0.3)	1 (0 2)	6 (1.1)	4 (0.7)	0	0
Deep Vein Thrombosis	7 (1.2)	2 (0.3)	8 (1.5)	2 (0.4)	1 (1.7)	1 (1.7)
Diastolic Hypertension	0	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Embolism Arterial	0	0	1 (0.2)	1 (0.2)	0	0
Flushing	5 (0.8)	0	10 (1.9)	0	3 (5.2)	0
Haematoma	16 (2.6)	0	16 (3.0)	0	5 (8.6)	0
Haemodynamic Instability	2 (0.3)	2 (0 3)	1 (0.2)	1 (0.2)	0	0
Haemorrhage	6 (1.0)	2 (0 3)	5 (0.9)	3 (0.6)	0	0
Haemorrhagic Infarction	0	0	1 (0.2)	1 (0.2)	0	0
Hot Flush	1 (0.2)	0	2 (0.4)	0	0	0
Hyperaemia	1 (0.2)	0	0	0	0	0
Hypertension	110 (18.2)	11 (1.8)	95 (17.6)	16 (3.0)	5 (8.6)	2 (3.4)
Hypertensive Crisis	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Hypotension	84 (13.9)	38 (6.3)	79 (14.7)	40 (7.4)	11 (19.0)	5 (8.6)
Hypovolaemic Shock	2 (0.3)	2 (0 3)	4 (0.7)	3 (0.6)	0	0
Intermittent Claudication	1 (0.2)	0	0	0	0	0
Ischaemia	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Jugular Vein Thrombosis	0	0	1 (0.2)	0	0	0
Labile Hypertension	0	0	1 (0.2)	0	0	0
Microangiopathy	1 (0.2)	1 (0 2)	0	0	0	0
Orthostatic Hypotension	16 (2.6)	2 (0 3)	7 (1.3)	0	1 (1.7)	0
Pallor	7 (1.2)	1 (0 2)	3 (0.6)	0	1 (1.7)	0
Peripheral Circulatory Failure	1 (0.2)	1 (0 2)	0	0	0	0
Peripheral Coldness	0	0	1 (0.2)	0	0	0
Peripheral Vascular Disorder	1 (0.2)	1 (0.2)	0	0	0	0
Peripheral Venous Disease	1 (0.2)	0	0	0	0	0
Phlebitis	7 (1.2)	0	8 (1.5)	0	1 (1.7)	0
Poor Peripheral Circulation	0	0	2 (0.4)	0	0	0
Postpartum Venous Thrombosis	1 (0.2)	0	0	0	0	0
Reperfusion Injury	0	0	1 (0.2)	0	0	0
Secondary Hypertension	0	0	1 (0.2)	0	0	0
Shock	0	0	4 (0.7)	4 (0.7)	0	0
Subclavian Vein Thrombosis	2 (0.3)	1 (0.2)	0	0	0	0
Superior Vena Cava Stenosis	0	0	1 (0.2)	0	0	0
Thrombophlebitis	5 (0.8)	0	6 (1.1)	0	0	0
Thrombophlebitis Superficial	0	0	1 (0.2)	0	1 (1.7)	0
Thrombosis	1 (0.2)	0	2 (0.4)	0	0	0
Varicose Vein	1 (0.2)	0	0	0	0	0
Vasculitis	1 (0.2)	0	0	0	1 (1.7)	0
Vasodilatation	0	0	1 (0.2)	1 (0.2)	1 (1.7)	0
Vein Disorder	1 (0.2)	0	0	0	0	0
Vena Cava Embolism	0	0	1 (0.2)	1 (0.2)	0	0
Venous Thrombosis	3 (0.5)	0	6 (1.1)	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Venous Thrombosis Limb	1 (0.2)	0	1 (0.2)	0	0	0

Every subject is counted a single time for each applicable row and column.
LT = life-threatening.
MedDRA Version 20.1

付録 2.7.4-20 副作用及び重度／生命を脅かす副作用の発現例数（%）
（いずれかの投与群で発現割合 0%超）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）
Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Subjects Reporting Any Adverse Event	**209 (34.5)**	**81 (13.4)**	**186 (34.5)**	**53 (9.8)**	**30 (51.7)**	**6 (10.3)**
Blood And Lymphatic System Disorders	**13 (2.1)**	**7 (1.2)**	**9 (1.7)**	**7 (1.3)**	**0**	**0**
Anaemia	5 (0.8)	4 (0.7)	2 (0.4)	1 (0.2)	0	0
Bone Marrow Failure	1 (0.2)	1 (0.2)	0	0	0	0
Coagulopathy	0	0	2 (0.4)	1 (0.2)	0	0
Eosinophilia	1 (0.2)	0	0	0	0	0
Febrile Neutropenia	1 (0.2)	0	0	0	0	0
Haemolytic Uraemic Syndrome	1 (0.2)	1 (0 2)	0	0	0	0
Leukopenia	2 (0.3)	1 (0 2)	0	0	0	0
Neutropenia	2 (0.3)	2 (0 3)	2 (0.4)	1 (0.2)	0	0
Pancytopenia	0	0	1 (0.2)	1 (0.2)	0	0
Splenomegaly	1 (0.2)	0	0	0	0	0
Thrombocytopenia	4 (0.7)	1 (0 2)	3 (0.6)	3 (0.6)	0	0
Thrombotic Thrombocytopenic Purpura	1 (0.2)	1 (0.2)	0	0	0	0
Cardiac Disorders	**13 (2.1)**	**4 (0.7)**	**6 (1.1)**	**1 (0.2)**	**2 (3.4)**	**0**
Angina Pectoris	0	0	1 (0.2)	0	0	0
Atrial Fibrillation	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	0	0
Bradycardia	1 (0.2)	1 (0 2)	0	0	1 (1.7)	0
Bundle Branch Block Left	2 (0.3)	0	0	0	0	0
Bundle Branch Block Right	0	0	1 (0.2)	0	0	0
Cardiomegaly	1 (0.2)	0	0	0	0	0
Extrasystoles	1 (0.2)	0	0	0	0	0
Left Ventricular Hypertrophy	1 (0.2)	0	0	0	0	0
Palpitations	1 (0.2)	0	0	0	0	0
Sinus Arrhythmia	1 (0.2)	0	0	0	0	0
Sinus Bradycardia	0	0	0	0	1 (1.7)	0
Sinus Tachycardia	0	0	1 (0.2)	0	0	0
Supraventricular Extrasystoles	1 (0.2)	0	1 (0.2)	0	0	0
Tachycardia	3 (0.5)	0	1 (0.2)	0	0	0
Torsade De Pointes	1 (0.2)	1 (0 2)	0	0	0	0
Ventricular Extrasystoles	2 (0.3)	0	0	0	0	0
Ear And Labyrinth Disorders	**1 (0.2)**	**0**	**2 (0.4)**	**0**	**0**	**0**
Deafness	0	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Ear Pain	1 (0.2)	0	0	0	0	0
Vertigo	0	0	1 (0.2)	0	0	0
Eye Disorders	**7 (1.2)**	**0**	**9 (1.7)**	**1 (0.2)**	**0**	**0**
Diplopia	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Dry Eye	2 (0.3)	0	2 (0.4)	0	0	0
Iridocyclitis	0	0	1 (0.2)	0	0	0
Lacrimation Increased	0	0	1 (0.2)	0	0	0
Photophobia	1 (0.2)	0	0	0	0	0
Photopsia	0	0	1 (0.2)	0	0	0
Retinal Haemorrhage	0	0	1 (0.2)	0	0	0
Vision Blurred	3 (0.5)	0	6 (1.1)	0	0	0
Gastrointestinal Disorders	**100 (16.5)**	**14 (2.3)**	**95 (17.6)**	**10 (1.9)**	**19 (32.8)**	**2 (3.4)**
Abdominal Discomfort	2 (0.3)	0	0	0	0	0
Abdominal Distension	4 (0.7)	1 (0 2)	2 (0.4)	0	0	0
Abdominal Pain	6 (1.0)	0	11 (2.0)	1 (0.2)	0	0
Abdominal Pain Upper	6 (1.0)	1 (0 2)	3 (0.6)	0	1 (1.7)	0
Abdominal Rigidity	0	0	2 (0.4)	1 (0.2)	0	0
Anal Incontinence	0	0	1 (0.2)	0	0	0
Aphthous Ulcer	1 (0.2)	0	0	0	1 (1.7)	0
Aptyalism	2 (0.3)	0	0	0	0	0
Ascites	1 (0.2)	0	0	0	0	0
Constipation	4 (0.7)	0	12 (2.2)	0	0	0
Diarrhoea	27 (4.5)	3 (0 5)	27 (5.0)	1 (0.2)	9 (15.5)	0
Diarrhoea Haemorrhagic	1 (0.2)	1 (0 2)	0	0	0	0
Dry Mouth	2 (0.3)	0	1 (0.2)	0	1 (1.7)	0
Duodenitis	0	0	1 (0.2)	0	0	0
Dyspepsia	7 (1.2)	1 (0 2)	9 (1.7)	0	0	0
Dysphagia	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Epigastric Discomfort	1 (0.2)	0	0	0	0	0
Flatulence	3 (0.5)	0	1 (0.2)	0	0	0
Gastric Disorder	0	0	0	0	1 (1.7)	0
Gastritis	2 (0.3)	0	3 (0.6)	2 (0.4)	0	0
Gastritis Haemorrhagic	1 (0.2)	1 (0 2)	0	0	0	0
Gastrointestinal Haemorrhage	0	0	1 (0.2)	1 (0.2)	0	0
Gastrointestinal Hypomotility	1 (0.2)	0	0	0	0	0
Gastrooesophageal Reflux Disease	3 (0.5)	0	0	0	0	0
Hypoaesthesia Oral	1 (0.2)	0	0	0	0	0
Ileus	0	0	1 (0.2)	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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All and Severe/Life Threatening
Number (%) of Subjects

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Intestinal Ulcer	0	0	1 (0.2)	1 (0.2)	0	0
Lip Dry	0	0	2 (0.4)	0	0	0
Lip Ulceration	0	0	1 (0.2)	0	0	0
Melaena	1 (0.2)	1 (0 2)	0	0	0	0
Mouth Ulceration	2 (0.3)	0	0	0	0	0
Nausea	46 (7.6)	5 (0.8)	46 (8.5)	1 (0.2)	10 (17.2)	2 (3.4)
Oesophageal Ulcer	1 (0.2)	0	0	0	0	0
Oesophagitis	2 (0.3)	0	0	0	0	0
Oral Mucosal Erythema	0	0	1 (0.2)	0	0	0
Oral Pain	0	0	1 (0.2)	0	0	0
Proctalgia	0	0	0	0	1 (1.7)	0
Tongue Coated	1 (0.2)	0	0	0	0	0
Tongue Discolouration	1 (0.2)	0	0	0	0	0
Tongue Discomfort	1 (0.2)	0	0	0	0	0
Tongue Ulceration	0	0	1 (0.2)	0	0	0
Tooth Discolouration	1 (0.2)	0	0	0	0	0
Trichoglossia	1 (0.2)	0	0	0	0	0
Vomiting	29 (4.8)	4 (0.7)	29 (5.4)	3 (0.6)	6 (10.3)	0
General Disorders And Administration Site Conditions	**28 (4.6)**	**6 (1.0)**	**15 (2.8)**	**3 (0.6)**	**0**	**0**
Asthenia	4 (0.7)	1 (0 2)	3 (0.6)	1 (0.2)	0	0
Chest Pain	1 (0.2)	0	0	0	0	0
Chills	0	0	1 (0.2)	0	0	0
Drug Interaction	2 (0.3)	2 (0 3)	1 (0.2)	1 (0.2)	0	0
Early Satiety	0	0	1 (0.2)	0	0	0
Fatigue	9 (1.5)	1 (0 2)	7 (1.3)	1 (0.2)	0	0
Feeling Cold	0	0	1 (0.2)	0	0	0
Generalised Oedema	1 (0.2)	0	0	0	0	0
Influenza Like Illness	1 (0.2)	0	0	0	0	0
Mucosal Inflammation	8 (1.3)	2 (0 3)	0	0	0	0
Oedema	1 (0.2)	0	1 (0.2)	0	0	0
Oedema Peripheral	0	0	3 (0.6)	0	0	0
Pain	1 (0.2)	0	0	0	0	0
Pyrexia	2 (0.3)	0	3 (0.6)	0	0	0
Thirst	1 (0.2)	0	0	0	0	0
Hepatobiliary Disorders	**23 (3.8)**	**16 (2.6)**	**11 (2.0)**	**6 (1.1)**	**2 (3.4)**	**1 (1.7)**
Cholelithiasis	1 (0.2)	0	1 (0.2)	0	0	0
Cholestasis	1 (0.2)	1 (0 2)	0	0	0	0

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All Randomized Subjects
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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Hepatic Failure	1 (0.2)	1 (0 2)	1 (0.2)	1 (0.2)	0	0
Hepatic Function Abnormal	0	0	1 (0.2)	0	0	0
Hepatitis	1 (0.2)	0	0	0	0	0
Hepatitis Acute	1 (0.2)	1 (0 2)	0	0	0	0
Hepatocellular Injury	3 (0.5)	3 (0 5)	0	0	0	0
Hepatosplenomegaly	1 (0.2)	0	0	0	0	0
Hepatotoxicity	2 (0.3)	2 (0 3)	0	0	0	0
Hyperbilirubinaemia	9 (1.5)	7 (1 2)	7 (1.3)	4 (0.7)	2 (3.4)	1 (1.7)
Hypertransaminasaemia	1 (0.2)	0	1 (0.2)	0	0	0
Jaundice	5 (0.8)	2 (0 3)	2 (0.4)	0	0	0
Liver Disorder	0	0	1 (0.2)	1 (0.2)	0	0
Immune System Disorders	**5 (0.8)**	**2 (0.3)**	**2 (0.4)**	**0**	**0**	**0**
Drug Hypersensitivity	1 (0.2)	0	0	0	0	0
Graft Versus Host Disease	2 (0.3)	2 (0.3)	0	0	0	0
Hypersensitivity	1 (0.2)	0	2 (0.4)	0	0	0
Sarcoidosis	1 (0.2)	0	0	0	0	0
Infections And Infestations	**5 (0.8)**	**2 (0.3)**	**5 (0.9)**	**3 (0.6)**	**1 (1.7)**	**0**
Candida Infection	0	0	1 (0.2)	1 (0.2)	0	0
Cavernous Sinus Thrombosis	0	0	1 (0.2)	1 (0.2)	0	0
Conjunctivitis	0	0	1 (0.2)	1 (0.2)	0	0
Device Related Sepsis	1 (0.2)	1 (0.2)	0	0	0	0
Encephalitis	1 (0.2)	1 (0 2)	0	0	0	0
Gingivitis	1 (0.2)	0	0	0	0	0
Infectious Disease Carrier	0	0	1 (0.2)	0	0	0
Periorbital Cellulitis	0	0	0	0	1 (1.7)	0
Pseudomonas Infection	1 (0.2)	0	0	0	0	0
Rhinitis	0	0	1 (0.2)	0	0	0
Upper Respiratory Tract Infection	1 (0.2)	0	0	0	0	0
Injury, Poisoning And Procedural Complications	**4 (0.7)**	**3 (0.5)**	**3 (0.6)**	**1 (0.2)**	**0**	**0**
Accidental Overdose	0	0	1 (0.2)	1 (0.2)	0	0
Fall	1 (0.2)	1 (0 2)	1 (0.2)	0	0	0
Toxicity To Various Agents	3 (0.5)	2 (0.3)	1 (0.2)	0	0	0
Investigations	**73 (12.1)**	**37 (6.1)**	**51 (9.5)**	**19 (3.5)**	**8 (13.8)**	**2 (3.4)**
Alanine Aminotransferase Abnormal	0	0	1 (0.2)	1 (0.2)	0	0
Alanine Aminotransferase Increased	16 (2.6)	7 (1.2)	6 (1.1)	6 (1.1)	1 (1.7)	1 (1.7)

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All Randomized Subjects
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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Aspartate Aminotransferase Abnormal	1 (0.2)	0	1 (0.2)	0	0	0
Aspartate Aminotransferase Increased	13 (2.1)	2 (0.3)	6 (1.1)	3 (0.6)	1 (1.7)	0
Bilirubin Conjugated Increased	1 (0.2)	1 (0.2)	0	0	0	0
Blood Alkaline Phosphatase Increased	6 (1.0)	2 (0.3)	6 (1.1)	0	1 (1.7)	0
Blood Bilirubin Increased	7 (1.2)	4 (0.7)	3 (0.6)	2 (0.4)	1 (1.7)	1 (1.7)
Blood Creatinine Increased	6 (1.0)	1 (0 2)	5 (0.9)	0	0	0
Blood Glucose Increased	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Blood Lactate Dehydrogenase Increased	5 (0.8)	0	0	0	0	0
Blood Magnesium Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Blood Potassium	1 (0.2)	0	0	0	0	0
Blood Potassium Decreased	0	0	1 (0.2)	0	0	0
Blood Urea Increased	0	0	2 (0.4)	0	0	0
Blood Uric Acid Increased	1 (0.2)	1 (0 2)	0	0	0	0
Coagulation Test Abnormal	1 (0.2)	0	0	0	0	0
Creatinine Renal Clearance Decreased	2 (0.3)	0	4 (0.7)	0	0	0
Cytomegalovirus Test Positive	0	0	1 (0.2)	0	0	0
Drug Level Changed	1 (0.2)	1 (0 2)	0	0	0	0
Drug Level Increased	4 (0.7)	2 (0.3)	2 (0.4)	2 (0.4)	0	0
Ejection Fraction Decreased	1 (0.2)	1 (0 2)	0	0	0	0
Electrocardiogram Abnormal	1 (0.2)	1 (0 2)	0	0	0	0
Electrocardiogram Qt Prolonged	14 (2.3)	1 (0.2)	6 (1.1)	0	4 (6.9)	0
Electrocardiogram T Wave Abnormal	1 (0.2)	1 (0.2)	0	0	0	0
Electroencephalogram Abnormal	1 (0.2)	1 (0 2)	0	0	0	0
Gamma-Glutamyltransferase Increased	14 (2.3)	10 (1.7)	8 (1.5)	4 (0.7)	1 (1.7)	0
Hepatic Enzyme Abnormal	0	0	1 (0.2)	1 (0.2)	0	0
Hepatic Enzyme Increased	3 (0.5)	2 (0.3)	1 (0.2)	1 (0.2)	0	0
Liver Function Test Abnormal	2 (0.3)	1 (0 2)	0	0	0	0
Liver Function Test Increased	5 (0.8)	5 (0.8)	4 (0.7)	1 (0.2)	0	0
Platelet Count Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Transaminases Increased	6 (1.0)	4 (0.7)	7 (1.3)	2 (0.4)	0	0
Vitamin K Decreased	1 (0.2)	0	0	0	0	0
Weight Decreased	1 (0.2)	1 (0 2)	4 (0.7)	0	0	0
Weight Increased	0	0	0	0	1 (1.7)	0
Metabolism And Nutrition Disorders	**22 (3.6)**	**6 (1.0)**	**22 (4.1)**	**3 (0.6)**	**2 (3.4)**	**1 (1.7)**

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Decreased Appetite	5 (0.8)	1 (0.2)	9 (1.7)	0	1 (1.7)	0
Electrolyte Imbalance	1 (0.2)	0	0	0	0	0
Enzyme Abnormality	0	0	1 (0.2)	0	0	0
Fluid Retention	1 (0.2)	0	0	0	0	0
Hypercholesterolaemia	1 (0.2)	0	0	0	0	0
Hyperglycaemia	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Hyperhomocysteinaemia	1 (0.2)	0	0	0	0	0
Hyperkalaemia	2 (0.3)	2 (0 3)	4 (0.7)	1 (0.2)	0	0
Hypertriglyceridaemia	1 (0.2)	0	0	0	0	0
Hypokalaemia	10 (1.7)	2 (0 3)	5 (0.9)	1 (0.2)	1 (1.7)	1 (1.7)
Hypomagnesaemia	1 (0.2)	1 (0.2)	4 (0.7)	0	0	0
Hyponatraemia	0	0	1 (0.2)	1 (0.2)	0	0
Hypophagia	1 (0.2)	0	0	0	0	0
Hypophosphataemia	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Magnesium Deficiency	0	0	1 (0.2)	0	0	0
Metabolic Acidosis	1 (0.2)	0	0	0	0	0
Obesity	0	0	1 (0.2)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**10 (1.7)**	**3 (0.5)**	**13 (2.4)**	**0**	**0**	**0**
Arthralgia	1 (0.2)	0	1 (0.2)	0	0	0
Joint Swelling	0	0	1 (0.2)	0	0	0
Muscle Spasms	3 (0.5)	1 (0.2)	3 (0.6)	0	0	0
Muscle Twitching	1 (0.2)	0	0	0	0	0
Muscular Weakness	2 (0.3)	2 (0.3)	3 (0.6)	0	0	0
Musculoskeletal Chest Pain	0	0	1 (0.2)	0	0	0
Myalgia	2 (0.3)	0	3 (0.6)	0	0	0
Pain In Extremity	2 (0.3)	0	1 (0.2)	0	0	0
Plantar Fasciitis	1 (0.2)	0	0	0	0	0
Torticollis	1 (0.2)	0	0	0	0	0
Nervous System Disorders	**33 (5.5)**	**7 (1.2)**	**34 (6.3)**	**3 (0.6)**	**2 (3.4)**	**0**
Ageusia	0	0	1 (0.2)	0	0	0
Areflexia	1 (0.2)	0	0	0	0	0
Asterixis	1 (0.2)	0	0	0	0	0
Ataxia	1 (0.2)	1 (0 2)	0	0	0	0
Burning Sensation	2 (0.3)	0	0	0	0	0
Disturbance In Attention	0	0	1 (0.2)	0	0	0
Dizziness	4 (0.7)	0	6 (1.1)	1 (0.2)	0	0
Dizziness Postural	0	0	1 (0.2)	0	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Dysaesthesia	1 (0.2)	0	0	0	0	0
Dysarthria	0	0	1 (0.2)	0	0	0
Dysgeusia	3 (0.5)	0	7 (1.3)	0	0	0
Encephalopathy	2 (0.3)	2 (0 3)	0	0	0	0
Headache	8 (1.3)	0	8 (1.5)	1 (0.2)	1 (1.7)	0
Hyperreflexia	0	0	1 (0.2)	0	0	0
Hypoaesthesia	0	0	2 (0.4)	0	0	0
Hyporeflexia	2 (0.3)	1 (0 2)	0	0	0	0
Intercostal Neuralgia	0	0	1 (0.2)	0	0	0
Lethargy	1 (0.2)	1 (0 2)	3 (0.6)	0	0	0
Meningism	1 (0.2)	1 (0 2)	0	0	0	0
Migraine	1 (0.2)	1 (0 2)	0	0	0	0
Neuropathy Peripheral	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Paraesthesia	2 (0.3)	0	3 (0.6)	0	0	0
Presyncope	0	0	0	0	1 (1.7)	0
Seizure	1 (0.2)	1 (0 2)	0	0	0	0
Sensory Loss	1 (0.2)	1 (0.2)	0	0	0	0
Somnolence	2 (0.3)	0	3 (0.6)	0	0	0
Stupor	1 (0.2)	1 (0 2)	0	0	0	0
Syncope	2 (0.3)	2 (0 3)	0	0	0	0
Tremor	4 (0.7)	0	6 (1.1)	1 (0.2)	0	0
Visual Field Defect	1 (0.2)	0	0	0	0	0
Psychiatric Disorders	**5 (0.8)**	**2 (0.3)**	**4 (0.7)**	**0**	**1 (1.7)**	**0**
Anxiety	0	0	1 (0.2)	0	0	0
Aversion	0	0	0	0	1 (1.7)	0
Confusional State	2 (0.3)	1 (0 2)	1 (0.2)	0	0	0
Depressed Mood	0	0	1 (0.2)	0	0	0
Disorientation	1 (0.2)	0	0	0	0	0
Insomnia	1 (0.2)	0	1 (0.2)	0	0	0
Mental Status Changes	2 (0.3)	1 (0 2)	0	0	0	0
Psychotic Disorder	1 (0.2)	0	0	0	0	0
Renal And Urinary Disorders	**8 (1.3)**	**3 (0.5)**	**10 (1.9)**	**2 (0.4)**	**0**	**0**
Acute Kidney Injury	1 (0.2)	1 (0 2)	0	0	0	0
Dysuria	2 (0.3)	0	1 (0.2)	0	0	0
Haematuria	1 (0.2)	0	1 (0.2)	0	0	0
Nephrolithiasis	1 (0.2)	0	0	0	0	0
Pollakiuria	1 (0.2)	0	1 (0.2)	0	0	0
Renal Failure	3 (0.5)	1 (0 2)	5 (0.9)	1 (0.2)	0	0

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	All	Severe/LT	All	Severe/LT	All	Severe/LT
Renal Impairment	2 (0.3)	1 (0 2)	4 (0.7)	1 (0.2)	0	0
Reproductive System And Breast Disorders	**0**	**0**	**1 (0.2)**	**0**	**0**	**0**
Erectile Dysfunction	0	0	1 (0.2)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**8 (1.3)**	**1 (0.2)**	**7 (1.3)**	**3 (0.6)**	**1 (1.7)**	**0**
Atelectasis	1 (0.2)	0	0	0	0	0
Cough	4 (0.7)	0	1 (0.2)	0	1 (1.7)	0
Dyspnoea	1 (0.2)	0	0	0	0	0
Epistaxis	0	0	1 (0.2)	0	0	0
Hiccups	0	0	1 (0.2)	0	0	0
Interstitial Lung Disease	1 (0.2)	1 (0 2)	0	0	0	0
Nasal Congestion	1 (0.2)	0	2 (0.4)	0	0	0
Oropharyngeal Pain	0	0	2 (0.4)	1 (0.2)	0	0
Pneumonitis	1 (0.2)	1 (0 2)	0	0	0	0
Productive Cough	0	0	1 (0.2)	1 (0.2)	0	0
Pulmonary Embolism	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0
Pulmonary Hypertension	1 (0.2)	0	0	0	0	0
Rales	1 (0.2)	0	0	0	0	0
Upper-Airway Cough Syndrome	1 (0.2)	0	0	0	0	0
Skin And Subcutaneous Tissue Disorders	**26 (4.3)**	**2 (0.3)**	**27 (5.0)**	**2 (0.4)**	**2 (3.4)**	**0**
Dermatitis Acneiform	1 (0.2)	0	0	0	0	0
Dermatitis Allergic	2 (0.3)	0	0	0	0	0
Drug Eruption	0	0	2 (0.4)	0	0	0
Dry Skin	1 (0.2)	0	0	0	0	0
Ecchymosis	1 (0.2)	0	0	0	0	0
Hyperhidrosis	1 (0.2)	0	0	0	1 (1.7)	0
Livedo Reticularis	0	0	1 (0.2)	0	0	0
Night Sweats	1 (0.2)	0	0	0	0	0
Papule	1 (0.2)	0	0	0	0	0
Petechiae	0	0	2 (0.4)	0	0	0
Pigmentation Disorder	0	0	1 (0.2)	0	0	0
Pruritus	4 (0.7)	0	4 (0.7)	0	0	0
Pruritus Generalised	0	0	1 (0.2)	0	0	0
Rash	9 (1.5)	1 (0 2)	10 (1.9)	1 (0.2)	1 (1.7)	0
Rash Follicular	1 (0.2)	0	1 (0.2)	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
All and Severe/Life Threatening
Number (%) of Subjects

	Posaconazole n = 605		Fluconazole n = 539		Itraconazole n = 58	
	All	Severe/LT	All	Severe/LT	All	Severe/LT
Rash Generalised	3 (0.5)	0	2 (0.4)	0	0	0
Rash Macular	1 (0.2)	0	1 (0.2)	0	0	0
Rash Maculo-Papular	3 (0.5)	1 (0 2)	1 (0.2)	0	0	0
Rash Papular	1 (0.2)	0	1 (0.2)	0	0	0
Rash Pruritic	2 (0.3)	0	4 (0.7)	1 (0.2)	0	0
Skin Discolouration	0	0	1 (0.2)	0	0	0
Skin Exfoliation	2 (0.3)	0	0	0	0	0
Skin Striae	0	0	1 (0.2)	0	0	0
Urticaria	1 (0.2)	0	1 (0.2)	0	0	0
Vascular Disorders	**4 (0.7)**	**0**	**10 (1.9)**	**2 (0.4)**	**1 (1.7)**	**0**
Deep Vein Thrombosis	1 (0.2)	0	0	0	0	0
Embolism Arterial	0	0	1 (0.2)	1 (0.2)	0	0
Flushing	0	0	1 (0.2)	0	0	0
Hot Flush	0	0	2 (0.4)	0	0	0
Hypertension	3 (0.5)	0	5 (0.9)	0	0	0
Hypotension	0	0	1 (0.2)	1 (0.2)	0	0
Vasculitis	0	0	0	0	1 (1.7)	0

Every subject is counted a single time for each applicable row and column.
LT = life-threatening.
MedDRA Version 20.1

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付録 2.7.4-21 有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**114 (99.1)**	**121 (97.6)**	**269 (95.4)**	**291 (95.7)**	**383 (96.5)**	**412 (96.3)**
Blood And Lymphatic System Disorders	**54 (47.0)**	**55 (44.4)**	**100 (35.5)**	**108 (35.5)**	**154 (38.8)**	**163 (38.1)**
Anaemia	20 (17.4)	21 (16.9)	56 (19.9)	60 (19.7)	76 (19.1)	81 (18.9)
Anaemia Megaloblastic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aplastic Anaemia	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Autoimmune Haemolytic Anaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bandaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Coagulopathy	2 (1.7)	3 (2.4)	3 (1.1)	4 (1.3)	5 (1.3)	7 (1.6)
Disseminated Intravascular Coagulation	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Eosinophilia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Febrile Neutropenia	5 (4.3)	5 (4.0)	14 (5.0)	17 (5.6)	19 (4.8)	22 (5.1)
Haemolysis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haemolytic Anaemia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Haemolytic Uraemic Syndrome	4 (3.5)	4 (3.2)	0	0	4 (1.0)	4 (0.9)
Hypercoagulation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Leukocytosis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Leukopenia	4 (3 5)	4 (3.2)	7 (2.5)	7 (2.3)	11 (2.8)	11 (2.6)
Lymphadenopathy	2 (1.7)	2 (1.6)	7 (2.5)	7 (2.3)	9 (2.3)	9 (2.1)
Neutropenia	12 (10.4)	12 (9.7)	26 (9 2)	27 (8.9)	38 (9.6)	39 (9.1)
Pancytopenia	6 (5.2)	6 (4.8)	13 (4.6)	13 (4.3)	19 (4.8)	19 (4.4)
Polycythaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Retroperitoneal Lymphadenopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Splenic Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Splenic Lesion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Splenomegaly	5 (4.3)	5 (4.0)	3 (1.1)	4 (1.3)	8 (2.0)	9 (2.1)
Thrombocytopenia	22 (19 1)	22 (17.7)	38 (13.5)	43 (14.1)	60 (15.1)	65 (15.2)
Thrombocytosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombotic Thrombocytopenic Purpura	5 (4.3)	5 (4.0)	1 (0.4)	1 (0.3)	6 (1.5)	6 (1.4)
Cardiac Disorders	**55 (47 8)**	**56 (45.2)**	**73 (25.9)**	**79 (26.0)**	**128 (32.2)**	**135 (31.5)**
Angina Pectoris	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Aortic Valve Incompetence	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aortic Valve Sclerosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Arrhythmia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Arrhythmia Supraventricular	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Arteriosclerosis Coronary Artery	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Atrial Fibrillation	7 (6.1)	7 (5.6)	11 (3 9)	11 (3.6)	18 (4 5)	18 (4.2)
Atrial Flutter	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Atrioventricular Block	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Atrioventricular Block First Degree	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Bradycardia	2 (1.7)	2 (1.6)	8 (2.8)	8 (2.6)	10 (2 5)	10 (2.3)
Bundle Branch Block	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Bundle Branch Block Left	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bundle Branch Block Right	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cardiac Arrest	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)
Cardiac Failure	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Cardiac Failure Congestive	2 (1.7)	2 (1.6)	11 (3 9)	11 (3.6)	13 (3 3)	13 (3.0)
Cardiac Valve Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	7 (6.1)	8 (6.5)	8 (2.8)	9 (3.0)	15 (3.8)	17 (4.0)
Cardiogenic Shock	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiomegaly	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Cardiomyopathy	4 (3.5)	4 (3.2)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1.2)
Cardiopulmonary Failure	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Coronary Artery Occlusion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cyanosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Defect Conduction Intraventricular	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dilatation Atrial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Extrasystoles	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Left Atrial Enlargement	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Left Ventricular Dysfunction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Left Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mitral Valve Calcification	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mitral Valve Incompetence	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mitral Valve Stenosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myocardial Infarction	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Palpitations	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Pericardial Effusion	9 (7.8)	9 (7.3)	5 (1.8)	5 (1.6)	14 (3 5)	14 (3.3)
Pericardial Rub	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Pericarditis	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pulseless Electrical Activity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Sinus Bradycardia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sinus Tachycardia	5 (4.3)	5 (4.0)	4 (1.4)	4 (1.3)	9 (2.3)	9 (2.1)
Supraventricular Tachycardia	6 (5.2)	6 (4.8)	8 (2.8)	8 (2.6)	14 (3 5)	14 (3.3)
Tachycardia	25 (21.7)	25 (20.2)	19 (6.7)	23 (7.6)	44 (11.1)	48 (11.2)
Tricuspid Valve Incompetence	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ventricular Extrasystoles	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Ventricular Fibrillation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Tachycardia	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Congenital, Familial And Genetic Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Aplasia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fanconi Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ear And Labyrinth Disorders	**12 (10.4)**	**13 (10.5)**	**19 (6.7)**	**20 (6.6)**	**31 (7 8)**	**33 (7.7)**
Cerumen Impaction	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Conductive Deafness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Deafness	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Ear Discomfort	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Ear Pain	6 (5.2)	6 (4.8)	5 (1.8)	6 (2.0)	11 (2.8)	12 (2.8)
Ear Pruritus	0	1 (0.8)	0	0	0	1 (0.2)
Excessive Cerumen Production	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
External Ear Inflammation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypoacusis	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Middle Ear Effusion	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Tinnitus	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Vertigo	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Vertigo Labyrinthine	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Endocrine Disorders	**9 (7.8)**	**9 (7.3)**	**8 (2.8)**	**8 (2.6)**	**17 (4 3)**	**17 (4.0)**
Adrenal Insufficiency	3 (2.6)	3 (2.4)	4 (1.4)	4 (1.3)	7 (1.8)	7 (1.6)
Adrenocortical Insufficiency Acute	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cushingoid	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Hyperthyroidism	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hypogonadism	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Hypothyroidism	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Eye Disorders	**34 (29.6)**	**35 (28.2)**	**51 (18.1)**	**55 (18.1)**	**85 (21.4)**	**90 (21.0)**
Blepharitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blindness	0	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.5)
Cataract	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Conjunctival Haemorrhage	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Conjunctival Hyperaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Conjunctival Irritation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Conjunctival Oedema	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Conjunctivitis Allergic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Corneal Epithelium Defect	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Corneal Erosion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Corneal Perforation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dacryostenosis Acquired	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Diplopia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Dry Eye	6 (5.2)	6 (4.8)	2 (0.7)	2 (0.7)	8 (2.0)	8 (1.9)
Erythema Of Eyelid	0	0	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.7)
Exophthalmos	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eye Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eye Irritation	2 (1.7)	2 (1.6)	7 (2.5)	7 (2.3)	9 (2.3)	9 (2.1)
Eye Movement Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Oedema	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Eye Pain	3 (2.6)	3 (2.4)	5 (1.8)	5 (1.6)	8 (2.0)	8 (1.9)
Eye Pruritus	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Eye Swelling	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Eyelid Cyst	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eyelid Oedema	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eyelid Ptosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypoaesthesia Eye	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Iridocyclitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Keratopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lacrimation Increased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mydriasis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Myopia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Ocular Hyperaemia	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Optic Atrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Papilloedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Periorbital Oedema	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Photophobia	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Photopsia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pinguecula	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pupillary Reflex Impaired	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pupils Unequal	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Retinal Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Retinal Exudates	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Scleral Discolouration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Scleral Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Scleral Oedema	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Uveitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Vision Blurred	11 (9.6)	11 (8.9)	13 (4.6)	16 (5.3)	24 (6.0)	27 (6.3)
Visual Impairment	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Gastrointestinal Disorders	**83 (72 2)**	**88 (71.0)**	**193 (68.4)**	**206 (67.8)**	**276 (69.5)**	**294 (68.7)**
Abdominal Discomfort	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Abdominal Distension	17 (14.8)	17 (13.7)	15 (5 3)	16 (5.3)	32 (8 1)	33 (7.7)
Abdominal Hernia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abdominal Pain	26 (22.6)	27 (21.8)	33 (11.7)	34 (11.2)	59 (14.9)	61 (14.3)
Abdominal Pain Lower	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Abdominal Pain Upper	14 (12 2)	14 (11.3)	27 (9.6)	29 (9.5)	41 (10.3)	43 (10.0)
Abdominal Rigidity	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Abdominal Tenderness	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Abdominal Wall Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Abnormal Faeces	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Anal Incontinence	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Anorectal Discomfort	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ascites	8 (7.0)	8 (6.5)	5 (1.8)	6 (2.0)	13 (3 3)	14 (3.3)
Barrett's Oesophagus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cheilitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Colitis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Constipation	18 (15.7)	18 (14.5)	35 (12.4)	39 (12.8)	53 (13.4)	57 (13.3)
Dental Caries	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Dental Discomfort	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diarrhoea	40 (34.8)	43 (34.7)	74 (26.2)	77 (25.3)	114 (28.7)	120 (28.0)
Diarrhoea Haemorrhagic	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Dry Mouth	4 (3.5)	4 (3.2)	5 (1.8)	5 (1.6)	9 (2.3)	9 (2.1)
Duodenal Ulcer	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Duodenitis	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Dyspepsia	7 (6.1)	7 (5.6)	13 (4.6)	13 (4.3)	20 (5.0)	20 (4.7)
Dysphagia	4 (3.5)	4 (3.2)	12 (4 3)	12 (3.9)	16 (4.0)	16 (3.7)
Enteritis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eructation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Faecaloma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Faeces Discoloured	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Faeces Soft	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Flatulence	4 (3.5)	4 (3.2)	13 (4.6)	14 (4.6)	17 (4 3)	18 (4.2)
Food Poisoning	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Gastric Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gastric Haemorrhage	0	0	0	1 (0.3)	0	1 (0.2)
Gastric Perforation	0	1 (0.8)	0	0	0	1 (0.2)
Gastric Polyps	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gastric Ulcer	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gastritis	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Gastrointestinal Haemorrhage	6 (5.2)	6 (4.8)	4 (1.4)	4 (1.3)	10 (2 5)	10 (2.3)
Gastrointestinal Hypermotility	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gastrointestinal Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal Sounds Abnormal	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gastrooesophageal Reflux Disease	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Gingival Bleeding	2 (1.7)	2 (1.6)	4 (1.4)	5 (1.6)	6 (1.5)	7 (1.6)
Gingival Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gingival Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gingival Swelling	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Glossitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Glossodynia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Haematemesis	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Haematochezia	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Haemorrhoidal Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Number (%) of Subjects

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Haemorrhoids	2 (1.7)	2 (1.6)	7 (2.5)	8 (2.6)	9 (2.3)	10 (2.3)
Hiatus Hernia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hypoaesthesia Oral	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Ileus	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Ileus Paralytic	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Intestinal Dilatation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intestinal Infarction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intestinal Ischaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intestinal Obstruction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intestinal Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Irritable Bowel Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Leukoplakia Oral	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lip Dry	0	1 (0.8)	6 (2.1)	7 (2.3)	6 (1.5)	8 (1.9)
Lip Swelling	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Mallory-Weiss Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Melaena	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Mouth Haemorrhage	1 (0.9)	1 (0.8)	2 (0.7)	3 (1.0)	3 (0.8)	4 (0.9)
Mouth Ulceration	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Nausea	35 (30.4)	36 (29.0)	85 (30.1)	91 (29.9)	120 (30.2)	127 (29.7)
Neutropenic Colitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Obstruction Gastric	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Odynophagia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Oesophageal Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oesophageal Perforation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oesophageal Stenosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oesophageal Ulcer	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Oesophagitis	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Oesophagitis Ulcerative	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oral Discomfort	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oral Disorder	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Oral Mucosal Blistering	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Oral Mucosal Erythema	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oral Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Palatal Swelling	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pancreatic Atrophy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Pancreatic Failure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancreatitis	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Pancreatitis Acute	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancreatitis Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumatosis Intestinalis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Proctalgia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Rectal Haemorrhage	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Rectal Lesion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Retching	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Salivary Hypersecretion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Stomatitis	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Submaxillary Gland Enlargement	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tongue Coated	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Tongue Oedema	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tongue Ulceration	4 (3.5)	4 (3.2)	0	0	4 (1.0)	4 (0.9)
Tooth Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Toothache	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Umbilical Hernia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Upper Gastrointestinal Haemorrhage	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Vomiting	34 (29.6)	35 (28.2)	72 (25.5)	77 (25.3)	106 (26.7)	112 (26.2)
General Disorders And Administration Site Conditions	**87 (75.7)**	**92 (74.2)**	**187 (66.3)**	**201 (66.1)**	**274 (69.0)**	**293 (68.5)**
Asthenia	20 (17.4)	20 (16.1)	47 (16.7)	49 (16.1)	67 (16.9)	69 (16.1)
Brain Death	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Catheter Site Discharge	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Catheter Site Erythema	1 (0.9)	1 (0.8)	6 (2.1)	6 (2.0)	7 (1.8)	7 (1.6)
Catheter Site Haematoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Catheter Site Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Catheter Site Pain	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Catheter Site Related Reaction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Catheter Site Swelling	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Chest Discomfort	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chest Pain	15 (13.0)	17 (13.7)	40 (14.2)	43 (14.1)	55 (13.9)	60 (14.0)
Chills	15 (13.0)	15 (12.1)	27 (9.6)	28 (9.2)	42 (10.6)	43 (10.0)

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Crepitations	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Crying	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cyst	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Death	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Discomfort	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Disease Progression	14 (12 2)	14 (11.3)	15 (5 3)	15 (4.9)	29 (7 3)	29 (6.8)
Drug Interaction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Intolerance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Early Satiety	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Face Oedema	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Facial Pain	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Fatigue	20 (17.4)	20 (16.1)	31 (11.0)	32 (10.5)	51 (12.8)	52 (12.1)
Feeling Cold	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Feeling Jittery	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gait Disturbance	2 (1.7)	2 (1.6)	9 (3.2)	9 (3.0)	11 (2.8)	11 (2.6)
Gait Inability	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
General Physical Health Deterioration	1 (0.9)	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.5)
Generalised Oedema	8 (7.0)	9 (7.3)	5 (1.8)	6 (2.0)	13 (3 3)	15 (3.5)
Granuloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hyperthermia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypothermia	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Inflammation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Influenza Like Illness	0	0	5 (1.8)	5 (1.6)	5 (1.3)	5 (1.2)
Infusion Site Erythema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Infusion Site Inflammation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Infusion Site Phlebitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Injection Site Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Localised Oedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Malaise	4 (3.5)	4 (3.2)	11 (3 9)	11 (3.6)	15 (3.8)	15 (3.5)
Mass	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mucosal Dryness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mucosal Inflammation	5 (4.3)	6 (4.8)	22 (7.8)	24 (7.9)	27 (6.8)	30 (7.0)
Multi-Organ Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Multiple Organ Dysfunction Syndrome	9 (7.8)	9 (7.3)	5 (1.8)	6 (2.0)	14 (3 5)	15 (3.5)
Nodule	3 (2.6)	3 (2.4)	1 (0.4)	2 (0.7)	4 (1.0)	5 (1.2)
Oedema	5 (4.3)	5 (4.0)	12 (4 3)	14 (4.6)	17 (4 3)	19 (4.4)

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Oedema Peripheral	23 (20.0)	24 (19.4)	36 (12.8)	38 (12.5)	59 (14.9)	62 (14.5)
Pain	5 (4.3)	5 (4.0)	14 (5.0)	14 (4.6)	19 (4.8)	19 (4.4)
Peripheral Swelling	6 (5.2)	6 (4.8)	12 (4 3)	13 (4.3)	18 (4 5)	19 (4.4)
Pseudocyst	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Puncture Site Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pyrexia	43 (37.4)	43 (34.7)	95 (33.7)	100 (32.9)	138 (34.8)	143 (33.4)
Secretion Discharge	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Sluggishness	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Suprapubic Pain	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Swelling	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Vessel Puncture Site Haematoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vessel Puncture Site Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatobiliary Disorders	**19 (16 5)**	**19 (15.3)**	**31 (11.0)**	**32 (10.5)**	**50 (12.6)**	**51 (11.9)**
Cholecystitis	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Cholelithiasis	4 (3.5)	4 (3.2)	2 (0.7)	3 (1.0)	6 (1.5)	7 (1.6)
Cholestasis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Deficiency Of Bile Secretion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gallbladder Enlargement	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gallbladder Polyp	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Cyst	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatic Failure	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Hepatic Function Abnormal	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Hepatic Lesion	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hepatic Necrosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hepatic Steatosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatitis Acute	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatocellular Injury	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatomegaly	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Hepatosplenomegaly	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatotoxicity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	4 (3.5)	4 (3.2)	5 (1.8)	5 (1.6)	9 (2.3)	9 (2.1)
Jaundice	4 (3.5)	4 (3.2)	7 (2.5)	7 (2.3)	11 (2.8)	11 (2.6)
Liver Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ocular Icterus	3 (2.6)	3 (2.4)	5 (1.8)	5 (1.6)	8 (2.0)	8 (1.9)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Immune System Disorders	**39 (33 9)**	**41 (33.1)**	**19 (6.7)**	**20 (6.6)**	**58 (14.6)**	**61 (14.3)**
Acute Graft Versus Host Disease In Intestine	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Acute Graft Versus Host Disease In Liver	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Graft Versus Host Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Drug Hypersensitivity	3 (2.6)	3 (2.4)	2 (0.7)	3 (1.0)	5 (1.3)	6 (1.4)
Graft Versus Host Disease	15 (13.0)	16 (12.9)	3 (1.1)	3 (1.0)	18 (4 5)	19 (4.4)
Graft Versus Host Disease In Gastrointestinal Tract	7 (6.1)	7 (5.6)	1 (0.4)	1 (0.3)	8 (2.0)	8 (1.9)
Graft Versus Host Disease In Liver	6 (5.2)	6 (4.8)	0	0	6 (1.5)	6 (1.4)
Graft Versus Host Disease In Lung	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Graft Versus Host Disease In Skin	19 (16 5)	20 (16.1)	3 (1.1)	3 (1.0)	22 (5 5)	23 (5.4)
Hypersensitivity	1 (0.9)	1 (0.8)	6 (2.1)	6 (2.0)	7 (1.8)	7 (1.6)
Hypogammaglobulinaemia	1 (0 9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Iodine Allergy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Kidney Transplant Rejection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Seasonal Allergy	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Transplant Rejection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Infections And Infestations	**89 (77.4)**	**93 (75.0)**	**176 (62.4)**	**187 (61.5)**	**265 (66.8)**	**280 (65.4)**
Abdominal Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abdominal Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abscess	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Abscess Limb	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Abscess Neck	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abscess Of Eyelid	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abscess Oral	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Acarodermatitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Acid Fast Bacilli Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Acinetobacter Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Acquired Immunodeficiency Syndrome	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Actinomycosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Adenovirus Infection	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Aids Related Complication	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Alpha Haemolytic Streptococcal Infection	1 (0 9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)

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Number (%) of Subjects

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Anal Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Arthritis Bacterial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Arthritis Infective	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aspergilloma	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Aspergillus Infection	4 (3.5)	4 (3.2)	1 (0.4)	3 (1.0)	5 (1.3)	7 (1.6)
Atypical Pneumonia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bacteraemia	10 (8.7)	10 (8.1)	11 (3 9)	11 (3.6)	21 (5 3)	21 (4.9)
Bacterial Disease Carrier	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bacterial Infection	6 (5.2)	6 (4.8)	9 (3.2)	11 (3.6)	15 (3.8)	17 (4.0)
Brain Abscess	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bronchiolitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchitis	4 (3.5)	4 (3.2)	11 (3 9)	11 (3.6)	15 (3.8)	15 (3.5)
Bronchitis Bacterial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchitis Viral	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bronchopulmonary Aspergillosis	0	1 (0.8)	5 (1.8)	5 (1.6)	5 (1.3)	6 (1.4)
Candida Infection	4 (3.5)	4 (3.2)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1.2)
Catheter Site Cellulitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Catheter Site Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cellulitis	3 (2.6)	3 (2.4)	11 (3 9)	11 (3.6)	14 (3 5)	14 (3.3)
Cellulitis Of Male External Genital Organ	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cellulitis Orbital	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Cerebral Aspergillosis	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Cerebral Toxoplasmosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Sinusitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Clostridium Difficile Colitis	3 (2.6)	3 (2.4)	4 (1.4)	4 (1.3)	7 (1.8)	7 (1.6)
Clostridium Difficile Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Conjunctivitis	4 (3.5)	4 (3.2)	10 (3 5)	10 (3.3)	14 (3 5)	14 (3.3)
Corynebacterium Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Corynebacterium Sepsis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Cystitis Bacterial	1 (0 9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cytomegalovirus Chorioretinitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cytomegalovirus Colitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Duodenitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cytomegalovirus Infection	9 (7.8)	10 (8.1)	3 (1.1)	3 (1.0)	12 (3.0)	13 (3.0)
Dacryocystitis	0	0	0	1 (0.3)	0	1 (0.2)
Device Related Infection	4 (3.5)	4 (3.2)	6 (2.1)	7 (2.3)	10 (2 5)	11 (2.6)

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Disseminated Tuberculosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diverticulitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ear Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Empyema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Encephalitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
End Stage Aids	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Endocarditis Bacterial	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Endophthalmitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Enterobacter Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Enterococcal Bacteraemia	0	0	4 (1.4)	5 (1.6)	4 (1.0)	5 (1.2)
Enterococcal Infection	14 (12 2)	14 (11.3)	7 (2.5)	8 (2.6)	21 (5 3)	22 (5.1)
Enterococcal Sepsis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Escherichia Bacteraemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Escherichia Infection	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Escherichia Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Escherichia Urinary Tract Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eye Infection Staphylococcal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eyelid Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Folliculitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fungaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fungal Infection	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Fungal Rhinitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fungal Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fungal Skin Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Furuncle	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Fusarium Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Gastroenteritis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastroenteritis Viral	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Genital Herpes	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Gingival Abscess	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gingivitis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Helicobacter Gastritis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatic Candidiasis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatosplenic Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Herpes Simplex	2 (1.7)	3 (2.4)	1 (0.4)	1 (0.3)	3 (0.8)	4 (0.9)
Herpes Simplex Pneumonia	0	0	0	1 (0.3)	0	1 (0.2)

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Herpes Zoster	3 (2.6)	3 (2.4)	6 (2.1)	6 (2.0)	9 (2.3)	9 (2.1)
Hiv Wasting Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hordeolum	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Human Polyomavirus Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Infection Parasitic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Influenza	0	0	6 (2.1)	6 (2.0)	6 (1.5)	6 (1.4)
Infusion Site Cellulitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intervertebral Discitis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Klebsiella Bacteraemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Klebsiella Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Klebsiella Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Localised Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Lower Respiratory Tract Infection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Lung Abscess	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Lung Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Infection Pseudomonal	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mastoiditis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Meningitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Meningitis Cryptococcal	0	0	8 (2.8)	8 (2.6)	8 (2.0)	8 (1.9)
Meningitis Tuberculous	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Molluscum Contagiosum	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mucormycosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mycobacterial Infection	0	0	5 (1.8)	5 (1.6)	5 (1.3)	5 (1.2)
Mycobacterium Avium Complex Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mycobacterium Kansasii Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Mycoplasma Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nasopharyngitis	0	0	7 (2.5)	7 (2.3)	7 (1.8)	7 (1.6)
Neurosyphilis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nocardiosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Oesophageal Candidiasis	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Onychomycosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oral Candidiasis	8 (7.0)	8 (6.5)	3 (1.1)	3 (1.0)	11 (2.8)	11 (2.6)
Oral Fungal Infection	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Oral Hairy Leukoplakia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oral Herpes	4 (3.5)	4 (3.2)	7 (2.5)	8 (2.6)	11 (2.8)	12 (2.8)

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Orchitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Osteomyelitis	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Otitis Media	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Parainfluenzae Virus Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Paronychia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pelvic Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Periorbital Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Peritonitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pharyngitis	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pharyngotonsillitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Plague	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pleural Infection Bacterial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumococcal Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumocystis Jirovecii Pneumonia	0	0	6 (2.1)	6 (2.0)	6 (1.5)	6 (1.4)
Pneumonia	17 (14.8)	17 (13.7)	28 (9 9)	32 (10.5)	45 (11.3)	49 (11.4)
Pneumonia Bacterial	4 (3.5)	4 (3.2)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1.2)
Pneumonia Cytomegaloviral	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumonia Escherichia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumonia Fungal	6 (5.2)	7 (5.6)	6 (2.1)	7 (2.3)	12 (3.0)	14 (3.3)
Pneumonia Klebsiella	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Pneumonia Pseudomonal	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pneumonia Staphylococcal	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Postoperative Wound Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Proctitis Herpes	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pseudallescheria Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pseudomembranous Colitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pseudomonas Infection	3 (2.6)	3 (2.4)	1 (0.4)	2 (0.7)	4 (1.0)	5 (1.2)
Pulmonary Mycosis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary Tuberculosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Purulent Discharge	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pyelonephritis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Syncytial Virus Infection	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Respiratory Tract Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Retinitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rhinitis	1 (0.9)	1 (0.8)	2 (0.7)	3 (1.0)	3 (0.8)	4 (0.9)
Salmonella Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Sepsis	9 (7.8)	9 (7.3)	12 (4 3)	12 (3.9)	21 (5 3)	21 (4.9)
Septic Embolus	4 (3.5)	4 (3.2)	0	0	4 (1.0)	4 (0.9)
Septic Shock	5 (4.3)	6 (4.8)	2 (0.7)	2 (0.7)	7 (1.8)	8 (1.9)
Serratia Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sinusitis	10 (8.7)	10 (8.1)	15 (5 3)	15 (4.9)	25 (6 3)	25 (5.8)
Sinusitis Aspergillus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sinusitis Bacterial	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Sinusitis Fungal	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Skin Bacterial Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Staphylococcal Bacteraemia	10 (8.7)	10 (8.1)	7 (2.5)	8 (2.6)	17 (4 3)	18 (4.2)
Staphylococcal Infection	7 (6.1)	7 (5.6)	13 (4.6)	13 (4.3)	20 (5.0)	20 (4.7)
Staphylococcal Sepsis	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)
Staphylococcal Skin Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Stenotrophomonas Infection	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Stenotrophomonas Sepsis	0	0	0	1 (0.3)	0	1 (0.2)
Subcutaneous Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Superinfection Fungal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Syphilis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Systemic Candida	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tooth Abscess	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Tooth Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Torulopsis Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tracheitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Trichosporon Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tuberculosis	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Upper Respiratory Tract Infection	8 (7.0)	8 (6.5)	11 (3 9)	11 (3.6)	19 (4.8)	19 (4.4)
Urinary Tract Infection	5 (4.3)	5 (4.0)	14 (5.0)	14 (4.6)	19 (4.8)	19 (4.4)
Urinary Tract Infection Staphylococcal	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Varicella	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Varicella Zoster Virus Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Viral Infection	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Viral Sinusitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Wound Infection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Wound Infection Fungal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Injury, Poisoning And Procedural Complications	**30 (26 1)**	**30 (24.2)**	**51 (18.1)**	**53 (17.4)**	**81 (20.4)**	**83 (19.4)**
Arthropod Bite	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Barotitis Media	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Contusion	6 (5.2)	6 (4.8)	3 (1.1)	3 (1.0)	9 (2.3)	9 (2.1)
Corneal Abrasion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eschar	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Excoriation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Eye Burns	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Eye Contusion	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fall	8 (7.0)	8 (6.5)	7 (2.5)	8 (2.6)	15 (3.8)	16 (3.7)
Femur Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Foot Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Graft Complication	1 (0 9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemolytic Transfusion Reaction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Head Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hip Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyphaema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Incision Site Haematoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Incision Site Pain	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Infusion Related Reaction	2 (1.7)	2 (1.6)	3 (1.1)	4 (1.3)	5 (1.3)	6 (1.4)
Injury	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Joint Injury	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Laceration	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Limb Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Muscle Strain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Overdose	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Post Lumbar Puncture Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Post Procedural Haemorrhage	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Procedural Complication	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Procedural Pain	4 (3.5)	4 (3.2)	7 (2.5)	7 (2.3)	11 (2.8)	11 (2.6)
Procedural Site Reaction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Scratch	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Skin Abrasion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Spinal Compression Fracture	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Spinal Cord Injury	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Stress Fracture	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Subarachnoid Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sunburn	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Toxicity To Various Agents	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Tracheal Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Transfusion Reaction	1 (0.9)	1 (0.8)	7 (2.5)	7 (2.3)	8 (2.0)	8 (1.9)
Wound	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Wound Complication	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Wound Decomposition	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Wound Necrosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Investigations	**71 (61.7)**	**73 (58.9)**	**133 (47.2)**	**140 (46.1)**	**204 (51.4)**	**213 (49.8)**
Activated Partial Thromboplastin Time Prolonged	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Alanine Aminotransferase	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Alanine Aminotransferase Increased	10 (8.7)	10 (8.1)	16 (5.7)	16 (5.3)	26 (6 5)	26 (6.1)
Ammonia Increased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Amylase Increased	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Anticoagulation Drug Level Above Therapeutic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aspartate Aminotransferase Increased	3 (2.6)	3 (2.4)	17 (6.0)	17 (5.6)	20 (5.0)	20 (4.7)
Aspiration Pleural Cavity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Atrial Pressure Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bacterial Test Positive	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Bilirubin Conjugated Increased	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Biopsy Brain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Biopsy Skin	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Biopsy Skin Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blast Cell Count Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Albumin Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Alkaline Phosphatase Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Alkaline Phosphatase Increased	9 (7.8)	9 (7.3)	15 (5 3)	15 (4.9)	24 (6.0)	24 (5.6)
Blood Bilirubin Increased	8 (7.0)	8 (6.5)	8 (2.8)	8 (2.6)	16 (4.0)	16 (3.7)
Blood Cholesterol Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)

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Blood Creatinine Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Creatinine Increased	13 (11 3)	13 (10.5)	13 (4.6)	13 (4.3)	26 (6 5)	26 (6.1)
Blood Culture Positive	1 (0.9)	1 (0.8)	6 (2.1)	7 (2.3)	7 (1.8)	8 (1.9)
Blood Electrolytes Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Fibrinogen Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Gases Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Glucose Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Glucose Increased	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Blood Immunoglobulin G Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Lactate Dehydrogenase Increased	4 (3.5)	4 (3.2)	6 (2.1)	6 (2.0)	10 (2 5)	10 (2.3)
Blood Lactic Acid Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Magnesium Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Phosphorus Increased	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Blood Potassium Decreased	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Blood Potassium Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Pressure Decreased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Blood Pressure Increased	3 (2.6)	3 (2.4)	3 (1.1)	5 (1.6)	6 (1.5)	8 (1.9)
Blood Pressure Orthostatic	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Blood Pressure Systolic Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Sodium Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Sodium Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Triglycerides Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Blood Urea Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Urea Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Urea Increased	7 (6.1)	7 (5.6)	3 (1.1)	3 (1.0)	10 (2 5)	10 (2.3)
Blood Uric Acid	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Uric Acid Increased	0	0	3 (1.1)	4 (1.3)	3 (0.8)	4 (0.9)
Blood Urine Present	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Body Temperature	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Body Temperature Increased	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Breath Sounds Abnormal	3 (2.6)	3 (2.4)	4 (1.4)	4 (1.3)	7 (1.8)	7 (1.6)
Carbon Dioxide Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cardiac Murmur	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cardioactive Drug Level Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardioactive Drug Level Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Chest X-Ray Abnormal	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)

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Clostridium Test	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Clostridium Test Positive	3 (2.6)	3 (2.4)	5 (1.8)	6 (2.0)	8 (2.0)	9 (2.1)
Computerised Tomogram Abnormal	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Csf Protein Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Culture Urine Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Test	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Cytomegalovirus Test Positive	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Drug Level Changed	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Drug Level Increased	5 (4.3)	5 (4.0)	3 (1.1)	3 (1.0)	8 (2.0)	8 (1.9)
Ejection Fraction Decreased	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Electrocardiogram Abnormal	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Electrocardiogram Change	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qrs Complex Prolonged	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qt Interval Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qt Prolonged	0	0	10 (3 5)	11 (3.6)	10 (2 5)	11 (2.6)
Electrocardiogram St Segment Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram St Segment Elevation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Electrocardiogram T Wave Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram T Wave Inversion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram T Wave Peaked	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Electroencephalogram Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eosinophil Count Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fundoscopy Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fungal Test Positive	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Gamma-Glutamyltransferase Increased	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
General Physical Condition Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Glucocorticoids Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Haemoglobin Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemoglobin Decreased	3 (2.6)	3 (2.4)	2 (0.7)	3 (1.0)	5 (1.3)	6 (1.4)
Heart Rate Irregular	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Hepatic Enzyme Increased	5 (4 3)	5 (4.0)	4 (1.4)	4 (1.3)	9 (2.3)	9 (2.1)
Hepatitis A Antibody Positive	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatitis C Virus Test Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Herpes Simplex Test Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
International Normalised Ratio Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
International Normalised Ratio Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Laboratory Test Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Increased	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Liver Function Test Abnormal	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Liver Function Test Increased	10 (8.7)	10 (8.1)	8 (2.8)	8 (2.6)	18 (4 5)	18 (4.2)
Medical Observation Normal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Myocardial Necrosis Marker Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Neutrophil Count Decreased	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Nuclear Magnetic Resonance Imaging Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nutritional Condition Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Occult Blood Positive	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Oxygen Saturation Decreased	7 (6.1)	7 (5.6)	1 (0.4)	1 (0.3)	8 (2.0)	8 (1.9)
Pancreatic Enzymes Increased	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Platelet Count Decreased	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Platelet Count Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Prostatic Specific Antigen Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Prothrombin Level Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Prothrombin Time Prolonged	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Prothrombin Time Shortened	1 (0.9)	3 (2.4)	0	0	1 (0.3)	3 (0.7)
Pulmonary Function Test Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pupillary Light Reflex Tests Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Qrs Axis Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal Scan	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Rate Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Right Ventricular Systolic Pressure Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Serum Ferritin Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Spleen Palpable	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sputum Culture Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Transaminases Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Troponin Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Urine Output Decreased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Viral Load Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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All Randomized Subjects
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by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Weight Decreased	7 (6.1)	7 (5.6)	18 (6.4)	19 (6.3)	25 (6 3)	26 (6.1)
Weight Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
White Blood Cell Count Decreased	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
White Blood Cell Count Increased	2 (1.7)	2 (1.6)	5 (1.8)	6 (2.0)	7 (1.8)	8 (1.9)
White Blood Cells Urine Positive	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
X-Ray Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolism And Nutrition Disorders	**77 (67.0)**	**81 (65.3)**	**115 (40.8)**	**126 (41.4)**	**192 (48.4)**	**207 (48.4)**
Acidosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Cachexia	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Decreased Appetite	23 (20.0)	23 (18.5)	42 (14.9)	43 (14.1)	65 (16.4)	66 (15.4)
Dehydration	11 (9.6)	11 (8.9)	19 (6.7)	19 (6.3)	30 (7.6)	30 (7.0)
Diabetes Mellitus	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Diabetes Mellitus Inadequate Control	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrolyte Imbalance	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Failure To Thrive	4 (3.5)	4 (3.2)	2 (0.7)	3 (1.0)	6 (1.5)	7 (1.6)
Fluid Overload	7 (6.1)	7 (5.6)	8 (2.8)	8 (2.6)	15 (3.8)	15 (3.5)
Fluid Retention	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Hypercalcaemia	7 (6.1)	7 (5.6)	2 (0.7)	3 (1.0)	9 (2.3)	10 (2.3)
Hypercholesterolaemia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hypercreatininaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hyperglycaemia	21 (18 3)	21 (16.9)	11 (3 9)	14 (4.6)	32 (8 1)	35 (8.2)
Hyperkalaemia	12 (10.4)	13 (10.5)	15 (5 3)	15 (4.9)	27 (6.8)	28 (6.5)
Hyperlipidaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypernatraemia	4 (3.5)	4 (3.2)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1.2)
Hyperphosphataemia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hypertriglyceridaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hyperuricaemia	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Hypervolaemia	0	0	1 (0.4)	3 (1.0)	1 (0.3)	3 (0.7)
Hypoalbuminaemia	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Hypocalcaemia	13 (11 3)	14 (11.3)	13 (4.6)	14 (4.6)	26 (6 5)	28 (6.5)
Hypoglycaemia	1 (0.9)	1 (0.8)	5 (1.8)	6 (2.0)	6 (1.5)	7 (1.6)
Hypokalaemia	17 (14.8)	18 (14.5)	35 (12.4)	38 (12.5)	52 (13.1)	56 (13.1)
Hypomagnesaemia	9 (7.8)	11 (8.9)	15 (5 3)	18 (5.9)	24 (6.0)	29 (6.8)
Hyponatraemia	5 (4.3)	6 (4.8)	8 (2.8)	8 (2.6)	13 (3 3)	14 (3.3)
Hypophagia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)

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Hypophosphataemia	3 (2.6)	4 (3.2)	5 (1.8)	6 (2.0)	8 (2.0)	10 (2.3)
Hypoproteinaemia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hypovolaemia	0	0	6 (2.1)	7 (2.3)	6 (1.5)	7 (1.6)
Iron Overload	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Lactic Acidosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Malnutrition	3 (2.6)	3 (2.4)	8 (2.8)	8 (2.6)	11 (2.8)	11 (2.6)
Metabolic Acidosis	11 (9.6)	11 (8.9)	9 (3.2)	9 (3.0)	20 (5.0)	20 (4.7)
Metabolic Alkalosis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Metabolic Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Polydipsia	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Tumour Lysis Syndrome	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Vitamin K Deficiency	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Musculoskeletal And Connective Tissue Disorders	**55 (47 8)**	**55 (44.4)**	**112 (39.7)**	**118 (38.8)**	**167 (42.1)**	**173 (40.4)**
Amyotrophy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Arthralgia	12 (10.4)	12 (9.7)	17 (6.0)	19 (6.3)	29 (7 3)	31 (7.2)
Arthritis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Back Pain	18 (15.7)	18 (14.5)	22 (7.8)	22 (7.2)	40 (10.1)	40 (9.3)
Bone Lesion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bone Pain	4 (3.5)	4 (3.2)	6 (2.1)	8 (2.6)	10 (2 5)	12 (2.8)
Bursitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chest Wall Mass	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Compartment Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dactylitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fistula	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Fistula Discharge	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Flank Pain	3 (2.6)	3 (2.4)	5 (1.8)	7 (2.3)	8 (2.0)	10 (2.3)
Groin Pain	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Haemarthrosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypercreatinaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Joint Range Of Motion Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Joint Stiffness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Joint Swelling	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Mobility Decreased	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Muscle Atrophy	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)

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Muscle Contracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Muscle Rigidity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Muscle Spasms	2 (1.7)	2 (1.6)	11 (3 9)	13 (4.3)	13 (3 3)	15 (3.5)
Muscle Twitching	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Muscular Weakness	10 (8.7)	10 (8.1)	14 (5.0)	14 (4.6)	24 (6.0)	24 (5.6)
Musculoskeletal Chest Pain	3 (2.6)	3 (2.4)	5 (1.8)	5 (1.6)	8 (2.0)	8 (1.9)
Musculoskeletal Discomfort	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Musculoskeletal Pain	7 (6.1)	7 (5.6)	18 (6.4)	18 (5.9)	25 (6 3)	25 (5.8)
Musculoskeletal Stiffness	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Myalgia	3 (2.6)	3 (2.4)	12 (4 3)	13 (4.3)	15 (3.8)	16 (3.7)
Myopathy	5 (4.3)	5 (4.0)	1 (0.4)	1 (0.3)	6 (1.5)	6 (1.4)
Myositis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neck Pain	2 (1.7)	2 (1.6)	9 (3.2)	9 (3.0)	11 (2.8)	11 (2.6)
Nuchal Rigidity	0	0	7 (2.5)	7 (2.3)	7 (1.8)	7 (1.6)
Osteoarthritis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Osteonecrosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pain In Extremity	23 (20.0)	23 (18.5)	29 (10.3)	30 (9.9)	52 (13.1)	53 (12.4)
Pain In Jaw	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Pathological Fracture	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Psoriatic Arthropathy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rhabdomyolysis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Rheumatoid Arthritis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rotator Cuff Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Soft Tissue Mass	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Spinal Osteoarthritis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Synovitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Systemic Lupus Erythematosus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tendon Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vertebral Lesion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**28 (24 3)**	**28 (22.6)**	**46 (16.3)**	**49 (16.1)**	**74 (18.6)**	**77 (18.0)**
Acute Lymphocytic Leukaemia Recurrent	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Acute Myeloid Leukaemia	10 (8.7)	10 (8.1)	20 (7 1)	21 (6.9)	30 (7.6)	31 (7.2)
Acute Myeloid Leukaemia Recurrent	2 (1.7)	2 (1.6)	9 (3.2)	9 (3.0)	11 (2.8)	11 (2.6)
Anogenital Warts	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)

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Blast Cell Crisis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blast Crisis In Myelogenous Leukaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Central Nervous System Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chloroma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Chronic Lymphocytic Leukaemia Recurrent	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Myeloid Leukaemia	4 (3.5)	4 (3.2)	2 (0.7)	4 (1.3)	6 (1.5)	8 (1.9)
Fibroadenoma Of Breast	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Cancer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Neoplasm	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Kaposi's Sarcoma	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Leukaemia	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Leukaemia Cutis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Leukaemic Retinopathy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipoma Of Breast	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lung Neoplasm	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lymphoma	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Metastases To Bone	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metastases To Meninges	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myelodysplastic Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neoplasm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Neoplasm Malignant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Non-Hodgkin's Lymphoma	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Plasma Cell Myeloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Tract Neoplasm	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
T-Cell Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorders	**71 (61.7)**	**74 (59.7)**	**155 (55.0)**	**163 (53.6)**	**226 (56.9)**	**237 (55.4)**
Ageusia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Amnesia	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Aphasia	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Arachnoiditis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Asterixis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ataxia	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Balance Disorder	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Brain Oedema	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Brain Stem Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cauda Equina Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Central Nervous System Inflammation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Central Nervous System Lesion	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Cerebral Atrophy	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Cerebral Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cerebral Haematoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cerebral Haemorrhage	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Cerebral Infarction	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Cerebrovascular Accident	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Choreoathetosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cognitive Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Coma	6 (5.2)	7 (5.6)	1 (0.4)	1 (0.3)	7 (1.8)	8 (1.9)
Coordination Abnormal	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Cranial Nerve Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Demyelination	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Depressed Level Of Consciousness	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Dizziness	18 (15.7)	18 (14.5)	29 (10.3)	30 (9.9)	47 (11.8)	48 (11.2)
Dizziness Postural	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dysarthria	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Dysgeusia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Dyskinesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dystonia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Embolic Stroke	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Encephalomalacia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Encephalopathy	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Facial Paralysis	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Facial Paresis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemorrhage Intracranial	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haemorrhagic Cerebral Infarction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Head Titubation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Headache	24 (20 9)	24 (19.4)	85 (30.1)	88 (28.9)	109 (27.5)	112 (26.2)
Hemianopia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Hemianopia Homonymous	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hemiparesis	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Hemiplegia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hyperreflexia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hypoaesthesia	7 (6.1)	7 (5.6)	10 (3 5)	10 (3.3)	17 (4 3)	17 (4.0)
Hypokinesia	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Hyporeflexia	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Hypotonia	0	0	3 (1.1)	4 (1.3)	3 (0.8)	4 (0.9)
IIIrd Nerve Paralysis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intellectual Disability	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intention Tremor	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intracranial Pressure Increased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Intraventricular Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ischaemic Stroke	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Lethargy	12 (10.4)	12 (9.7)	6 (2.1)	7 (2.3)	18 (4 5)	19 (4.4)
Loss Of Consciousness	1 (0.9)	3 (2.4)	2 (0.7)	2 (0.7)	3 (0.8)	5 (1.2)
Memory Impairment	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Mental Impairment	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Metabolic Encephalopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Migraine	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mononeuropathy Multiplex	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Motor Dysfunction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myoclonus	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Nervous System Disorder	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Neurological Decompensation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neuropathy Peripheral	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Nystagmus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Occipital Neuralgia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	6 (5.2)	6 (4.8)	13 (4.6)	13 (4.3)	19 (4.8)	19 (4.4)
Parkinsonism	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Peroneal Nerve Palsy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Post Herpetic Neuralgia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Postural Tremor	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Presyncope	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Psychomotor Skills Impaired	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Restless Legs Syndrome	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)

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Sciatica	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Sedation	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Seizure	7 (6.1)	7 (5.6)	10 (3 5)	10 (3.3)	17 (4 3)	17 (4.0)
Sensory Loss	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Sinus Headache	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Slow Response To Stimuli	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Somnolence	9 (7.8)	9 (7.3)	12 (4 3)	12 (3.9)	21 (5 3)	21 (4.9)
Speech Disorder	2 (1.7)	2 (1.6)	4 (1.4)	5 (1.6)	6 (1.5)	7 (1.6)
Syncope	0	0	3 (1.1)	4 (1.3)	3 (0.8)	4 (0.9)
Tension Headache	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Toxic Encephalopathy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tremor	10 (8.7)	11 (8.9)	20 (7 1)	20 (6.6)	30 (7.6)	31 (7.2)
Unresponsive To Stimuli	9 (7.8)	10 (8.1)	5 (1.8)	5 (1.6)	14 (3 5)	15 (3.5)
Visual Field Defect	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vocal Cord Paralysis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Product Issues	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Device Occlusion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombosis In Device	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Psychiatric Disorders	**65 (56 5)**	**66 (53.2)**	**87 (30.9)**	**94 (30.9)**	**152 (38.3)**	**160 (37.4)**
Adjustment Disorder	0	0	0	1 (0.3)	0	1 (0.2)
Aggression	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Agitation	7 (6.1)	7 (5.6)	9 (3.2)	10 (3.3)	16 (4.0)	17 (4.0)
Anxiety	17 (14.8)	17 (13.7)	30 (10.6)	32 (10.5)	47 (11.8)	49 (11.4)
Belligerence	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blunted Affect	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Confusional State	18 (15.7)	18 (14.5)	16 (5.7)	17 (5.6)	34 (8.6)	35 (8.2)
Delirium	1 (0.9)	1 (0.8)	2 (0.7)	3 (1.0)	3 (0.8)	4 (0.9)
Delusion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Depressed Mood	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Depression	23 (20.0)	23 (18.5)	27 (9.6)	27 (8.9)	50 (12.6)	50 (11.7)
Disorientation	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Eating Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Echolalia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Flat Affect	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)

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Hallucination	3 (2.6)	3 (2.4)	1 (0.4)	2 (0.7)	4 (1.0)	5 (1.2)
Hallucination, Auditory	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hallucination, Visual	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Insomnia	21 (18 3)	22 (17.7)	29 (10.3)	31 (10.2)	50 (12.6)	53 (12.4)
Irritability	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Libido Decreased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mental Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Mental Status Changes	15 (13.0)	15 (12.1)	16 (5.7)	17 (5.6)	31 (7.8)	32 (7.5)
Mood Altered	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mood Swings	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Nervousness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nightmare	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Organic Brain Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paranoia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Perseveration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Posturing	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Psychomotor Retardation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Psychotic Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Restlessness	6 (5.2)	6 (4.8)	2 (0.7)	2 (0.7)	8 (2.0)	8 (1.9)
Sleep Disorder	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Staring	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Substance-Induced Psychotic Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tearfulness	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal And Urinary Disorders	**61 (53.0)**	**63 (50.8)**	**58 (20.6)**	**60 (19.7)**	**119 (30.0)**	**123 (28.7)**
Acute Kidney Injury	9 (7.8)	9 (7.3)	4 (1.4)	5 (1.6)	13 (3 3)	14 (3.3)
Anuria	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Azotaemia	0	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.5)
Bladder Pain	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bladder Spasm	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Kidney Disease	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Cystitis Haemorrhagic	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Dysuria	10 (8.7)	10 (8.1)	5 (1.8)	5 (1.6)	15 (3.8)	15 (3.5)
End Stage Renal Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haematuria	4 (3.5)	4 (3.2)	6 (2.1)	6 (2.0)	10 (2 5)	10 (2.3)

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Hydronephrosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Incontinence	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Micturition Urgency	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Nephritis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nephrolithiasis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Nephropathy Toxic	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Nocturia	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Oliguria	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Pollakiuria	5 (4.3)	5 (4.0)	3 (1.1)	3 (1.0)	8 (2.0)	8 (1.9)
Polyuria	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Renal Colic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Cyst	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Disorder	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Renal Failure	33 (28.7)	34 (27.4)	20 (7 1)	21 (6.9)	53 (13.4)	55 (12.9)
Renal Impairment	5 (4.3)	5 (4.0)	3 (1.1)	3 (1.0)	8 (2.0)	8 (1.9)
Renal Mass	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Tubular Acidosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Renal Tubular Necrosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Urinary Hesitation	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Urinary Incontinence	3 (2.6)	3 (2.4)	5 (1.8)	5 (1.6)	8 (2.0)	8 (1.9)
Urinary Retention	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Urine Flow Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Reproductive System And Breast Disorders	**10 (8.7)**	**11 (8.9)**	**22 (7 8)**	**23 (7.6)**	**32 (8 1)**	**34 (7.9)**
Amenorrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Benign Prostatic Hyperplasia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Breast Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Breast Swelling	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Breast Tenderness	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Dysmenorrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Erectile Dysfunction	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hypomenorrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Menstruation Delayed	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nipple Exudate Bloody	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ovarian Cyst	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Pelvic Fluid Collection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Premature Menopause	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Prostatitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pruritus Genital	0	1 (0.8)	0	0	0	1 (0.2)
Scrotal Mass	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Scrotal Oedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Scrotal Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Scrotal Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Testicular Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Uterine Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Vaginal Discharge	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vaginal Haemorrhage	5 (4.3)	5 (4.0)	5 (1.8)	6 (2.0)	10 (2 5)	11 (2.6)
Vulvovaginal Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vulvovaginal Pruritus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**89 (77.4)**	**93 (75.0)**	**149 (52.8)**	**164 (53.9)**	**238 (59.9)**	**257 (60.0)**
Acute Respiratory Distress Syndrome	6 (5.2)	6 (4.8)	1 (0.4)	1 (0.3)	7 (1.8)	7 (1.6)
Acute Respiratory Failure	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Allergic Sinusitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Apnoea	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Asthma	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Atelectasis	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Bronchial Obstruction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchial Wall Thickening	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bronchiectasis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bronchospasm	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Cheyne-Stokes Respiration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Obstructive Pulmonary Disease	0	0	5 (1.8)	6 (2.0)	5 (1.3)	6 (1.4)
Cough	27 (23 5)	27 (21.8)	55 (19 5)	58 (19.1)	82 (20.7)	85 (19.9)
Dysphonia	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Dyspnoea	32 (27.8)	33 (26.6)	59 (20.9)	66 (21.7)	91 (22.9)	99 (23.1)
Dyspnoea Exertional	5 (4.3)	5 (4.0)	4 (1.4)	4 (1.3)	9 (2.3)	9 (2.1)
Emphysema	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Epistaxis	22 (19 1)	24 (19.4)	22 (7.8)	24 (7.9)	44 (11.1)	48 (11.2)
Haemoptysis	20 (17.4)	21 (16.9)	18 (6.4)	18 (5.9)	38 (9.6)	39 (9.1)

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Number (%) of Subjects

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Haemothorax	2 (1.7)	3 (2.4)	1 (0.4)	1 (0.3)	3 (0.8)	4 (0.9)
Hiccups	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Hypercapnia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypopnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypoxia	11 (9.6)	11 (8.9)	8 (2.8)	10 (3.3)	19 (4.8)	21 (4.9)
Interstitial Lung Disease	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Lower Respiratory Tract Congestion	0	0	0	1 (0.3)	0	1 (0.2)
Lung Consolidation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Disorder	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Lung Infiltration	9 (7.8)	9 (7.3)	11 (3 9)	12 (3.9)	20 (5.0)	21 (4.9)
Mediastinal Haematoma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nasal Congestion	6 (5.2)	7 (5.6)	8 (2.8)	9 (3.0)	14 (3 5)	16 (3.7)
Nasal Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nasal Dryness	1 (0.9)	1 (0.8)	3 (1.1)	4 (1.3)	4 (1.0)	5 (1.2)
Nasal Obstruction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nasal Oedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nasal Septum Perforation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nasal Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Obliterative Bronchiolitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Obstructive Airways Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Organising Pneumonia	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Oropharyngeal Pain	10 (8.7)	10 (8.1)	21 (7.4)	22 (7.2)	31 (7.8)	32 (7.5)
Oropharyngeal Plaque	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Orthopnoea	1 (0 9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Painful Respiration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Paranasal Sinus Hypersecretion	1 (0 9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pharyngeal Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pharyngeal Erythema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pharyngeal Ulceration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pleural Effusion	17 (14.8)	17 (13.7)	20 (7 1)	20 (6.6)	37 (9 3)	37 (8.6)
Pleural Fibrosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pleuritic Pain	7 (6.1)	7 (5.6)	9 (3.2)	9 (3.0)	16 (4.0)	16 (3.7)
Pneumomediastinum	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumonia Aspiration	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pneumonitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumothorax	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)

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Productive Cough	5 (4.3)	5 (4.0)	9 (3.2)	9 (3.0)	14 (3 5)	14 (3.3)
Pulmonary Alveolar Haemorrhage	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pulmonary Congestion	0	0	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.7)
Pulmonary Fibrosis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary Haemorrhage	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Pulmonary Hypertension	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pulmonary Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Mass	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary Oedema	5 (4.3)	5 (4.0)	9 (3.2)	10 (3.3)	14 (3 5)	15 (3.5)
Rales	5 (4.3)	5 (4.0)	8 (2.8)	8 (2.6)	13 (3 3)	13 (3.0)
Respiratory Acidosis	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Respiratory Alkalosis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Arrest	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Disorder	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Distress	9 (7.8)	9 (7.3)	11 (3 9)	12 (3.9)	20 (5.0)	21 (4.9)
Respiratory Failure	21 (18 3)	23 (18.5)	20 (7 1)	21 (6.9)	41 (10.3)	44 (10.3)
Respiratory Tract Congestion	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Rhinitis Allergic	1 (0.9)	1 (0.8)	5 (1.8)	6 (2.0)	6 (1.5)	7 (1.6)
Rhinorrhoea	10 (8.7)	10 (8.1)	9 (3.2)	9 (3.0)	19 (4.8)	19 (4.4)
Rhonchi	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Sinus Congestion	7 (6.1)	7 (5.6)	4 (1.4)	5 (1.6)	11 (2.8)	12 (2.8)
Sinus Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sneezing	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sputum Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Tachypnoea	6 (5.2)	6 (4.8)	11 (3 9)	12 (3.9)	17 (4 3)	18 (4.2)
Throat Irritation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Throat Tightness	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Upper-Airway Cough Syndrome	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Vocal Cord Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Wheezing	6 (5.2)	6 (4.8)	12 (4 3)	13 (4.3)	18 (4 5)	19 (4.4)
Skin And Subcutaneous Tissue Disorders	**57 (49.6)**	**59 (47.6)**	**119 (42.2)**	**125 (41.1)**	**176 (44.3)**	**184 (43.0)**
Acne	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Alopecia	1 (0.9)	1 (0.8)	12 (4 3)	14 (4.6)	13 (3 3)	15 (3.5)
Blister	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)

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Blood Blister	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cold Sweat	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cutaneous Lupus Erythematosus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Decubitus Ulcer	3 (2.6)	3 (2.4)	6 (2.1)	6 (2.0)	9 (2.3)	9 (2.1)
Dermal Cyst	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dermatitis Allergic	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Dermatitis Atopic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dermatosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Eruption	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Dry Skin	4 (3.5)	4 (3.2)	8 (2.8)	8 (2.6)	12 (3.0)	12 (2.8)
Ecchymosis	7 (6.1)	7 (5.6)	5 (1.8)	6 (2.0)	12 (3.0)	13 (3.0)
Erythema	8 (7.0)	8 (6.5)	8 (2.8)	9 (3.0)	16 (4.0)	17 (4.0)
Hyperhidrosis	2 (1.7)	2 (1.6)	8 (2.8)	8 (2.6)	10 (2 5)	10 (2.3)
Ingrowing Nail	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Lipodystrophy Acquired	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Livedo Reticularis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Macule	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Miliaria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Neutrophilic Dermatosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Night Sweats	3 (2.6)	3 (2.4)	10 (3 5)	10 (3.3)	13 (3 3)	13 (3.0)
Onychoclasis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Palmar Erythema	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Petechiae	6 (5.2)	6 (4.8)	5 (1.8)	8 (2.6)	11 (2.8)	14 (3.3)
Photosensitivity Reaction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pigmentation Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Prurigo	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pruritus	14 (12 2)	15 (12.1)	13 (4.6)	14 (4.6)	27 (6.8)	29 (6.8)
Pruritus Allergic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pruritus Generalised	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Psoriasis	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Purpura	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash	16 (13 9)	17 (13.7)	28 (9 9)	29 (9.5)	44 (11.1)	46 (10.7)
Rash Erythematous	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Rash Generalised	1 (0.9)	2 (1.6)	5 (1.8)	6 (2.0)	6 (1.5)	8 (1.9)
Rash Macular	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Rash Maculo-Papular	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)

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Rash Papular	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Rash Pruritic	0	0	8 (2.8)	8 (2.6)	8 (2.0)	8 (1.9)
Rash Vesicular	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Scab	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin Burning Sensation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Skin Discolouration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Skin Disorder	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Skin Exfoliation	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Skin Haemorrhage	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Skin Hyperpigmentation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Skin Irritation	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Skin Lesion	8 (7.0)	8 (6.5)	10 (3 5)	11 (3.6)	18 (4 5)	19 (4.4)
Skin Mass	5 (4.3)	5 (4.0)	3 (1.1)	3 (1.0)	8 (2.0)	8 (1.9)
Skin Ulcer	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Skin Ulcer Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Stevens-Johnson Syndrome	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Subcutaneous Emphysema	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Swelling Face	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Urticaria	2 (1.7)	2 (1.6)	6 (2.1)	7 (2.3)	8 (2.0)	9 (2.1)
Urticaria Papular	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Social Circumstances	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Treatment Noncompliance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Surgical And Medical Procedures	**19 (16 5)**	**19 (15.3)**	**38 (13.5)**	**41 (13.5)**	**57 (14.4)**	**60 (14.0)**
Abdominal Cavity Drainage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Autologous Bone Marrow Transplantation Therapy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bone Marrow Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cataract Operation	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Catheter Removal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Central Venous Catheter Removal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chemotherapy	0	0	4 (1.4)	5 (1.6)	4 (1.0)	5 (1.2)
Choledocholithotomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Corneal Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Debridement	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Endotracheal Intubation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Exploratory Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Laser Surgery	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastrostomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Haemofiltration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Laparotomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lung Lobectomy	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Lung Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Maxillofacial Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Medical Device Implantation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolic Abnormality Management	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nail Operation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Omentectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Orthopaedic Procedure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Photopheresis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Plastic Surgery To The Face	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumonectomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Polypectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Resection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Sinus Operation	4 (3.5)	4 (3.2)	6 (2.1)	7 (2.3)	10 (2 5)	11 (2.6)
Skin Graft	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Splenectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Stem Cell Transplant	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Surgery	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Therapeutic Procedure	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Thoracotomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tooth Extraction	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Transfusion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Transplant	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Wisdom Teeth Removal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Wound Drainage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vascular Disorders	**58 (50.4)**	**60 (48.4)**	**78 (27.7)**	**86 (28.3)**	**136 (34.3)**	**146 (34.1)**
Aneurysm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Angiopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Aortic Aneurysm	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Arterial Insufficiency	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Arteriosclerosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Circulatory Collapse	0	1 (0.8)	0	0	0	1 (0.2)
Deep Vein Thrombosis	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Flushing	5 (4.3)	5 (4.0)	3 (1.1)	3 (1.0)	8 (2.0)	8 (1.9)
Haematoma	4 (3.5)	4 (3.2)	5 (1.8)	7 (2.3)	9 (2.3)	11 (2.6)
Haemodynamic Instability	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemorrhage	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Hot Flush	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypertension	24 (20 9)	24 (19.4)	28 (9 9)	31 (10.2)	52 (13.1)	55 (12.9)
Hypoperfusion	0	1 (0.8)	0	0	0	1 (0.2)
Hypotension	28 (24 3)	29 (23.4)	31 (11.0)	34 (11.2)	59 (14.9)	63 (14.7)
Hypovolaemic Shock	0	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.5)
Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intermittent Claudication	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ischaemia	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Orthostatic Hypertension	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Orthostatic Hypotension	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Pallor	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Peripheral Artery Thrombosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Peripheral Ischaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Peripheral Venous Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Phlebitis	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Poor Peripheral Circulation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Raynaud's Phenomenon	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Shock Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Thrombophlebitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Thrombophlebitis Superficial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vasodilatation	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Venous Thrombosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-22 副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**36 (31 3)**	**37 (29.8)**	**122 (43.3)**	**127 (41.8)**	**158 (39.8)**	**164 (38.3)**
Blood And Lymphatic System Disorders	**0**	**0**	**8 (2.8)**	**8 (2.6)**	**8 (2.0)**	**8 (1.9)**
Anaemia	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Eosinophilia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancytopenia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombocytopenia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cardiac Disorders	**4 (3.5)**	**4 (3.2)**	**10 (3 5)**	**10 (3.3)**	**14 (3 5)**	**14 (3.3)**
Aortic Valve Sclerosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Arteriosclerosis Coronary Artery	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Atrial Fibrillation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Atrial Flutter	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bundle Branch Block	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Extrasystoles	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Left Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mitral Valve Stenosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myocardial Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Supraventricular Tachycardia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Tachycardia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Extrasystoles	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Tachycardia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ear And Labyrinth Disorders	**1 (0.9)**	**1 (0.8)**	**1 (0.4)**	**1 (0.3)**	**2 (0.5)**	**2 (0.5)**
Ear Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypoacusis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tinnitus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Endocrine Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Adrenal Insufficiency	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Adrenocortical Insufficiency Acute	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypogonadism	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
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Number (%) of Subjects

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Eye Disorders	**1 (0.9)**	**1 (0.8)**	**5 (1.8)**	**6 (2.0)**	**6 (1.5)**	**7 (1.6)**
Conjunctival Hyperaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Erythema Of Eyelid	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Irritation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vision Blurred	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Gastrointestinal Disorders	**19 (16 5)**	**19 (15.3)**	**60 (21.3)**	**62 (20.4)**	**79 (19.9)**	**81 (18.9)**
Abdominal Discomfort	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Abdominal Distension	0	0	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.7)
Abdominal Pain	2 (1.7)	2 (1.6)	4 (1.4)	5 (1.6)	6 (1.5)	7 (1.6)
Abdominal Pain Upper	1 (0.9)	1 (0.8)	10 (3 5)	11 (3.6)	11 (2.8)	12 (2.8)
Abdominal Tenderness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abnormal Faeces	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Constipation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Diarrhoea	3 (2.6)	3 (2.4)	12 (4 3)	12 (3.9)	15 (3.8)	15 (3.5)
Dry Mouth	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Dyspepsia	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Dysphagia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eructation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Faeces Soft	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Flatulence	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Gastrointestinal Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gastrooesophageal Reflux Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypoaesthesia Oral	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ileus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lip Dry	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Lip Swelling	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nausea	10 (8.7)	10 (8.1)	25 (8 9)	25 (8.2)	35 (8.8)	35 (8.2)
Oesophageal Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oral Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancreatitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Retching	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Vomiting	8 (7.0)	8 (6.5)	18 (6.4)	18 (5.9)	26 (6 5)	26 (6.1)

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All Randomized Subjects
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Number (%) of Subjects

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General Disorders And Administration Site Conditions	**4 (3.5)**	**4 (3.2)**	**15 (5 3)**	**15 (4.9)**	**19 (4 8)**	**19 (4.4)**
Asthenia	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	5 (1.3)	5 (1.2)
Chest Pain	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Chills	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Death	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fatigue	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Malaise	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mucosal Inflammation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oedema Peripheral	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pyrexia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hepatobiliary Disorders	**2 (1.7)**	**2 (1.6)**	**5 (1.8)**	**5 (1.6)**	**7 (1.8)**	**7 (1.6)**
Cholestasis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatic Failure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Function Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatocellular Injury	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatomegaly	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatosplenomegaly	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Jaundice	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Immune System Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Drug Hypersensitivity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Infections And Infestations	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**4 (1.0)**	**4 (0.9)**
Conjunctivitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Meningitis Cryptococcal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oesophageal Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Injury, Poisoning And Procedural Complications	**1 (0.9)**	**1 (0.8)**	**4 (1.4)**	**4 (1.3)**	**5 (1.3)**	**5 (1.2)**
Excoriation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Overdose	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Toxicity To Various Agents	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Transfusion Reaction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Investigations	**9 (7.8)**	**9 (7.3)**	**42 (14.9)**	**43 (14.1)**	**51 (12.8)**	**52 (12.1)**
Alanine Aminotransferase Increased	2 (1.7)	2 (1.6)	9 (3.2)	9 (3.0)	11 (2.8)	11 (2.6)
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aspartate Aminotransferase Increased	1 (0.9)	1 (0.8)	8 (2.8)	8 (2.6)	9 (2.3)	9 (2.1)
Bilirubin Conjugated Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Alkaline Phosphatase Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Alkaline Phosphatase Increased	0	0	5 (1.8)	5 (1.6)	5 (1.3)	5 (1.2)
Blood Bilirubin Increased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Blood Creatinine Increased	0	0	5 (1.8)	5 (1.6)	5 (1.3)	5 (1.2)
Blood Gases Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Triglycerides Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Urea Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardioactive Drug Level Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardioactive Drug Level Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Level Changed	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Level Increased	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Electrocardiogram Change	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qrs Complex Prolonged	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qt Prolonged	0	0	6 (2.1)	6 (2.0)	6 (1.5)	6 (1.4)
Gamma-Glutamyltransferase Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Glucocorticoids Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Enzyme Increased	1 (0 9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Laboratory Test Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Liver Function Test Abnormal	0	0	0	1 (0.3)	0	1 (0.2)
Liver Function Test Increased	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Pancreatic Enzymes Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Platelet Count Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Qrs Axis Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Weight Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Weight Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Metabolism And Nutrition Disorders	**3 (2.6)**	**3 (2.4)**	**11 (3 9)**	**11 (3.6)**	**14 (3 5)**	**14 (3.3)**
Decreased Appetite	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)
Electrolyte Imbalance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperkalaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperphosphataemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperuricaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypokalaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Metabolic Acidosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Polydipsia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Musculoskeletal And Connective Tissue Disorders	**4 (3.5)**	**4 (3.2)**	**7 (2.5)**	**8 (2.6)**	**11 (2 8)**	**12 (2.8)**
Arthralgia	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Back Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bone Pain	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fistula	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mobility Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Muscular Weakness	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Musculoskeletal Chest Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myalgia	0	0	0	1 (0.3)	0	1 (0.2)
Nuchal Rigidity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pain In Extremity	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pain In Jaw	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorders	**7 (6.1)**	**7 (5.6)**	**30 (10.6)**	**32 (10.5)**	**37 (9 3)**	**39 (9.1)**
Balance Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dizziness	1 (0.9)	1 (0.8)	6 (2.1)	6 (2.0)	7 (1.8)	7 (1.6)
Dysgeusia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Headache	3 (2.6)	3 (2.4)	15 (5 3)	17 (5.6)	18 (4 5)	20 (4.7)
Hyperreflexia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hypoaesthesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypotonia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Memory Impairment	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Mental Impairment	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mononeuropathy Multiplex	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Neuropathy Peripheral	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Seizure	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Somnolence	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Speech Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tremor	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Psychiatric Disorders	**0**	**0**	**6 (2.1)**	**6 (2.0)**	**6 (1.5)**	**6 (1.4)**
Anxiety	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Confusional State	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Delirium	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mental Status Changes	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Renal And Urinary Disorders	**2 (1.7)**	**2 (1.6)**	**7 (2.5)**	**7 (2.3)**	**9 (2.3)**	**9 (2.1)**
Acute Kidney Injury	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Kidney Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nephropathy Toxic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nocturia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Renal Failure	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Renal Tubular Acidosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Urinary Hesitation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Reproductive System And Breast Disorders	**0**	**0**	**3 (1.1)**	**3 (1.0)**	**3 (0.8)**	**3 (0.7)**
Breast Swelling	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Breast Tenderness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypomenorrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Menstruation Delayed	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**4 (1.0)**	**4 (0.9)**
Dyspnoea	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Epistaxis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Infiltration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Skin And Subcutaneous Tissue Disorders	**4 (3.5)**	**5 (4.0)**	**24 (8 5)**	**24 (7.9)**	**28 (7 1)**	**29 (6.8)**
Alopecia	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Dermatitis Atopic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dermatosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dry Skin	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hyperhidrosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pruritus	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Rash	1 (0.9)	2 (1.6)	5 (1.8)	5 (1.6)	6 (1.5)	7 (1.6)
Rash Macular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Maculo-Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Pruritic	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Rash Vesicular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Urticaria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Urticaria Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Surgical And Medical Procedures	**0**	**0**	**0**	**1 (0.3)**	**0**	**1 (0.2)**
Therapeutic Procedure	0	0	0	1 (0.3)	0	1 (0.2)
Vascular Disorders	**3 (2.6)**	**3 (2.4)**	**3 (1.1)**	**3 (1.0)**	**6 (1.5)**	**6 (1.4)**
Haematoma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypertension	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hypotension	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Ischaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-23 重度／生命を脅かす有害事象の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Subjects Reporting Any Adverse Event	**89 (77.4)**	**91 (73.4)**	**55 (47.8)**	**58 (46.8)**	**166 (58 9)**	**179 (58.9)**	**81 (28.7)**	**88 (28.9)**	**255 (64.2)**	**270 (63.1)**	**136 (34.3)**	**146 (34.1)**
Blood And Lymphatic System Disorders	**25 (21.7)**	**26 (21.0)**	**9 (7.8)**	**9 (7.3)**	**43 (15.2)**	**50 (16.4)**	**14 (5.0)**	**14 (4.6)**	**68 (17.1)**	**76 (17.8)**	**23 (5.8)**	**23 (5.4)**
Anaemia	2 (1.7)	3 (2.4)	1 (0.9)	1 (0.8)	12 (4.3)	14 (4.6)	4 (1.4)	4 (1.3)	14 (3.5)	17 (4.0)	5 (1.3)	5 (1.2)
Aplastic Anaemia	0	0	0	0	1 (0.4)	2 (0.7)	0	0	1 (0.3)	2 (0.5)	0	0
Autoimmune Haemolytic Anaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Coagulopathy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Disseminated Intravascular Coagulation	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Febrile Neutropenia	3 (2.6)	3 (2.4)	0	0	9 (3 2)	12 (3.9)	1 (0.4)	1 (0.3)	12 (3.0)	15 (3 5)	1 (0.3)	1 (0.2)
Haemolysis	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Haemolytic Anaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Haemolytic Uraemic Syndrome	3 (2.6)	3 (2.4)	0	0	0	0	0	0	3 (0.8)	3 (0.7)	0	0
Hypercoagulation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Leukocytosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Leukopenia	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Neutropenia	4 (3.5)	4 (3.2)	1 (0.9)	1 (0.8)	11 (3.9)	11 (3.6)	2 (0.7)	2 (0.7)	15 (3.8)	15 (3 5)	3 (0.8)	3 (0.7)
Pancytopenia	3 (2.6)	3 (2.4)	1 (0.9)	1 (0.8)	7 (2 5)	7 (2.3)	0	0	10 (2.5)	10 (2 3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Splenic Infarction	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Splenomegaly	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Thrombocytopenia	10 (8.7)	10 (8.1)	6 (5.2)	6 (4.8)	12 (4.3)	16 (5.3)	8 (2.8)	8 (2.6)	22 (5.5)	26 (6 1)	14 (3.5)	14 (3.3)
Thrombotic Thrombocytopenic Purpura	4 (3.5)	4 (3.2)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	5 (1.3)	5 (1 2)	1 (0.3)	1 (0.2)
Cardiac Disorders	**14 (12.2)**	**14 (11.3)**	**12 (10.4)**	**13 (10.5)**	**18 (6.4)**	**19 (6.3)**	**20 (7.1)**	**21 (6.9)**	**32 (8.1)**	**33 (7.7)**	**32 (8.1)**	**34 (7.9)**
Arrhythmia Supraventricular	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Arteriosclerosis Coronary Artery	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Atrial Fibrillation	1 (0.9)	1 (0.8)	0	0	3 (1 1)	3 (1.0)	0	0	4 (1.0)	4 (0 9)	0	0
Atrial Flutter	3 (2.6)	3 (2.4)	0	0	1 (0.4)	1 (0.3)	0	0	4 (1.0)	4 (0 9)	0	0
Bradycardia	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	3 (1.1)	3 (1.0)	2 (0.5)	2 (0 5)	4 (1.0)	4 (0.9)
Bundle Branch Block	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cardiac Arrest	0	0	2 (1.7)	2 (1.6)	0	0	6 (2.1)	6 (2.0)	0	0	8 (2.0)	8 (1.9)
Cardiac Failure	1 (0.9)	1 (0.8)	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)	4 (1.0)	4 (0.9)
Cardiac Failure Congestive	1 (0.9)	1 (0.8)	0	0	4 (1.4)	4 (1.3)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1 2)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	1 (0.9)	1 (0.8)	6 (5.2)	7 (5.6)	0	0	8 (2.8)	9 (3.0)	1 (0.3)	1 (0 2)	14 (3.5)	16 (3.7)
Cardiogenic Shock	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Cardiopulmonary Failure	1 (0.9)	1 (0.8)	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Coronary Artery Occlusion	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Myocardial Infarction	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

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Pericardial Effusion	2 (1.7)	2 (1.6)	0	0	1 (0.4)	1 (0.3)	0	0	3 (0.8)	3 (0.7)	0	0
Pericarditis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Pulseless Electrical Activity	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Sinus Tachycardia	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Supraventricular Tachycardia	3 (2.6)	3 (2.4)	0	0	4 (1.4)	4 (1.3)	0	0	7 (1.8)	7 (1.6)	0	0
Tachycardia	1 (0.9)	1 (0.8)	0	0	3 (1 1)	4 (1.3)	0	0	4 (1.0)	5 (1 2)	0	0
Ventricular Extrasystoles	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Ventricular Fibrillation	0	0	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)
Ventricular Hypertrophy	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Ventricular Tachycardia	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Ear And Labyrinth Disorders	**0**	**0**	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**0**	**0**
Deafness	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Vertigo Labyrinthine	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Endocrine Disorders	**0**	**0**	**1 (0.9)**	**1 (0.8)**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**1 (0.3)**	**1 (0.2)**
Adrenal Insufficiency	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Adrenocortical Insufficiency Acute	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Hyperthyroidism	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Eye Disorders	**3 (2.6)**	**3 (2.4)**	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**0**	**0**	**7 (1.8)**	**7 (1.6)**	**0**	**0**

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Conjunctival Haemorrhage	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Conjunctivitis Allergic	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Corneal Perforation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Dacryostenosis Acquired	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Dry Eye	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Eye Pain	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Pupils Unequal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Retinal Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Scleral Oedema	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Gastrointestinal Disorders	**24 (20.9)**	**26 (21.0)**	**2 (1.7)**	**3 (2.4)**	**42 (14.9)**	**44 (14.5)**	**4 (1.4)**	**4 (1.3)**	**66 (16.6)**	**70 (16.4)**	**6 (1.5)**	**7 (1.6)**
Abdominal Distension	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Abdominal Pain	5 (4.3)	6 (4.8)	0	0	8 (2.8)	8 (2.6)	0	0	13 (3.3)	14 (3.3)	0	0
Abdominal Pain Lower	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Abdominal Pain Upper	2 (1.7)	2 (1.6)	0	0	0	1 (0.3)	0	0	2 (0.5)	3 (0.7)	0	0
Abdominal Tenderness	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Ascites	2 (1.7)	2 (1.6)	0	0	2 (0.7)	3 (1.0)	1 (0.4)	1 (0.3)	4 (1.0)	5 (1.2)	1 (0.3)	1 (0.2)
Colitis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Constipation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Dental Discomfort	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Diarrhoea	8 (7.0)	8 (6.5)	0	0	10 (3.5)	10 (3.3)	0	0	18 (4.5)	18 (4.2)	0	0

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Diarrhoea Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Duodenal Ulcer	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Dysphagia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Enteritis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Food Poisoning	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Gastric Haemorrhage	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Gastric Perforation	0	0	0	1 (0.8)	0	0	0	0	0	0	0	1 (0.2)
Gastritis	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Gastrointestinal Haemorrhage	2 (1.7)	2 (1.6)	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0 9)	1 (0.3)	1 (0.2)
Gastrooesophageal Reflux Disease	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Haematemesis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Haematochezia	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Haemorrhoids	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.2)	0	0
Ileus	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Ileus Paralytic	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Intestinal Ischaemia	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Intestinal Obstruction	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Mallory-Weiss Syndrome	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Melaena	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Mouth Ulceration	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Nausea	3 (2.6)	4 (3.2)	0	0	11 (3.9)	11 (3.6)	0	0	14 (3.5)	15 (3.5)	0	0

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Oesophageal Stenosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Oesophageal Ulcer	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Oesophagitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Oesophagitis Ulcerative	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Pancreatitis	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Pancreatitis Haemorrhagic	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Pneumatosis Intestinalis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Vomiting	2 (1.7)	3 (2.4)	0	0	12 (4.3)	12 (3.9)	1 (0.4)	1 (0.3)	14 (3.5)	15 (3 5)	1 (0.3)	1 (0.2)
General Disorders And Administration Site Conditions	**39 (33.9)**	**40 (32.3)**	**16 (13.9)**	**16 (12.9)**	**50 (17.7)**	**57 (18.8)**	**8 (2.8)**	**9 (3.0)**	**89 (22.4)**	**97 (22.7)**	**24 (6.0)**	**25 (5.8)**
Asthenia	10 (8.7)	10 (8.1)	0	0	6 (2 1)	7 (2.3)	0	0	16 (4.0)	17 (4.0)	0	0
Brain Death	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Chest Pain	3 (2.6)	4 (3.2)	0	0	5 (1.8)	7 (2.3)	0	0	8 (2.0)	11 (2.6)	0	0
Chills	6 (5.2)	6 (4.8)	0	0	1 (0.4)	1 (0.3)	0	0	7 (1.8)	7 (1.6)	0	0
Death	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Disease Progression	4 (3.5)	4 (3.2)	9 (7.8)	9 (7.3)	9 (3 2)	9 (3.0)	5 (1.8)	5 (1.6)	13 (3.3)	13 (3.0)	14 (3.5)	14 (3.3)
Drug Interaction	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Facial Pain	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Fatigue	6 (5.2)	6 (4.8)	0	0	2 (0.7)	3 (1.0)	0	0	8 (2.0)	9 (2 1)	0	0
General Physical Health Deterioration	1 (0.9)	1 (0.8)	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0 5)	0	0

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Generalised Oedema	3 (2.6)	3 (2.4)	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	0	0	4 (1.0)	5 (1.2)	1 (0.3)	1 (0.2)
Malaise	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Mucosal Inflammation	1 (0.9)	1 (0.8)	0	0	2 (0.7)	3 (1.0)	0	0	3 (0.8)	4 (0 9)	0	0
Multi-Organ Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Multiple Organ Dysfunction Syndrome	3 (2.6)	3 (2.4)	6 (5.2)	6 (4.8)	1 (0.4)	1 (0.3)	3 (1.1)	4 (1.3)	4 (1.0)	4 (0.9)	9 (2.3)	10 (2.3)
Oedema	1 (0.9)	1 (0.8)	0	0	1 (0.4)	2 (0.7)	0	0	2 (0.5)	3 (0.7)	0	0
Oedema Peripheral	0	0	0	0	3 (1 1)	3 (1.0)	0	0	3 (0.8)	3 (0.7)	0	0
Pain	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Pyrexia	11 (9.6)	11 (8.9)	0	0	22 (7.8)	24 (7.9)	0	0	33 (8.3)	35 (8.2)	0	0
Swelling	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hepatobiliary Disorders	**8 (7.0)**	**8 (6.5)**	**0**	**0**	**7 (2 5)**	**7 (2.3)**	**3 (1.1)**	**3 (1.0)**	**15 (3.8)**	**15 (3 5)**	**3 (0.8)**	**3 (0.7)**
Cholecystitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Cholelithiasis	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Hepatic Failure	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)	2 (0.5)	2 (0.5)
Hepatic Function Abnormal	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hepatic Necrosis	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Hepatitis Acute	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Hepatocellular Injury	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hepatosplenomegaly	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hyperbilirubinaemia	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0

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Jaundice	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Liver Disorder	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Immune System Disorders	**13 (11.3)**	**13 (10.5)**	**7 (6.1)**	**9 (7.3)**	**2 (0.7)**	**2 (0.7)**	**1 (0.4)**	**1 (0.3)**	**15 (3.8)**	**15 (3 5)**	**8 (2.0)**	**10 (2.3)**
Acute Graft Versus Host Disease In Liver	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Chronic Graft Versus Host Disease	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Drug Hypersensitivity	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Graft Versus Host Disease	4 (3.5)	4 (3.2)	5 (4.3)	6 (4.8)	1 (0.4)	1 (0.3)	0	0	5 (1.3)	5 (1.2)	5 (1.3)	6 (1.4)
Graft Versus Host Disease In Gastrointestinal Tract	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Graft Versus Host Disease In Liver	2 (1.7)	2 (1.6)	1 (0.9)	1 (0.8)	0	0	0	0	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Graft Versus Host Disease In Lung	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Graft Versus Host Disease In Skin	6 (5.2)	6 (4.8)	0	1 (0.8)	0	0	0	0	6 (1.5)	6 (1.4)	0	1 (0.2)
Transplant Rejection	0	0	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)
Infections And Infestations	**39 (33.9)**	**39 (31.5)**	**12 (10.4)**	**14 (11.3)**	**56 (19.9)**	**61 (20.1)**	**26 (9.2)**	**31 (10.2)**	**95 (23.9)**	**100 (23.4)**	**38 (9.6)**	**45 (10.5)**
Abdominal Infection	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Abscess Neck	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Acquired Immunodeficiency Syndrome	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Anal Abscess	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Aspergilloma	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Aspergillus Infection	3 (2.6)	3 (2.4)	0	0	0	0	1 (0.4)	2 (0.7)	3 (0.8)	3 (0.7)	1 (0.3)	2 (0.5)
Atypical Pneumonia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Bacteraemia	5 (4.3)	5 (4.0)	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	7 (1.8)	7 (1.6)	1 (0.3)	1 (0.2)
Bacterial Infection	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	2 (0.7)	4 (1.3)	0	0	3 (0.8)	5 (1 2)	1 (0.3)	1 (0.2)
Brain Abscess	0	0	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)
Bronchitis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Bronchitis Viral	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Bronchopulmonary Aspergillosis	0	0	0	1 (0.8)	3 (1 1)	3 (1.0)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)	1 (0.3)	2 (0.5)
Catheter Site Infection	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Cellulitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Cellulitis Of Male External Genital Organ	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cellulitis Orbital	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Cerebral Aspergillosis	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Clostridium Difficile Colitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Conjunctivitis	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Cytomegalovirus Colitis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Cytomegalovirus Infection	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Device Related Infection	1 (0.9)	1 (0.8)	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0 5)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

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Disseminated Tuberculosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Empyema	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Encephalitis	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
End Stage Aids	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Endocarditis Bacterial	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Enterobacter Infection	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Enterococcal Bacteraemia	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Enterococcal Infection	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Enterococcal Sepsis	0	0	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.2)
Escherichia Sepsis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Fungaemia	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Fungal Infection	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Fungal Sepsis	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Furuncle	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Fusarium Infection	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Hepatosplenic Candidiasis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Herpes Zoster	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Infection Parasitic	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Intervertebral Discitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Klebsiella Infection	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lung Abscess	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

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Meningitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Meningitis Cryptococcal	0	0	0	0	2 (0.7)	2 (0.7)	6 (2.1)	6 (2.0)	2 (0.5)	2 (0.5)	6 (1.5)	6 (1.4)
Mycobacterial Infection	0	0	0	0	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Oesophageal Candidiasis	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Oral Herpes	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.2)	0	0
Osteomyelitis	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Otitis Media	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Pelvic Abscess	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Peritonitis	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Pneumococcal Sepsis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pneumonia	7 (6.1)	7 (5.6)	3 (2.6)	3 (2.4)	14 (5.0)	14 (4.6)	0	2 (0.7)	21 (5.3)	21 (4.9)	3 (0.8)	5 (1.2)
Pneumonia Bacterial	3 (2.6)	3 (2.4)	0	0	0	0	0	0	3 (0.8)	3 (0.7)	0	0
Pneumonia Fungal	3 (2.6)	3 (2.4)	2 (1.7)	3 (2.4)	1 (0.4)	1 (0.3)	3 (1.1)	4 (1.3)	4 (1.0)	4 (0 9)	5 (1.3)	7 (1.6)
Pneumonia Pseudomonal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pneumonia Staphylococcal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pseudallescheria Infection	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Pseudomembranous Colitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Pulmonary Mycosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Pulmonary Tuberculosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pyelonephritis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Respiratory Syncytial Virus Infection	2 (1.7)	2 (1.6)	0	0	1 (0.4)	1 (0.3)	0	0	3 (0.8)	3 (0.7)	0	0

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Number (%) of Subjects

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Sepsis	7 (6.1)	7 (5.6)	1 (0.9)	1 (0.8)	4 (1.4)	4 (1.3)	6 (2.1)	6 (2.0)	11 (2.8)	11 (2.6)	7 (1.8)	7 (1.6)
Septic Embolus	3 (2.6)	3 (2.4)	0	0	0	0	0	0	3 (0.8)	3 (0.7)	0	0
Septic Shock	3 (2.6)	3 (2.4)	2 (1.7)	3 (2.4)	0	0	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)	4 (1.0)	5 (1.2)
Sinusitis	4 (3.5)	4 (3.2)	0	0	1 (0.4)	1 (0.3)	0	0	5 (1.3)	5 (1 2)	0	0
Sinusitis Bacterial	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Sinusitis Fungal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Staphylococcal Bacteraemia	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Staphylococcal Sepsis	1 (0.9)	1 (0.8)	0	0	4 (1.4)	4 (1.3)	0	0	5 (1.3)	5 (1 2)	0	0
Stenotrophomonas Sepsis	0	0	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.2)
Tuberculosis	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Upper Respiratory Tract Infection	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Urinary Tract Infection	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Viral Sinusitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Injury, Poisoning And Procedural Complications	**3 (2.6)**	**3 (2.4)**	**1 (0.9)**	**1 (0.8)**	**11 (3.9)**	**12 (3.9)**	**1 (0.4)**	**1 (0.3)**	**14 (3.5)**	**15 (3 5)**	**2 (0.5)**	**2 (0.5)**
Barotitis Media	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Contusion	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Fall	0	0	0	0	1 (0.4)	2 (0.7)	0	0	1 (0.3)	2 (0.5)	0	0
Femur Fracture	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Foot Fracture	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0

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Head Injury	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hip Fracture	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hyphaema	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Injury	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Post Lumbar Puncture Syndrome	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Post Procedural Haemorrhage	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Procedural Pain	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Subarachnoid Haemorrhage	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Toxicity To Various Agents	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Transfusion Reaction	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Wound Complication	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Investigations	**20 (17.4)**	**20 (16.1)**	**4 (3.5)**	**4 (3.2)**	**35 (12.4)**	**38 (12.5)**	**5 (1.8)**	**5 (1.6)**	**55 (13.9)**	**58 (13.6)**	**9 (2.3)**	**9 (2.1)**
Activated Partial Thromboplastin Time Prolonged	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Alanine Aminotransferase Increased	0	0	0	0	3 (1 1)	3 (1.0)	0	0	3 (0.8)	3 (0.7)	0	0
Amylase	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Anticoagulation Drug Level Above Therapeutic	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Aspartate Aminotransferase Increased	1 (0.9)	1 (0.8)	0	0	3 (1 1)	3 (1.0)	0	0	4 (1.0)	4 (0 9)	0	0
Aspiration Pleural Cavity	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Bacterial Test Positive	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Blast Cell Count Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Blood Alkaline Phosphatase Increased	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Blood Bilirubin Increased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Blood Creatinine Increased	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Blood Culture Positive	1 (0.9)	1 (0.8)	0	0	2 (0.7)	3 (1.0)	0	0	3 (0.8)	4 (0 9)	0	0
Blood Lactate Dehydrogenase Increased	2 (1.7)	2 (1.6)	0	0	3 (1 1)	3 (1.0)	1 (0.4)	1 (0.3)	5 (1.3)	5 (1 2)	1 (0.3)	1 (0.2)
Blood Lactic Acid Increased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Blood Pressure Decreased	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Blood Urea Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Body Temperature Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Carbon Dioxide Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cardioactive Drug Level Decreased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Chest X-Ray Abnormal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Clostridium Test Positive	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Cytomegalovirus Test	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Drug Level Changed	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Drug Level Increased	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Electrocardiogram Qt Prolonged	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Eosinophil Count Increased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Gamma-Glutamyltransferase Increased	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
General Physical Condition Abnormal	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Glucocorticoids Decreased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Haemoglobin Abnormal	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Haemoglobin Decreased	1 (0.9)	1 (0.8)	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0 5)	0	0
Lipase	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lipase Abnormal	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Liver Function Test Increased	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)	2 (0.5)	2 (0.5)
Nuclear Magnetic Resonance Imaging Abnormal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Oxygen Saturation Decreased	3 (2.6)	3 (2.4)	0	0	0	0	0	0	3 (0.8)	3 (0.7)	0	0
Pancreatic Enzymes Increased	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Platelet Count Decreased	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Prothrombin Time Prolonged	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Urine Output Decreased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Weight Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
White Blood Cell Count Decreased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
White Blood Cell Count Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Metabolism And Nutrition Disorders	**21 (18.3)**	**22 (17.7)**	**4 (3.5)**	**4 (3.2)**	**17 (6.0)**	**20 (6.6)**	**4 (1.4)**	**4 (1.3)**	**38 (9.6)**	**42 (9 8)**	**8 (2.0)**	**8 (1.9)**
Acidosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0

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Cachexia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Decreased Appetite	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Dehydration	4 (3.5)	4 (3.2)	0	0	4 (1.4)	4 (1.3)	0	0	8 (2.0)	8 (1 9)	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Electrolyte Imbalance	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Failure To Thrive	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Fluid Overload	2 (1.7)	2 (1.6)	0	0	1 (0.4)	1 (0.3)	0	0	3 (0.8)	3 (0.7)	0	0
Hypercreatininaemia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hyperglycaemia	5 (4.3)	5 (4.0)	0	0	1 (0.4)	1 (0.3)	0	0	6 (1.5)	6 (1.4)	0	0
Hyperkalaemia	2 (1.7)	3 (2.4)	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.0)	5 (1.2)	3 (0.8)	3 (0.7)
Hypervolaemia	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.2)	0	0
Hypoalbuminaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hypocalcaemia	0	0	1 (0.9)	1 (0.8)	0	1 (0.3)	0	0	0	1 (0 2)	1 (0.3)	1 (0.2)
Hypoglycaemia	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Hypokalaemia	0	0	0	0	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0 5)	1 (0.3)	1 (0.2)
Hypomagnesaemia	1 (0.9)	1 (0.8)	0	0	1 (0.4)	2 (0.7)	0	0	2 (0.5)	3 (0.7)	0	0
Hyponatraemia	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Hypophagia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hypovolaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Iron Overload	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Lactic Acidosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Malnutrition	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Metabolic Acidosis	3 (2.6)	3 (2.4)	2 (1.7)	2 (1.6)	3 (1 1)	3 (1.0)	1 (0.4)	1 (0.3)	6 (1.5)	6 (1.4)	3 (0.8)	3 (0.7)
Metabolic Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Tumour Lysis Syndrome	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Musculoskeletal And Connective Tissue Disorders	**12 (10.4)**	**12 (9.7)**	**0**	**0**	**14 (5.0)**	**18 (5.9)**	**0**	**0**	**26 (6.5)**	**30 (7.0)**	**0**	**0**
Amyotrophy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Arthralgia	2 (1.7)	2 (1.6)	0	0	3 (1 1)	4 (1.3)	0	0	5 (1.3)	6 (1.4)	0	0
Back Pain	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Bone Pain	1 (0.9)	1 (0.8)	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0 5)	0	0
Dactylitis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Flank Pain	1 (0.9)	1 (0.8)	0	0	1 (0.4)	3 (1.0)	0	0	2 (0.5)	4 (0 9)	0	0
Hypercreatinaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Muscle Spasms	0	0	0	0	1 (0.4)	2 (0.7)	0	0	1 (0.3)	2 (0 5)	0	0
Muscular Weakness	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Musculoskeletal Pain	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Myalgia	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Myopathy	3 (2.6)	3 (2.4)	0	0	1 (0.4)	1 (0.3)	0	0	4 (1.0)	4 (0 9)	0	0
Pain In Extremity	2 (1.7)	2 (1.6)	0	0	2 (0.7)	3 (1.0)	0	0	4 (1.0)	5 (1 2)	0	0
Soft Tissue Mass	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0

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Synovitis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Systemic Lupus Erythematosus	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**11 (9.6)**	**11 (8.9)**	**13 (11.3)**	**13 (10.5)**	**28 (9.9)**	**30 (9.9)**	**12 (4.3)**	**13 (4.3)**	**39 (9.8)**	**41 (9.6)**	**25 (6.3)**	**26 (6.1)**
Acute Lymphocytic Leukaemia Recurrent	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Acute Myeloid Leukaemia	6 (5.2)	6 (4.8)	4 (3.5)	4 (3.2)	12 (4.3)	13 (4.3)	3 (1.1)	3 (1.0)	18 (4.5)	19 (4.4)	7 (1.8)	7 (1.6)
Acute Myeloid Leukaemia Recurrent	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	6 (2 1)	6 (2.0)	2 (0.7)	2 (0.7)	7 (1.8)	7 (1.6)	3 (0.8)	3 (0.7)
Blast Cell Crisis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Blast Crisis In Myelogenous Leukaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Central Nervous System Lymphoma	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Chronic Lymphocytic Leukaemia	0	0	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)
Chronic Lymphocytic Leukaemia Recurrent	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Chronic Myeloid Leukaemia	1 (0.9)	1 (0.8)	3 (2.6)	3 (2.4)	2 (0.7)	3 (1.0)	0	1 (0.3)	3 (0.8)	4 (0.9)	3 (0.8)	4 (0.9)
Hepatic Cancer	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Kaposi's Sarcoma	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Leukaemia	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)

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Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Lymphoma	1 (0.9)	1 (0.8)	0	0	3 (1 1)	3 (1.0)	0	0	4 (1.0)	4 (0.9)	0	0
Myelodysplastic Syndrome	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Neoplasm Malignant	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Non-Hodgkin's Lymphoma	2 (1.7)	2 (1.6)	1 (0.9)	1 (0.8)	0	0	0	0	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Plasma Cell Myeloma	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Respiratory Tract Neoplasm	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
T-Cell Lymphoma	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Nervous System Disorders	**29 (25.2)**	**30 (24.2)**	**9 (7.8)**	**10 (8.1)**	**28 (9.9)**	**30 (9.9)**	**7 (2.5)**	**7 (2.3)**	**57 (14.4)**	**60 (14.0)**	**16 (4.0)**	**17 (4.0)**
Ageusia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Amnesia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Arachnoiditis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Asterixis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Brain Oedema	0	0	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Cauda Equina Syndrome	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Cerebral Atrophy	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Cerebral Haemorrhage	0	0	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)
Cerebral Infarction	2 (1.7)	2 (1.6)	0	0	0	0	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Cerebrovascular Accident	2 (1.7)	2 (1.6)	0	0	0	0	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Coma	3 (2.6)	3 (2.4)	2 (1.7)	3 (2.4)	0	0	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)	3 (0.8)	4 (0.9)

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Demyelination	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Depressed Level Of Consciousness	2 (1.7)	2 (1.6)	1 (0.9)	1 (0.8)	0	0	0	0	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Dizziness	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Embolic Stroke	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Encephalomalacia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Encephalopathy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Facial Paralysis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Haemorrhage Intracranial	1 (0.9)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Haemorrhagic Cerebral Infarction	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Headache	5 (4.3)	5 (4.0)	0	0	13 (4.6)	13 (4.3)	1 (0.4)	1 (0.3)	18 (4.5)	18 (4 2)	1 (0.3)	1 (0.2)
Hemiparesis	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.2)
Hemiplegia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Intracranial Pressure Increased	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Intraventricular Haemorrhage	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Ischaemic Stroke	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Lethargy	3 (2.6)	3 (2.4)	0	0	1 (0.4)	2 (0.7)	0	0	4 (1.0)	5 (1 2)	0	0
Loss Of Consciousness	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Nervous System Disorder	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Neurological Decompensation	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Neuropathy Peripheral	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Occipital Neuralgia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Presyncope	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Sedation	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Seizure	4 (3.5)	4 (3.2)	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	0	0	6 (1.5)	6 (1.4)	1 (0.3)	1 (0.2)
Somnolence	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Speech Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Syncope	0	0	0	0	1 (0.4)	2 (0.7)	0	0	1 (0.3)	2 (0 5)	0	0
Unresponsive To Stimuli	4 (3.5)	5 (4.0)	4 (3.5)	4 (3.2)	4 (1.4)	4 (1.3)	0	0	8 (2.0)	9 (2.1)	4 (1.0)	4 (0.9)
Psychiatric Disorders	**12 (10.4)**	**12 (9.7)**	**0**	**0**	**11 (3.9)**	**12 (3.9)**	**0**	**0**	**23 (5.8)**	**24 (5.6)**	**0**	**0**
Agitation	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Anxiety	3 (2.6)	3 (2.4)	0	0	0	0	0	0	3 (0.8)	3 (0.7)	0	0
Confusional State	4 (3.5)	4 (3.2)	0	0	2 (0.7)	3 (1.0)	0	0	6 (1.5)	7 (1.6)	0	0
Delirium	1 (0.9)	1 (0.8)	0	0	1 (0.4)	2 (0.7)	0	0	2 (0.5)	3 (0.7)	0	0
Delusion	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Depression	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Disorientation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Hallucination	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Mental Status Changes	7 (6.1)	7 (5.6)	0	0	5 (1.8)	5 (1.6)	0	0	12 (3.0)	12 (2.8)	0	0
Restlessness	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Renal And Urinary Disorders	**23 (20.0)**	**24 (19.4)**	**5 (4.3)**	**5 (4.0)**	**18 (6.4)**	**18 (5.9)**	**4 (1.4)**	**5 (1.6)**	**41 (10.3)**	**42 (9 8)**	**9 (2.3)**	**10 (2.3)**

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Acute Kidney Injury	5 (4.3)	5 (4.0)	1 (0.9)	1 (0.8)	3 (1 1)	3 (1.0)	1 (0.4)	2 (0.7)	8 (2.0)	8 (1.9)	2 (0.5)	3 (0.7)
Anuria	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Azotaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Bladder Spasm	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Choluria	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Chronic Kidney Disease	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Cystitis Haemorrhagic	2 (1.7)	2 (1.6)	0	0	3 (1 1)	3 (1.0)	0	0	5 (1.3)	5 (1 2)	0	0
Dysuria	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
End Stage Renal Disease	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Incontinence	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Nephritis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Nephrolithiasis	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Nephropathy Toxic	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	0	0	0	0	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Oliguria	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Renal Disorder	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Renal Failure	10 (8.7)	11 (8.9)	2 (1.7)	2 (1.6)	9 (3 2)	9 (3.0)	3 (1.1)	3 (1.0)	19 (4.8)	20 (4.7)	5 (1.3)	5 (1.2)
Renal Impairment	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Renal Tubular Acidosis	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Renal Tubular Necrosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Urinary Retention	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Reproductive System And Breast Disorders	**0**	**0**	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**0**	**0**
Scrotal Pain	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Vaginal Haemorrhage	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Respiratory, Thoracic And Mediastinal Disorders	**42 (36.5)**	**42 (33.9)**	**26 (22.6)**	**28 (22.6)**	**46 (16.3)**	**48 (15.8)**	**23 (8.2)**	**28 (9.2)**	**88 (22.2)**	**90 (21.0)**	**49 (12.3)**	**56 (13.1)**
Acute Respiratory Distress Syndrome	3 (2.6)	3 (2.4)	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	0	0	4 (1.0)	4 (0 9)	3 (0.8)	3 (0.7)
Acute Respiratory Failure	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Apnoea	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Asthma	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Atelectasis	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Bronchiectasis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Bronchospasm	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Cheyne-Stokes Respiration	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Chronic Obstructive Pulmonary Disease	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Cough	2 (1.7)	2 (1.6)	0	0	4 (1.4)	4 (1.3)	0	0	6 (1.5)	6 (1.4)	0	0
Dyspnoea	13 (11.3)	13 (10.5)	0	0	17 (6.0)	17 (5.6)	2 (0.7)	3 (1.0)	30 (7.6)	30 (7.0)	2 (0.5)	3 (0.7)
Dyspnoea Exertional	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0

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Epistaxis	2 (1.7)	2 (1.6)	0	0	2 (0.7)	2 (0.7)	0	0	4 (1.0)	4 (0 9)	0	0
Haemoptysis	6 (5.2)	6 (4.8)	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)	8 (2.0)	8 (1.9)	2 (0.5)	2 (0.5)
Haemothorax	2 (1.7)	2 (1.6)	0	1 (0.8)	0	0	0	0	2 (0.5)	2 (0 5)	0	1 (0.2)
Hiccups	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Hypercapnia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hypoxia	2 (1.7)	2 (1.6)	1 (0.9)	1 (0.8)	3 (1 1)	3 (1.0)	2 (0.7)	4 (1.3)	5 (1.3)	5 (1.2)	3 (0.8)	5 (1.2)
Interstitial Lung Disease	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lung Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Lung Infiltration	3 (2.6)	3 (2.4)	0	0	6 (2 1)	6 (2.0)	0	0	9 (2.3)	9 (2 1)	0	0
Obliterative Bronchiolitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Obstructive Airways Disorder	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Organising Pneumonia	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Oropharyngeal Pain	0	0	0	0	0	1 (0.3)	0	0	0	1 (0 2)	0	0
Pleural Effusion	4 (3.5)	4 (3.2)	0	0	6 (2 1)	6 (2.0)	0	0	10 (2.5)	10 (2.3)	0	0
Pleuritic Pain	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Pneumonia Aspiration	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Pneumonitis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Pneumothorax	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Pulmonary Alveolar Haemorrhage	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	1 (0.3)	1 (0.2)
Pulmonary Haemorrhage	1 (0.9)	1 (0.8)	2 (1.7)	2 (1.6)	0	0	0	0	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Pulmonary Hypertension	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0

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Pulmonary Infarction	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pulmonary Mass	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Pulmonary Oedema	2 (1.7)	2 (1.6)	0	0	3 (1 1)	4 (1.3)	1 (0.4)	1 (0.3)	5 (1.3)	6 (1.4)	1 (0.3)	1 (0.2)
Respiratory Acidosis	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Respiratory Arrest	0	0	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)
Respiratory Disorder	1 (0.9)	1 (0.8)	0	0	0	0	2 (0.7)	2 (0.7)	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Respiratory Distress	3 (2.6)	3 (2.4)	5 (4.3)	5 (4.0)	6 (2 1)	6 (2.0)	3 (1.1)	4 (1.3)	9 (2.3)	9 (2.1)	8 (2.0)	9 (2.1)
Respiratory Failure	8 (7.0)	8 (6.5)	12 (10.4)	14 (11.3)	4 (1.4)	4 (1.3)	16 (5.7)	17 (5.6)	12 (3.0)	12 (2.8)	28 (7.1)	31 (7.2)
Respiratory Tract Congestion	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Sinus Congestion	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Tachypnoea	2 (1.7)	2 (1.6)	0	0	3 (1 1)	4 (1.3)	0	0	5 (1.3)	6 (1.4)	0	0
Skin And Subcutaneous Tissue Disorders	**3 (2.6)**	**3 (2.4)**	**0**	**0**	**12 (4.3)**	**13 (4.3)**	**0**	**0**	**15 (3.8)**	**16 (3.7)**	**0**	**0**
Alopecia	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.2)	0	0
Dermatitis Allergic	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Ecchymosis	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Hyperhidrosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Livedo Reticularis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Night Sweats	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Pruritus	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Rash	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Rash Macular	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Rash Maculo-Papular	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Skin Lesion	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Stevens-Johnson Syndrome	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Swelling Face	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Surgical And Medical Procedures	**6 (5.2)**	**6 (4.8)**	**1 (0.9)**	**1 (0.8)**	**9 (3 2)**	**9 (3.0)**	**1 (0.4)**	**1 (0.3)**	**15 (3.8)**	**15 (3 5)**	**2 (0.5)**	**2 (0.5)**
Autologous Bone Marrow Transplantation Therapy	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cataract Operation	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Catheter Removal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Debridement	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Endotracheal Intubation	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Haemofiltration	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Laparotomy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Lung Lobectomy	2 (1.7)	2 (1.6)	0	0	0	0	0	0	2 (0.5)	2 (0 5)	0	0
Lung Operation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lung Transplant	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Omentectomy	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Pneumonectomy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Pulmonary Resection	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Splenectomy	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Stem Cell Transplant	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Thoracotomy	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Tooth Extraction	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Vascular Disorders	**13 (11.3)**	**13 (10.5)**	**8 (7.0)**	**10 (8.1)**	**16 (5.7)**	**19 (6.3)**	**6 (2.1)**	**6 (2.0)**	**29 (7.3)**	**32 (7 5)**	**14 (3.5)**	**16 (3.7)**
Angiopathy	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Aortic Aneurysm	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Circulatory Collapse	0	0	0	1 (0.8)	0	0	0	0	0	0	0	1 (0.2)
Deep Vein Thrombosis	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Haematoma	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Haemodynamic Instability	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Haemorrhage	0	0	0	0	1 (0.4)	1 (0.3)	2 (0.7)	2 (0.7)	1 (0.3)	1 (0 2)	2 (0.5)	2 (0.5)
Hypertension	3 (2.6)	3 (2.4)	0	0	1 (0.4)	1 (0.3)	0	0	4 (1.0)	4 (0 9)	0	0
Hypoperfusion	0	0	0	1 (0.8)	0	0	0	0	0	0	0	1 (0.2)
Hypotension	10 (8.7)	10 (8.1)	6 (5.2)	7 (5.6)	10 (3.5)	13 (4.3)	4 (1.4)	4 (1.3)	20 (5.0)	23 (5.4)	10 (2.5)	11 (2.6)
Hypovolaemic Shock	0	0	0	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	1 (0.2)
Peripheral Artery Thrombosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Peripheral Venous Disease	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Shock Haemorrhagic	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
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Thrombosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Every subject is counted a single time for each applicable row and column.												
MedDRA Version 20.1												

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付録 2.7.4-24 重度／生命を脅かす副作用の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893

All Randomized Subjects

Summary of Grade 3 and 4 Treatment Related Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses

Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Subjects Reporting Any Adverse Event	**9 (7.8)**	**9 (7.3)**	**2 (1.7)**	**2 (1.6)**	**27 (9.6)**	**28 (9.2)**	**4 (1.4)**	**4 (1.3)**	**36 (9.1)**	**37 (8.6)**	**6 (1.5)**	**6 (1.4)**
Blood And Lymphatic System Disorders	**0**	**0**	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**0**	**0**
Anaemia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Pancytopenia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cardiac Disorders	**0**	**0**	**1 (0.9)**	**1 (0.8)**	**3 (1 1)**	**3 (1.0)**	**1 (0.4)**	**1 (0.3)**	**3 (0.8)**	**3 (0.7)**	**2 (0.5)**	**2 (0.5)**
Arteriosclerosis Coronary Artery	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Atrial Fibrillation	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Atrial Flutter	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cardio-Respiratory Arrest	0	0	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)
Myocardial Infarction	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Supraventricular Tachycardia	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Ventricular Extrasystoles	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Ventricular Hypertrophy	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Endocrine Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**
Adrenal Insufficiency	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Related Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Adrenocortical Insufficiency Acute	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Eye Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**
Eye Pain	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Gastrointestinal Disorders	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**3 (1 1)**	**4 (1.3)**	**1 (0.4)**	**1 (0.3)**	**4 (1.0)**	**5 (1.2)**	**1 (0.3)**	**1 (0.2)**
Abdominal Pain	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Abdominal Pain Upper	1 (0.9)	1 (0.8)	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0 5)	0	0
Diarrhoea	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Nausea	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0.5)	0	0
Pancreatitis	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Vomiting	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
General Disorders And Administration Site Conditions	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**	**1 (0.3)**	**1 (0.2)**
Death	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Fatigue	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Hepatobiliary Disorders	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**1 (0.4)**	**1 (0.3)**	**3 (0.8)**	**3 (0.7)**	**1 (0.3)**	**1 (0.2)**
Hepatic Failure	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Hepatocellular Injury	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Related Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT				Non-BMT				Overall rIFI Pool			
	800 mg/day Grade 3 n = 115	All Doses Grade 3 n = 124	800 mg/day Grade 4 n = 115	All Doses Grade 4 n = 124	800 mg/day Grade 3 n = 282	All Doses Grade 3 n = 304	800 mg/day Grade 4 n = 282	All Doses Grade 4 n = 304	800 mg/day Grade 3 n = 397	All Doses Grade 3 n = 428	800 mg/day Grade 4 n = 397	All Doses Grade 4 n = 428
Hepatosplenomegaly	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Jaundice	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Infections And Infestations	**0**	**0**	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**0**	**0**
Meningitis Cryptococcal	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Oesophageal Candidiasis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Injury, Poisoning And Procedural Complications	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**	**1 (0.3)**	**1 (0.2)**
Toxicity To Various Agents	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)
Investigations	**3 (2.6)**	**3 (2.4)**	**1 (0.9)**	**1 (0.8)**	**12 (4.3)**	**12 (3.9)**	**2 (0.7)**	**2 (0.7)**	**15 (3.8)**	**15 (3 5)**	**3 (0.8)**	**3 (0.7)**
Alanine Aminotransferase Increased	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0 5)	0	0
Amylase	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Aspartate Aminotransferase Increased	1 (0.9)	1 (0.8)	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	3 (0.7)	0	0
Blood Alkaline Phosphatase Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Blood Bilirubin Increased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Blood Creatinine Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Blood Urea Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Cardioactive Drug Level Decreased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Drug Level Increased	0	0	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Related Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Gamma-Glutamyltransferase Increased	0	0	0	0	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Glucocorticoids Decreased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lipase	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Lipase Abnormal	0	0	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)
Liver Function Test Increased	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Pancreatic Enzymes Increased	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Metabolism And Nutrition Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**
Electrolyte Imbalance	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Musculoskeletal And Connective Tissue Disorders	**2 (1.7)**	**2 (1.6)**	**0**	**0**	**0**	**0**	**0**	**0**	**2 (0.5)**	**2 (0.5)**	**0**	**0**
Arthralgia	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)	0	0
Bone Pain	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Nervous System Disorders	**2 (1.7)**	**2 (1.6)**	**1 (0.9)**	**1 (0.8)**	**2 (0.7)**	**2 (0.7)**	**0**	**0**	**4 (1.0)**	**4 (0.9)**	**1 (0.3)**	**1 (0.2)**
Dizziness	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Headache	1 (0.9)	1 (0.8)	0	0	1 (0.4)	1 (0.3)	0	0	2 (0.5)	2 (0 5)	0	0
Seizure	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	0	0	0	0	1 (0.3)	1 (0 2)	1 (0.3)	1 (0.2)
Psychiatric Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Delirium	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Renal And Urinary Disorders	**0**	**0**	**1 (0.9)**	**1 (0.8)**	**4 (1.4)**	**4 (1.3)**	**0**	**0**	**4 (1.0)**	**4 (0.9)**	**1 (0.3)**	**1 (0.2)**
Acute Kidney Injury	0	0	0	0	2 (0.7)	2 (0.7)	0	0	2 (0.5)	2 (0.5)	0	0
Choluria	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Nephropathy Toxic	0	0	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Renal Failure	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Renal Tubular Acidosis	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**
Dyspnoea	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Skin And Subcutaneous Tissue Disorders	**0**	**0**	**0**	**0**	**3 (1 1)**	**3 (1.0)**	**0**	**0**	**3 (0.8)**	**3 (0.7)**	**0**	**0**
Rash	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0 2)	0	0
Rash Macular	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Rash Maculo-Papular	0	0	0	0	1 (0.4)	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0
Vascular Disorders	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**0**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Grade 3 and 4 Treatment Related Treatment Emergent Adverse Events by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Hypotension	1 (0.9)	1 (0.8)	0	0	0	0	0	0	1 (0.3)	1 (0 2)	0	0
Every subject is counted a single time for each applicable row and column. MedDRA Version 20.1												

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付録 2.7.4-25 有害事象の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	77	(100.0)	37	(97.4)
with no adverse events	0	(0.0)	1	(2.6)
Blood and lymphatic system disorders	**8**	**(10.4)**	**4**	**(10.5)**
Anaemia	2	(2.6)	2	(5.3)
Eosinophilia	1	(1.3)	0	(0.0)
Febrile neutropenia	4	(5.2)	1	(2.6)
Hypochromic anaemia	1	(1.3)	0	(0.0)
Iron deficiency anaemia	0	(0.0)	1	(2.6)
Thrombocytopenia	2	(2.6)	0	(0.0)
Cardiac disorders	**8**	**(10.4)**	**4**	**(10.5)**
Atrioventricular block first degree	0	(0.0)	1	(2.6)
Bundle branch block right	0	(0.0)	1	(2.6)
Cardiac failure	4	(5.2)	0	(0.0)
Cardiac failure congestive	2	(2.6)	0	(0.0)
Cor pulmonale	1	(1.3)	0	(0.0)
Sinus bradycardia	0	(0.0)	1	(2.6)
Supraventricular extrasystoles	1	(1.3)	0	(0.0)
Tachycardia	0	(0.0)	1	(2.6)
Ear and labyrinth disorders	**0**	**(0.0)**	**1**	**(2.6)**
Tinnitus	0	(0.0)	1	(2.6)
Eye disorders	**12**	**(15.6)**	**23**	**(60.5)**
Blepharitis	1	(1.3)	0	(0.0)
Colour blindness acquired	0	(0.0)	5	(13.2)
Conjunctival hyperaemia	1	(1.3)	0	(0.0)
Diplopia	1	(1.3)	0	(0.0)
Dry eye	0	(0.0)	1	(2.6)
Dyschromatopsia	0	(0.0)	1	(2.6)
Ocular hyperaemia	3	(3.9)	0	(0.0)
Ocular hypertension	1	(1.3)	0	(0.0)
Photophobia	5	(6.5)	11	(28.9)
Vision blurred	1	(1.3)	4	(10.5)
Visual impairment	0	(0.0)	5	(13.2)
Gastrointestinal disorders	**30**	**(39.0)**	**17**	**(44.7)**
Abdominal discomfort	3	(3.9)	1	(2.6)
Abdominal pain upper	0	(0.0)	1	(2.6)
Cheilitis	1	(1.3)	1	(2.6)
Constipation	13	(16.9)	6	(15.8)
Dental caries	1	(1.3)	1	(2.6)

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Gastrointestinal disorders	**30**	**(39.0)**	**17**	**(44.7)**
Diarrhoea	6	(7.8)	4	(10.5)
Enterocolitis	1	(1.3)	1	(2.6)
Faeces hard	0	(0.0)	1	(2.6)
Faeces soft	1	(1.3)	0	(0.0)
Gastrointestinal disorder	0	(0.0)	1	(2.6)
Gastrointestinal pain	0	(0.0)	1	(2.6)
Haemorrhoidal haemorrhage	1	(1.3)	0	(0.0)
Haemorrhoids	1	(1.3)	1	(2.6)
Hypoaesthesia oral	1	(1.3)	0	(0.0)
Lip dry	2	(2.6)	2	(5.3)
Melaena	1	(1.3)	0	(0.0)
Nausea	7	(9.1)	1	(2.6)
Oral discomfort	1	(1.3)	1	(2.6)
Oral dysaesthesia	1	(1.3)	0	(0.0)
Stomatitis	5	(6.5)	0	(0.0)
Trichoglossia	1	(1.3)	0	(0.0)
Vomiting	3	(3.9)	2	(5 3)
General disorders and administration site conditions	**38**	**(49.4)**	**9**	**(23.7)**
Catheter site erythema	0	(0.0)	1	(2.6)
Chest discomfort	1	(1.3)	1	(2.6)
Chest pain	2	(2.6)	0	(0.0)
Chills	1	(1.3)	0	(0.0)
Fatigue	2	(2.6)	1	(2.6)
Gait disturbance	0	(0.0)	1	(2.6)
Injection site hypoaesthesia	0	(0.0)	1	(2.6)
Malaise	2	(2.6)	1	(2.6)
Mucosal inflammation	1	(1.3)	0	(0.0)
Multiple organ dysfunction syndrome	1	(1.3)	0	(0.0)
Oedema	1	(1.3)	0	(0.0)
Oedema peripheral	7	(9.1)	1	(2.6)
Peripheral swelling	1	(1.3)	0	(0.0)
Pyrexia	25	(32.5)	2	(5.3)
Thirst	3	(3.9)	1	(2.6)
Hepatobiliary disorders	**14**	**(18.2)**	**8**	**(21.1)**
Hepatic function abnormal	14	(18.2)	6	(15.8)
Hepatobiliary disease	0	(0.0)	2	(5.3)
Immune system disorders	**2**	**(2.6)**	**0**	**(0.0)**
Cytokine release syndrome	1	(1.3)	0	(0.0)

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Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Immune system disorders	**2**	**(2.6)**	**0**	**(0.0)**
Graft versus host disease in gastrointestinal tract	1	(1.3)	0	(0.0)
Infections and infestations	**44**	**(57.1)**	**12**	**(31.6)**
Angular cheilitis	2	(2.6)	1	(2.6)
Bacterial sepsis	1	(1.3)	0	(0.0)
Blister infected	1	(1.3)	1	(2.6)
Bronchiolitis	2	(2.6)	0	(0.0)
Bronchitis	2	(2.6)	1	(2.6)
Bronchopulmonary aspergillosis	1	(1.3)	1	(2.6)
Cellulitis	2	(2.6)	0	(0.0)
Conjunctivitis	3	(3.9)	1	(2.6)
Conjunctivitis bacterial	1	(1.3)	0	(0.0)
Cystitis viral	1	(1.3)	0	(0.0)
Cytomegalovirus infection	1	(1.3)	0	(0.0)
Device related infection	2	(2.6)	0	(0.0)
Enterocolitis viral	1	(1.3)	0	(0.0)
Gastroenteritis bacterial	1	(1.3)	0	(0.0)
Gingivitis	0	(0.0)	1	(2.6)
Infected dermal cyst	1	(1.3)	0	(0.0)
Influenza	1	(1.3)	0	(0.0)
Lower respiratory tract infection	1	(1.3)	0	(0.0)
Nasopharyngitis	3	(3.9)	7	(18.4)
Oral herpes	1	(1.3)	0	(0.0)
Osteomyelitis	1	(1.3)	0	(0.0)
Paronychia	1	(1.3)	0	(0.0)
Periodontitis	1	(1.3)	0	(0.0)
Pharyngitis	2	(2.6)	1	(2.6)
Pneumonia	12	(15.6)	2	(5 3)
Pneumonia bacterial	6	(7.8)	1	(2.6)
Pneumonia fungal	0	(0.0)	1	(2.6)
Pyelonephritis	1	(1.3)	0	(0.0)
Sepsis	3	(3.9)	0	(0.0)
Staphylococcal bacteraemia	1	(1.3)	0	(0.0)
Tinea pedis	0	(0.0)	1	(2.6)
Upper respiratory tract infection	4	(5.2)	0	(0.0)
Urinary tract infection	2	(2.6)	0	(0.0)
Injury, poisoning and procedural complications	**13**	**(16.9)**	**3**	**(7.9)**
Accidental overdose	0	(0.0)	1	(2.6)
Allergic transfusion reaction	1	(1.3)	0	(0.0)
Arthropod bite	1	(1.3)	0	(0.0)

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Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Injury, poisoning and procedural complications	**13**	**(16.9)**	**3**	**(7.9)**
Complications of bone marrow transplant	1	(1.3)	0	(0.0)
Contusion	1	(1.3)	1	(2.6)
Fall	1	(1.3)	0	(0.0)
Laceration	1	(1.3)	0	(0.0)
Ligament sprain	1	(1.3)	0	(0.0)
Limb injury	1	(1.3)	0	(0.0)
Post procedural complication	1	(1.3)	0	(0.0)
Postoperative fever	1	(1.3)	0	(0.0)
Skin abrasion	1	(1.3)	0	(0.0)
Spinal compression fracture	1	(1.3)	1	(2.6)
Thermal burn	0	(0.0)	1	(2.6)
Transplantation complication	1	(1.3)	0	(0.0)
Wound	1	(1.3)	0	(0.0)
Investigations	**30**	**(39.0)**	**15**	**(39.5)**
Alanine aminotransferase increased	9	(11.7)	2	(5.3)
Aspartate aminotransferase increased	10	(13.0)	4	(10.5)
Blood alkaline phosphatase increased	3	(3.9)	5	(13.2)
Blood creatinine increased	3	(3.9)	3	(7.9)
Blood glucose increased	1	(1.3)	0	(0.0)
Blood lactate dehydrogenase increased	1	(1.3)	1	(2.6)
Blood potassium decreased	2	(2.6)	0	(0.0)
Blood pressure increased	1	(1.3)	0	(0.0)
Blood urea decreased	1	(1.3)	0	(0.0)
C-reactive protein increased	5	(6.5)	0	(0.0)
Cytomegalovirus test positive	0	(0.0)	1	(2.6)
Electrocardiogram QT prolonged	7	(9.1)	2	(5.3)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Eosinophil count increased	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.3)	4	(10.5)
Liver function test increased	1	(1.3)	2	(5.3)
Neutrophil count decreased	2	(2.6)	1	(2.6)
Platelet count decreased	5	(6.5)	2	(5.3)
Renal function test abnormal	0	(0.0)	1	(2.6)
Weight decreased	1	(1.3)	0	(0.0)
White blood cell count decreased	2	(2.6)	1	(2.6)
Metabolism and nutrition disorders	**31**	**(40.3)**	**5**	**(13.2)**
Decreased appetite	14	(18.2)	0	(0.0)
Dehydration	0	(0.0)	1	(2.6)
Hyperkalaemia	1	(1.3)	3	(7.9)
Hyperuricaemia	0	(0.0)	1	(2.6)

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Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Metabolism and nutrition disorders	**31**	**(40.3)**	**5**	**(13.2)**
Hypoalbuminaemia	4	(5.2)	0	(0.0)
Hypoglycaemia	2	(2.6)	0	(0.0)
Hypokalaemia	16	(20.8)	1	(2.6)
Hyponatraemia	2	(2.6)	1	(2.6)
Musculoskeletal and connective tissue disorders	**13**	**(16.9)**	**4**	**(10.5)**
Arthralgia	2	(2.6)	0	(0.0)
Arthritis	1	(1.3)	0	(0.0)
Back pain	1	(1.3)	1	(2.6)
Chondrocalcinosis pyrophosphate	1	(1.3)	0	(0.0)
Cytarabine syndrome	1	(1.3)	0	(0.0)
Flank pain	0	(0.0)	1	(2.6)
Joint effusion	1	(1.3)	0	(0.0)
Limb mass	1	(1.3)	0	(0.0)
Muscle spasms	1	(1.3)	0	(0.0)
Muscular weakness	1	(1.3)	0	(0.0)
Musculoskeletal pain	0	(0.0)	1	(2.6)
Osteoporosis	1	(1.3)	0	(0.0)
Pain in extremity	2	(2.6)	2	(5.3)
Periarthritis	1	(1.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**(5.2)**	**2**	**(5.3)**
Acute myeloid leukaemia	1	(1.3)	0	(0.0)
Cancer pain	1	(1.3)	0	(0.0)
Gastric cancer	0	(0.0)	1	(2.6)
Lung cancer metastatic	1	(1.3)	0	(0.0)
Skin papilloma	0	(0.0)	1	(2.6)
Squamous cell carcinoma of lung	1	(1.3)	0	(0.0)
Tumour associated fever	1	(1.3)	0	(0.0)
Tumour inflammation	1	(1.3)	0	(0.0)
Nervous system disorders	**8**	**(10.4)**	**8**	**(21.1)**
Dizziness	1	(1.3)	0	(0.0)
Dysgeusia	1	(1.3)	3	(7.9)
Head discomfort	0	(0.0)	1	(2.6)
Headache	3	(3.9)	1	(2.6)
Hypoaesthesia	1	(1.3)	0	(0.0)
Hypogeusia	0	(0.0)	1	(2.6)
Loss of consciousness	1	(1.3)	0	(0.0)
Mental impairment	0	(0.0)	1	(2.6)
Neuropathy peripheral	1	(1.3)	0	(0.0)

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Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Nervous system disorders	**8**	**(10.4)**	**8**	**(21.1)**
Parosmia	1	(1.3)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	1	(2.6)
Somnolence	0	(0.0)	1	(2.6)
Psychiatric disorders	**5**	**(6.5)**	**12**	**(31.6)**
Anxiety	1	(1.3)	0	(0.0)
Delirium	0	(0.0)	3	(7 9)
Hallucination	0	(0.0)	3	(7 9)
Hallucination, auditory	0	(0.0)	1	(2.6)
Hallucination, visual	0	(0.0)	1	(2.6)
Insomnia	3	(3.9)	6	(15.8)
Mental disorder	1	(1.3)	0	(0.0)
Renal and urinary disorders	**6**	**(7.8)**	**3**	**(7.9)**
Acute kidney injury	1	(1.3)	0	(0.0)
Hypertonic bladder	1	(1.3)	0	(0.0)
Neurogenic bladder	1	(1.3)	1	(2.6)
Pollakiuria	0	(0.0)	1	(2.6)
Renal impairment	3	(3.9)	0	(0.0)
Urethral pain	0	(0.0)	1	(2.6)
Urinary incontinence	0	(0.0)	1	(2.6)
Reproductive system and breast disorders	**3**	**(3.9)**	**0**	**(0.0)**
Benign prostatic hyperplasia	3	(3.9)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**23**	**(29.9)**	**9**	**(23.7)**
Asthma	2	(2.6)	2	(5.3)
Bronchitis chronic	0	(0.0)	1	(2.6)
Chronic obstructive pulmonary disease	2	(2.6)	0	(0.0)
Cough	1	(1.3)	0	(0.0)
Dyspnoea	1	(1.3)	0	(0.0)
Epistaxis	3	(3.9)	1	(2.6)
Haemoptysis	4	(5.2)	1	(2.6)
Hypercapnia	1	(1.3)	0	(0.0)
Interstitial lung disease	2	(2.6)	0	(0.0)
Laryngeal pain	1	(1.3)	0	(0.0)
Organising pneumonia	0	(0.0)	1	(2.6)
Oropharyngeal discomfort	0	(0.0)	1	(2.6)
Oropharyngeal pain	4	(5.2)	0	(0.0)
Pleural effusion	2	(2.6)	0	(0.0)
Pneumonia aspiration	1	(1.3)	0	(0.0)

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**23**	**(29.9)**	**9**	**(23.7)**
Pneumothorax	0	(0.0)	1	(2.6)
Pneumothorax spontaneous	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)
Upper respiratory tract inflammation	1	(1.3)	2	(5.3)
Skin and subcutaneous tissue disorders	**26**	**(33.8)**	**8**	**(21.1)**
Alopecia	1	(1.3)	0	(0.0)
Decubitus ulcer	2	(2.6)	0	(0.0)
Dermatitis acneiform	1	(1.3)	0	(0.0)
Dermatitis contact	2	(2.6)	1	(2.6)
Drug eruption	1	(1.3)	0	(0.0)
Dry skin	4	(5.2)	0	(0.0)
Eczema asteatotic	1	(1.3)	0	(0.0)
Erythema	3	(3.9)	0	(0.0)
Erythema nodosum	2	(2.6)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(2.6)
Hyperkeratosis	1	(1.3)	1	(2.6)
Ingrowing nail	1	(1.3)	0	(0.0)
Perivascular dermatitis	1	(1.3)	0	(0.0)
Petechiae	2	(2.6)	0	(0.0)
Photosensitivity reaction	0	(0.0)	2	(5.3)
Pruritus	0	(0.0)	1	(2.6)
Rash	6	(7.8)	2	(5 3)
Rash maculo-papular	1	(1.3)	0	(0.0)
Rash pruritic	1	(1.3)	0	(0.0)
Skin exfoliation	0	(0.0)	1	(2.6)
Skin irritation	1	(1.3)	0	(0.0)
Vascular disorders	**15**	**(19.5)**	**2**	**(5.3)**
Hypertension	14	(18.2)	1	(2.6)
Orthostatic hypotension	1	(1.3)	0	(0.0)
Thrombophlebitis	0	(0.0)	1	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-26 重度／生命を脅かす有害事象の発現例数（%）
（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）
Subjects With Adverse Events of CTC Grade 3 to 5
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events of CTC grade 3 to 5	45	(58.4)	10	(26.3)
with no adverse events of CTC grade 3 to 5	32	(41.6)	28	(73.7)
Blood and lymphatic system disorders	**5**	**(6.5)**	**2**	**(5.3)**
Anaemia	0	(0.0)	1	(2.6)
Febrile neutropenia	4	(5.2)	1	(2.6)
Hypochromic anaemia	1	(1.3)	0	(0.0)
Cardiac disorders	**4**	**(5.2)**	**0**	**(0.0)**
Cardiac failure	2	(2.6)	0	(0.0)
Cardiac failure congestive	1	(1.3)	0	(0.0)
Cor pulmonale	1	(1.3)	0	(0.0)
Gastrointestinal disorders	**2**	**(2.6)**	**0**	**(0.0)**
Constipation	1	(1.3)	0	(0.0)
Stomatitis	1	(1.3)	0	(0.0)
General disorders and administration site conditions	**3**	**(3.9)**	**1**	**(2.6)**
Gait disturbance	0	(0.0)	1	(2.6)
Multiple organ dysfunction syndrome	1	(1.3)	0	(0.0)
Pyrexia	2	(2.6)	0	(0.0)
Hepatobiliary disorders	**4**	**(5.2)**	**0**	**(0.0)**
Hepatic function abnormal	4	(5.2)	0	(0.0)
Immune system disorders	**1**	**(1.3)**	**0**	**(0.0)**
Graft versus host disease in gastrointestinal tract	1	(1.3)	0	(0.0)
Infections and infestations	**25**	**(32.5)**	**2**	**(5.3)**
Bacterial sepsis	1	(1.3)	0	(0.0)
Blister infected	1	(1.3)	1	(2.6)
Bronchitis	2	(2.6)	0	(0.0)
Bronchopulmonary aspergillosis	1	(1.3)	1	(2.6)
Cystitis viral	1	(1.3)	0	(0.0)
Cytomegalovirus infection	1	(1.3)	0	(0.0)
Device related infection	2	(2.6)	0	(0.0)
Lower respiratory tract infection	1	(1.3)	0	(0.0)
Osteomyelitis	1	(1.3)	0	(0.0)
Pharyngitis	1	(1.3)	0	(0.0)

Subjects With Adverse Events of CTC Grade 3 to 5 (Incidence >0% in One or More Treatment Groups) Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Infections and infestations	**25**	**(32.5)**	**2**	**(5.3)**
Pneumonia	11	(14.3)	1	(2.6)
Pneumonia bacterial	5	(6.5)	0	(0.0)
Pyelonephritis	1	(1.3)	0	(0.0)
Sepsis	2	(2.6)	0	(0.0)
Staphylococcal bacteraemia	1	(1.3)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(1.3)**	**1**	**(2.6)**
Spinal compression fracture	0	(0.0)	1	(2.6)
Transplantation complication	1	(1.3)	0	(0.0)
Investigations	**9**	**(11.7)**	**4**	**(10.5)**
Alanine aminotransferase increased	1	(1.3)	0	(0.0)
C-reactive protein increased	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.3)	2	(5.3)
Liver function test increased	1	(1.3)	0	(0.0)
Neutrophil count decreased	2	(2.6)	1	(2.6)
Platelet count decreased	2	(2.6)	2	(5.3)
White blood cell count decreased	2	(2.6)	1	(2.6)
Metabolism and nutrition disorders	**11**	**(14.3)**	**0**	**(0.0)**
Decreased appetite	4	(5.2)	0	(0.0)
Hypoalbuminaemia	2	(2.6)	0	(0.0)
Hypokalaemia	5	(6.5)	0	(0.0)
Hyponatraemia	1	(1.3)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(1.3)**	**0**	**(0.0)**
Joint effusion	1	(1.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(2.6)**	**1**	**(2.6)**
Gastric cancer	0	(0.0)	1	(2.6)
Lung cancer metastatic	1	(1.3)	0	(0.0)
Squamous cell carcinoma of lung	1	(1.3)	0	(0.0)
Renal and urinary disorders	**1**	**(1.3)**	**0**	**(0.0)**
Acute kidney injury	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**9**	**(11.7)**	**1**	**(2.6)**
Asthma	1	(1.3)	0	(0.0)
Chronic obstructive pulmonary disease	2	(2.6)	0	(0.0)

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Subjects With Adverse Events of CTC Grade 3 to 5 (Incidence >0% in One or More Treatment Groups) Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**9**	**(11.7)**	**1**	**(2.6)**
Hypercapnia	1	(1.3)	0	(0.0)
Interstitial lung disease	2	(2.6)	0	(0.0)
Organising pneumonia	0	(0.0)	1	(2.6)
Oropharyngeal pain	1	(1.3)	0	(0.0)
Pneumonia aspiration	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(1.3)**	**0**	**(0.0)**
Rash	1	(1.3)	0	(0.0)
Vascular disorders	**6**	**(7.8)**	**0**	**(0.0)**
Hypertension	6	(7.8)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-27 副作用の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	56	(72.7)	34	(89.5)
with no drug-related adverse events	21	(27.3)	4	(10.5)
Blood and lymphatic system disorders	**2**	**(2.6)**	**1**	**(2.6)**
Anaemia	1	(1.3)	1	(2.6)
Thrombocytopenia	2	(2.6)	0	(0.0)
Cardiac disorders	**2**	**(2.6)**	**2**	**(5.3)**
Bundle branch block right	0	(0.0)	1	(2.6)
Cardiac failure	1	(1.3)	0	(0.0)
Sinus bradycardia	0	(0.0)	1	(2.6)
Supraventricular extrasystoles	1	(1.3)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**1**	**(2.6)**
Tinnitus	0	(0.0)	1	(2.6)
Eye disorders	**2**	**(2.6)**	**23**	**(60.5)**
Colour blindness acquired	0	(0.0)	5	(13.2)
Diplopia	1	(1.3)	0	(0.0)
Dyschromatopsia	0	(0.0)	1	(2.6)
Photophobia	0	(0.0)	11	(28.9)
Vision blurred	1	(1.3)	4	(10.5)
Visual impairment	0	(0.0)	5	(13.2)
Gastrointestinal disorders	**9**	**(11.7)**	**7**	**(18.4)**
Abdominal discomfort	1	(1.3)	1	(2.6)
Constipation	2	(2.6)	0	(0.0)
Diarrhoea	3	(3.9)	0	(0.0)
Gastrointestinal pain	0	(0.0)	1	(2.6)
Lip dry	0	(0.0)	2	(5.3)
Nausea	4	(5.2)	1	(2.6)
Oral discomfort	0	(0.0)	1	(2.6)
Oral dysaesthesia	1	(1.3)	0	(0.0)
Stomatitis	1	(1.3)	0	(0.0)
Vomiting	0	(0.0)	1	(2.6)
General disorders and administration site conditions	**24**	**(31.2)**	**4**	**(10.5)**
Chest pain	1	(1.3)	0	(0.0)
Fatigue	2	(2.6)	1	(2.6)
Gait disturbance	0	(0.0)	1	(2.6)
Injection site hypoaesthesia	0	(0.0)	1	(2.6)

Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
General disorders and administration site conditions	**24**	**(31.2)**	**4**	**(10.5)**
Malaise	2	(2.6)	1	(2.6)
Oedema	1	(1.3)	0	(0.0)
Oedema peripheral	3	(3.9)	0	(0.0)
Pyrexia	17	(22.1)	0	(0.0)
Thirst	1	(1.3)	0	(0.0)
Hepatobiliary disorders	**10**	**(13.0)**	**8**	**(21.1)**
Hepatic function abnormal	10	(13.0)	6	(15.8)
Hepatobiliary disease	0	(0.0)	2	(5.3)
Infections and infestations	**4**	**(5.2)**	**0**	**(0.0)**
Cellulitis	1	(1.3)	0	(0.0)
Pharyngitis	1	(1.3)	0	(0.0)
Pneumonia	3	(3.9)	0	(0.0)
Investigations	**15**	**(19.5)**	**10**	**(26.3)**
Alanine aminotransferase increased	7	(9.1)	2	(5.3)
Aspartate aminotransferase increased	7	(9.1)	3	(7.9)
Blood alkaline phosphatase increased	2	(2.6)	4	(10.5)
Blood creatinine increased	0	(0.0)	1	(2.6)
Blood lactate dehydrogenase increased	1	(1.3)	1	(2.6)
Blood potassium decreased	1	(1.3)	0	(0.0)
C-reactive protein increased	2	(2.6)	0	(0.0)
Electrocardiogram QT prolonged	6	(7.8)	2	(5.3)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.3)	4	(10.5)
Liver function test increased	1	(1.3)	1	(2.6)
Platelet count decreased	1	(1.3)	0	(0.0)
Metabolism and nutrition disorders	**18**	**(23.4)**	**2**	**(5.3)**
Decreased appetite	9	(11.7)	0	(0.0)
Hyperkalaemia	0	(0.0)	2	(5.3)
Hypokalaemia	10	(13.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(3.9)**	**0**	**(0.0)**
Arthralgia	1	(1.3)	0	(0.0)
Arthritis	1	(1.3)	0	(0.0)
Limb mass	1	(1.3)	0	(0.0)
Nervous system disorders	**1**	**(1.3)**	**4**	**(10.5)**
Dizziness	1	(1.3)	0	(0.0)

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Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Nervous system disorders	**1**	**(1.3)**	**4**	**(10.5)**
Dysgeusia	0	(0.0)	2	(5.3)
Head discomfort	0	(0.0)	1	(2.6)
Hypogeusia	0	(0.0)	1	(2.6)
Mental impairment	0	(0.0)	1	(2.6)
Psychiatric disorders	**2**	**(2.6)**	**9**	**(23.7)**
Delirium	0	(0.0)	2	(5 3)
Hallucination	0	(0.0)	3	(7 9)
Hallucination, auditory	0	(0.0)	1	(2.6)
Hallucination, visual	0	(0.0)	1	(2.6)
Insomnia	2	(2.6)	3	(7 9)
Renal and urinary disorders	**1**	**(1.3)**	**0**	**(0.0)**
Hypertonic bladder	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**4**	**(5.2)**	**0**	**(0.0)**
Epistaxis	1	(1.3)	0	(0.0)
Oropharyngeal pain	1	(1.3)	0	(0.0)
Pleural effusion	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**10**	**(13.0)**	**3**	**(7.9)**
Dermatitis acneiform	1	(1.3)	0	(0.0)
Dry skin	3	(3.9)	0	(0.0)
Erythema	2	(2.6)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(2.6)
Photosensitivity reaction	0	(0.0)	1	(2.6)
Rash	4	(5.2)	1	(2.6)
Rash maculo-papular	1	(1.3)	0	(0.0)
Vascular disorders	**11**	**(14.3)**	**1**	**(2.6)**
Hypertension	11	(14.3)	1	(2.6)

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Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-28 重度／生命を脅かす副作用の発現例数（%）
（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）
Subjects With Drug-Related Adverse Events of CTC Grade 3 to 5
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events of CTC grade 3 to 5	16	(20.8)	3	(7.9)
with no drug-related adverse events of CTC grade 3 to 5	61	(79.2)	35	(92.1)
Cardiac disorders	**1**	**(1.3)**	**0**	**(0.0)**
Cardiac failure	1	(1.3)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(2.6)**
Gait disturbance	0	(0.0)	1	(2.6)
Hepatobiliary disorders	**1**	**(1.3)**	**0**	**(0.0)**
Hepatic function abnormal	1	(1.3)	0	(0.0)
Infections and infestations	**3**	**(3.9)**	**0**	**(0.0)**
Pharyngitis	1	(1.3)	0	(0.0)
Pneumonia	3	(3.9)	0	(0.0)
Investigations	**3**	**(3.9)**	**2**	**(5.3)**
Alanine aminotransferase increased	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.3)	2	(5.3)
Liver function test increased	1	(1.3)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(6.5)**	**0**	**(0.0)**
Decreased appetite	4	(5.2)	0	(0.0)
Hypokalaemia	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(1.3)**	**0**	**(0.0)**
Respiratory failure	1	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(1.3)**	**0**	**(0.0)**
Rash	1	(1.3)	0	(0.0)
Vascular disorders	**4**	**(5.2)**	**0**	**(0.0)**
Hypertension	4	(5.2)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-29 死亡に至った有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**121 (20.0)**	**139 (25.8)**	**9 (15.5)**
Blood And Lymphatic System Disorders	**19 (3.1)**	**14 (2.6)**	**1 (1.7)**
Bone Marrow Failure	1 (0.2)	0	0
Coagulopathy	1 (0.2)	0	0
Disseminated Intravascular Coagulation	0	1 (0 2)	0
Febrile Neutropenia	1 (0.2)	3 (0.6)	0
Haemolysis	2 (0.3)	1 (0 2)	0
Haemorrhagic Diathesis	0	1 (0 2)	0
Leukopenia	0	1 (0.2)	0
Lymphadenopathy	1 (0.2)	0	0
Neutropenia	0	0	1 (1.7)
Pancytopenia	4 (0.7)	0	0
Thrombocytopenia	8 (1.3)	7 (1 3)	1 (1.7)
Thrombotic Thrombocytopenic Purpura	1 (0.2)	1 (0 2)	0
Cardiac Disorders	**24 (4.0)**	**27 (5.0)**	**2 (3.4)**
Atrial Fibrillation	0	1 (0.2)	0
Cardiac Arrest	10 (1.7)	7 (1 3)	1 (1.7)
Cardiac Failure	4 (0.7)	3 (0.6)	0
Cardiac Failure Congestive	2 (0.3)	1 (0 2)	0
Cardio-Respiratory Arrest	5 (0.8)	9 (1.7)	0
Cardiomyopathy	1 (0.2)	0	0
Cardiopulmonary Failure	1 (0.2)	0	0
Cardiotoxicity	0	1 (0 2)	0
Cardiovascular Disorder	0	1 (0 2)	0
Cardiovascular Insufficiency	2 (0.3)	1 (0 2)	0
Myocardial Infarction	1 (0.2)	0	1 (1.7)
Sinus Tachycardia	0	2 (0.4)	0
Subendocardial Ischaemia	0	1 (0 2)	0
Tachycardia	0	1 (0 2)	0
Ventricular Tachycardia	1 (0.2)	0	0
Eye Disorders	**0**	**1 (0.2)**	**0**
Mydriasis	0	1 (0 2)	0
Gastrointestinal Disorders	**9 (1.5)**	**9 (1.7)**	**2 (3.4)**
Abdominal Compartment Syndrome	0	1 (0 2)	0
Acute Abdomen	0	1 (0 2)	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Ascites	1 (0.2)	3 (0.6)	0
Diarrhoea Haemorrhagic	0	1 (0 2)	0
Gastrointestinal Haemorrhage	4 (0.7)	4 (0.7)	1 (1.7)
Haematemesis	0	1 (0 2)	0
Ileus	1 (0.2)	0	0
Intestinal Infarction	1 (0.2)	0	0
Intestinal Ischaemia	1 (0.2)	0	0
Intra-Abdominal Haemorrhage	1 (0.2)	0	0
Large Intestinal Ulcer	1 (0.2)	0	0
Neutropenic Colitis	0	0	1 (1.7)
Small Intestinal Obstruction	1 (0.2)	0	0
Upper Gastrointestinal Haemorrhage	1 (0.2)	0	0
General Disorders And Administration Site Conditions	**24 (4.0)**	**18 (3.3)**	**1 (1.7)**
Death	0	1 (0 2)	0
Disease Progression	2 (0.3)	4 (0.7)	0
General Physical Health Deterioration	1 (0.2)	0	0
Mucosal Haemorrhage	0	1 (0 2)	0
Multi-Organ Disorder	1 (0.2)	0	0
Multiple Organ Dysfunction Syndrome	20 (3.3)	11 (2.0)	1 (1.7)
Necrosis	1 (0.2)	0	0
Pyrexia	0	1 (0 2)	0
Sudden Death	0	1 (0 2)	0
Therapy Non-Responder	1 (0.2)	0	0
Hepatobiliary Disorders	**10 (1.7)**	**5 (0.9)**	**0**
Acute Hepatic Failure	1 (0.2)	0	0
Cholestasis	1 (0.2)	0	0
Hepatic Failure	5 (0.8)	3 (0.6)	0
Hepatic Necrosis	1 (0.2)	0	0
Hepatitis	0	1 (0.2)	0
Hyperbilirubinaemia	2 (0.3)	2 (0.4)	0
Liver Injury	1 (0.2)	0	0
Immune System Disorders	**26 (4.3)**	**21 (3.9)**	**0**
Chronic Graft Versus Host Disease	0	1 (0.2)	0
Graft Versus Host Disease	22 (3.6)	12 (2.2)	0
Graft Versus Host Disease In Gastrointestinal Tract	4 (0.7)	3 (0.6)	0
Graft Versus Host Disease In Liver	4 (0.7)	2 (0.4)	0
Graft Versus Host Disease In Lung	0	2 (0.4)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Graft Versus Host Disease In Skin	3 (0.5)	1 (0.2)	0
Infections And Infestations	**48 (7.9)**	**70 (13.0)**	**5 (8.6)**
Abscess Fungal	0	1 (0 2)	0
Acinetobacter Infection	0	1 (0 2)	0
Aspergillus Infection	1 (0.2)	8 (1.5)	0
Bacteraemia	3 (0.5)	2 (0.4)	0
Bacterial Infection	1 (0.2)	1 (0 2)	0
Bacterial Sepsis	2 (0.3)	0	0
Bronchiolitis	0	1 (0 2)	0
Bronchopulmonary Aspergillosis	2 (0.3)	9 (1.7)	1 (1.7)
Candida Infection	0	1 (0 2)	0
Cerebral Fungal Infection	0	1 (0 2)	0
Cerebral Toxoplasmosis	1 (0.2)	3 (0.6)	0
Clostridium Difficile Colitis	0	1 (0 2)	0
Corynebacterium Infection	0	1 (0 2)	0
Cytomegalovirus Gastroenteritis	0	1 (0 2)	0
Cytomegalovirus Infection	2 (0.3)	1 (0 2)	0
Encephalitis	2 (0.3)	1 (0 2)	0
Enterococcal Bacteraemia	0	0	1 (1.7)
Enterococcal Infection	0	4 (0.7)	0
Enterococcal Sepsis	1 (0.2)	0	0
Epstein-Barr Virus Infection	0	1 (0 2)	0
Fungaemia	0	1 (0 2)	0
Fungal Infection	4 (0.7)	3 (0.6)	0
Fungal Sepsis	1 (0.2)	1 (0 2)	0
Influenza	0	1 (0 2)	0
Klebsiella Sepsis	1 (0.2)	0	0
Meningitis Pneumococcal	0	1 (0 2)	0
Mucormycosis	0	0	1 (1.7)
Neutropenic Sepsis	0	1 (0 2)	1 (1.7)
Nocardiosis	0	1 (0 2)	0
Peritonitis	0	2 (0.4)	0
Pneumonia	10 (1.7)	12 (2.2)	1 (1.7)
Pneumonia Bacterial	2 (0.3)	0	0
Pneumonia Cytomegaloviral	0	2 (0.4)	0
Pneumonia Fungal	1 (0.2)	2 (0.4)	0
Pneumonia Necrotising	0	1 (0 2)	0
Pneumonia Pseudomonal	1 (0.2)	0	0
Pneumonia Staphylococcal	2 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Pseudomonal Sepsis	1 (0.2)	0	0
Sepsis	14 (2.3)	18 (3.3)	0
Septic Embolus	1 (0.2)	0	0
Septic Shock	11 (1.8)	10 (1.9)	3 (5.2)
Sinusitis	0	1 (0 2)	0
Staphylococcal Bacteraemia	1 (0.2)	0	0
Staphylococcal Infection	1 (0.2)	0	0
Subcutaneous Abscess	0	1 (0.2)	0
Systemic Candida	0	1 (0 2)	0
Varicella Zoster Pneumonia	1 (0.2)	0	0
Varicella Zoster Virus Infection	3 (0.5)	0	0
Viral Infection	0	1 (0 2)	0
Injury, Poisoning And Procedural Complications	**7 (1.2)**	**2 (0.4)**	**1 (1.7)**
Brain Herniation	0	0	1 (1.7)
Complications Of Transplant Surgery	1 (0.2)	0	0
Subarachnoid Haemorrhage	1 (0.2)	0	0
Subdural Haematoma	2 (0.3)	2 (0.4)	0
Subdural Haemorrhage	1 (0.2)	0	0
Toxicity To Various Agents	1 (0.2)	0	0
Transplant Failure	1 (0.2)	0	0
Investigations	**2 (0.3)**	**4 (0.7)**	**0**
Bacterial Test Positive	1 (0.2)	1 (0 2)	0
Blood Creatinine Increased	1 (0.2)	0	0
Blood Lactate Dehydrogenase Increased	1 (0.2)	0	0
Computerised Tomogram Abnormal	0	1 (0 2)	0
Karnofsky Scale Worsened	0	1 (0.2)	0
Pulse Absent	0	1 (0 2)	0
Metabolism And Nutrition Disorders	**3 (0.5)**	**2 (0.4)**	**0**
Acidosis	1 (0.2)	1 (0 2)	0
Cachexia	1 (0.2)	0	0
Fluid Overload	0	1 (0 2)	0
Hypoalbuminaemia	1 (0.2)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**32 (5.3)**	**33 (6.1)**	**1 (1.7)**
Acute Lymphocytic Leukaemia Recurrent	0	4 (0.7)	0
Acute Myeloid Leukaemia	10 (1.7)	9 (1.7)	1 (1.7)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Acute Myeloid Leukaemia Recurrent	9 (1.5)	5 (0 9)	0
Adult T-Cell Lymphoma/Leukaemia	0	1 (0 2)	0
B-Cell Lymphoma	0	1 (0 2)	0
Blast Cell Crisis	0	1 (0 2)	0
Chronic Myeloid Leukaemia	1 (0.2)	0	0
Hodgkin's Disease	0	1 (0 2)	0
Leukaemia	0	1 (0 2)	0
Leukaemia Recurrent	4 (0.7)	3 (0.6)	0
Lymphoma	3 (0.5)	1 (0 2)	0
Metastases To Kidney	0	1 (0.2)	0
Metastases To Liver	0	1 (0.2)	0
Metastatic Neoplasm	1 (0.2)	0	0
Myelodysplastic Syndrome	1 (0.2)	1 (0 2)	0
Neoplasm Malignant	1 (0.2)	3 (0.6)	0
Non-Hodgkin's Lymphoma	1 (0.2)	2 (0.4)	0
Plasma Cell Myeloma	0	1 (0 2)	0
Renal Cancer	1 (0.2)	0	0
Nervous System Disorders	**21 (3.5)**	**17 (3.2)**	**1 (1.7)**
Brain Compression	0	0	1 (1.7)
Brain Oedema	1 (0.2)	0	0
Brain Stem Haemorrhage	1 (0.2)	0	0
Central Nervous System Lesion	0	1 (0.2)	0
Cerebellar Haemorrhage	2 (0.3)	0	1 (1.7)
Cerebral Haemorrhage	6 (1.0)	4 (0.7)	0
Cerebral Infarction	1 (0.2)	0	0
Cerebrovascular Accident	1 (0.2)	1 (0 2)	0
Coma	2 (0.3)	2 (0.4)	0
Demyelination	1 (0.2)	0	0
Encephalopathy	2 (0.3)	0	0
Guillain-Barre Syndrome	0	1 (0 2)	0
Haemorrhage Intracranial	3 (0.5)	7 (1 3)	0
Haemorrhagic Stroke	1 (0.2)	1 (0 2)	0
Headache	0	0	1 (1.7)
Hemiparesis	0	3 (0.6)	0
Hydrocephalus	0	0	1 (1.7)
Hypoglycaemic Coma	1 (0.2)	0	0
Leukoencephalopathy	1 (0.2)	0	0
Loss Of Consciousness	3 (0.5)	3 (0.6)	0
Metabolic Encephalopathy	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Unresponsive To Stimuli	1 (0.2)	0	0
Renal And Urinary Disorders	**7 (1.2)**	**16 (3.0)**	**0**
Acute Kidney Injury	1 (0.2)	4 (0.7)	0
Anuria	1 (0.2)	0	0
Haematuria	1 (0.2)	0	0
Oliguria	1 (0.2)	1 (0 2)	0
Renal Failure	4 (0.7)	11 (2.0)	0
Reproductive System And Breast Disorders	**0**	**1 (0.2)**	**0**
Menorrhagia	0	1 (0 2)	0
Respiratory, Thoracic And Mediastinal Disorders	**41 (6.8)**	**51 (9.5)**	**2 (3.4)**
Acute Respiratory Distress Syndrome	4 (0.7)	2 (0.4)	1 (1.7)
Acute Respiratory Failure	3 (0.5)	1 (0 2)	0
Bronchopneumopathy	1 (0.2)	0	0
Diffuse Alveolar Damage	0	1 (0 2)	0
Dyspnoea	3 (0.5)	2 (0.4)	0
Haemoptysis	3 (0.5)	1 (0 2)	0
Hydrothorax	1 (0.2)	0	0
Hypoxia	5 (0.8)	4 (0.7)	0
Lung Infiltration	1 (0.2)	2 (0.4)	0
Obliterative Bronchiolitis	0	1 (0 2)	0
Pleural Effusion	1 (0.2)	0	0
Pneumonia Aspiration	0	2 (0.4)	0
Pneumonitis	1 (0.2)	1 (0 2)	0
Pulmonary Alveolar Haemorrhage	1 (0.2)	2 (0.4)	1 (1.7)
Pulmonary Embolism	1 (0.2)	0	1 (1.7)
Pulmonary Fibrosis	0	1 (0 2)	0
Pulmonary Haemorrhage	5 (0.8)	3 (0.6)	0
Pulmonary Mass	0	2 (0.4)	0
Pulmonary Oedema	3 (0.5)	3 (0.6)	0
Respiratory Arrest	1 (0.2)	0	0
Respiratory Distress	4 (0.7)	3 (0.6)	0
Respiratory Failure	18 (3.0)	33 (6.1)	0
Tachypnoea	1 (0.2)	2 (0.4)	0
Tonsillar Disorder	1 (0.2)	0	0
Vascular Disorders	**14 (2.3)**	**19 (3.5)**	**0**
Circulatory Collapse	1 (0.2)	4 (0.7)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Haemodynamic Instability	1 (0.2)	0	0
Haemorrhage	1 (0.2)	4 (0.7)	0
Haemorrhagic Infarction	0	1 (0 2)	0
Hypotension	9 (1.5)	6 (1 1)	0
Hypovolaemic Shock	2 (0.3)	3 (0.6)	0
Microangiopathy	1 (0.2)	0	0
Shock	0	3 (0.6)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-30 死亡に至った副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment-Related Adverse Events Leading to Death
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**4 (0.7)**	**1 (0.2)**	**0**
Hepatobiliary Disorders	**2 (0.3)**	**0**	**0**
Hepatic Failure	1 (0.2)	0	0
Hyperbilirubinaemia	1 (0.2)	0	0
Injury, Poisoning And Procedural Complications	**1 (0.2)**	**0**	**0**
Toxicity To Various Agents	1 (0.2)	0	0
Nervous System Disorders	**2 (0.3)**	**0**	**0**
Encephalopathy	2 (0.3)	0	0
Renal And Urinary Disorders	**0**	**1 (0.2)**	**0**
Renal Failure	0	1 (0 2)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-31 死亡に至った有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Death
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**61 (53.0)**	**63 (50.8)**	**83 (29.4)**	**88 (28.9)**	**144 (36.3)**	**151 (35.3)**
Blood And Lymphatic System Disorders	**1 (0.9)**	**1 (0.8)**	**3 (1.1)**	**3 (1.0)**	**4 (1.0)**	**4 (0.9)**
Anaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aplastic Anaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancytopenia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Thrombotic Thrombocytopenic Purpura	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiac Disorders	**12 (10.4)**	**12 (9.7)**	**22 (7 8)**	**23 (7.6)**	**34 (8.6)**	**35 (8.2)**
Arrhythmia Supraventricular	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bradycardia	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Cardiac Arrest	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)
Cardiac Failure	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Cardiac Failure Congestive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	5 (4.3)	5 (4.0)	8 (2.8)	9 (3.0)	13 (3 3)	14 (3.3)
Cardiogenic Shock	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiopulmonary Failure	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Myocardial Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulseless Electrical Activity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ventricular Fibrillation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Ventricular Tachycardia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gastrointestinal Disorders	**3 (2.6)**	**4 (3.2)**	**4 (1.4)**	**4 (1.3)**	**7 (1.8)**	**8 (1.9)**
Ascites	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diarrhoea	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Gastric Perforation	0	1 (0.8)	0	0	0	1 (0.2)
Haematochezia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intestinal Ischaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pancreatitis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pancreatitis Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Upper Gastrointestinal Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
General Disorders And Administration Site Conditions	**22 (19 1)**	**22 (17.7)**	**17 (6.0)**	**18 (5.9)**	**39 (9 8)**	**40 (9.3)**
Brain Death	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Death
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Death	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Disease Progression	12 (10.4)	12 (9.7)	13 (4.6)	13 (4.3)	25 (6 3)	25 (5.8)
Multiple Organ Dysfunction Syndrome	9 (7.8)	9 (7.3)	5 (1.8)	6 (2.0)	14 (3 5)	15 (3.5)
Pyrexia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatobiliary Disorders	**1 (0.9)**	**1 (0.8)**	**5 (1.8)**	**5 (1.6)**	**6 (1.5)**	**6 (1.4)**
Hepatic Failure	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Immune System Disorders	**10 (8.7)**	**11 (8.9)**	**1 (0.4)**	**1 (0.3)**	**11 (2 8)**	**12 (2.8)**
Chronic Graft Versus Host Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Graft Versus Host Disease	6 (5.2)	7 (5.6)	0	0	6 (1.5)	7 (1.6)
Graft Versus Host Disease In Gastrointestinal Tract	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Graft Versus Host Disease In Liver	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Graft Versus Host Disease In Lung	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Transplant Rejection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Infections And Infestations	**19 (16 5)**	**21 (16.9)**	**34 (12.1)**	**39 (12.8)**	**53 (13.4)**	**60 (14.0)**
Acquired Immunodeficiency Syndrome	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Acute Sinusitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aspergilloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Aspergillus Infection	2 (1.7)	2 (1.6)	1 (0.4)	2 (0.7)	3 (0.8)	4 (0.9)
Bacteraemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Brain Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchopulmonary Aspergillosis	0	1 (0.8)	2 (0.7)	2 (0.7)	2 (0.5)	3 (0.7)
Cerebral Aspergillosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
End Stage Aids	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Enterococcal Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Enterococcal Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fungaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fungal Infection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fungal Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Fusarium Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Infection Parasitic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Meningitis Cryptococcal	0	0	6 (2.1)	6 (2.0)	6 (1.5)	6 (1.4)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Death
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Mucormycosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Mycobacterial Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pneumonia	4 (3.5)	4 (3.2)	5 (1.8)	7 (2.3)	9 (2.3)	11 (2.6)
Pneumonia Fungal	4 (3.5)	4 (3.2)	3 (1.1)	4 (1.3)	7 (1.8)	8 (1.9)
Sepsis	3 (2.6)	3 (2.4)	7 (2.5)	7 (2.3)	10 (2 5)	10 (2.3)
Septic Embolus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Septic Shock	2 (1.7)	3 (2.4)	2 (0.7)	2 (0.7)	4 (1.0)	5 (1.2)
Stenotrophomonas Sepsis	0	0	0	1 (0.3)	0	1 (0.2)
Tuberculosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Injury, Poisoning And Procedural Complications	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**
Subarachnoid Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Investigations	**1 (0.9)**	**1 (0.8)**	**1 (0.4)**	**1 (0.3)**	**2 (0.5)**	**2 (0.5)**
Blood Culture Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Pressure Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolism And Nutrition Disorders	**2 (1.7)**	**2 (1.6)**	**4 (1.4)**	**4 (1.3)**	**6 (1.5)**	**6 (1.4)**
Cachexia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperglycaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperkalaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hyponatraemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Metabolic Acidosis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**23 (20.0)**	**23 (18.5)**	**29 (10.3)**	**30 (9.9)**	**52 (13.1)**	**53 (12.4)**
Acute Lymphocytic Leukaemia Recurrent	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Acute Myeloid Leukaemia	11 (9.6)	11 (8.9)	13 (4.6)	13 (4.3)	24 (6.0)	24 (5.6)
Acute Myeloid Leukaemia Recurrent	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Blast Crisis In Myelogenous Leukaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Chronic Lymphocytic Leukaemia Recurrent	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Myeloid Leukaemia	3 (2.6)	3 (2.4)	2 (0.7)	3 (1.0)	5 (1.3)	6 (1.4)
Hepatic Cancer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Death
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Hodgkin's Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Kaposi's Sarcoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Leukaemia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lymphoma	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Myelodysplastic Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neoplasm Malignant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Non-Hodgkin's Lymphoma	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Plasma Cell Myeloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Tract Neoplasm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
T-Cell Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorders	**12 (10.4)**	**13 (10.5)**	**7 (2.5)**	**7 (2.3)**	**19 (4 8)**	**20 (4.7)**
Brain Oedema	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cerebral Haemorrhage	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cerebral Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cerebrovascular Accident	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Coma	3 (2.6)	4 (3.2)	1 (0.4)	1 (0.3)	4 (1.0)	5 (1.2)
Depressed Level Of Consciousness	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Encephalopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemorrhage Intracranial	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hemiparesis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intraventricular Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Loss Of Consciousness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Unresponsive To Stimuli	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Renal And Urinary Disorders	**6 (5.2)**	**6 (4.8)**	**5 (1.8)**	**5 (1.6)**	**11 (2 8)**	**11 (2.6)**
End Stage Renal Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Failure	5 (4.3)	5 (4.0)	5 (1.8)	5 (1.6)	10 (2 5)	10 (2.3)
Respiratory, Thoracic And Mediastinal Disorders	**28 (24 3)**	**30 (24.2)**	**26 (9 2)**	**28 (9.2)**	**54 (13.6)**	**58 (13.6)**
Acute Respiratory Distress Syndrome	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Acute Respiratory Failure	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Apnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Death
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Atelectasis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cheyne-Stokes Respiration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dyspnoea	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haemoptysis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemothorax	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Interstitial Lung Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Infiltration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Obliterative Bronchiolitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pleural Effusion	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pneumonia Aspiration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Alveolar Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Haemorrhage	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Oedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory Arrest	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Distress	3 (2.6)	3 (2.4)	4 (1.4)	5 (1.6)	7 (1.8)	8 (1.9)
Respiratory Failure	16 (13 9)	18 (14.5)	16 (5.7)	17 (5.6)	32 (8 1)	35 (8.2)
Tachypnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vascular Disorders	**3 (2.6)**	**5 (4.0)**	**5 (1.8)**	**6 (2.0)**	**8 (2.0)**	**11 (2.6)**
Circulatory Collapse	0	1 (0.8)	0	0	0	1 (0.2)
Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypotension	3 (2.6)	3 (2.4)	4 (1.4)	5 (1.6)	7 (1.8)	8 (1.9)
Hypovolaemic Shock	0	1 (0.8)	0	0	0	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-32 重篤な有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**381 (63.0)**	**364 (67.5)**	**32 (55.2)**
Blood And Lymphatic System Disorders	**145 (24.0)**	**133 (24.7)**	**15 (25.9)**
Agranulocytosis	0	2 (0.4)	0
Anaemia	41 (6.8)	21 (3.9)	5 (8.6)
Bone Marrow Disorder	0	1 (0 2)	0
Bone Marrow Failure	2 (0.3)	0	0
Coagulopathy	1 (0.2)	2 (0.4)	0
Disseminated Intravascular Coagulation	2 (0.3)	2 (0.4)	0
Febrile Neutropenia	33 (5.5)	37 (6.9)	4 (6.9)
Granulocytopenia	0	1 (0 2)	0
Haemolysis	2 (0.3)	1 (0 2)	0
Haemolytic Uraemic Syndrome	6 (1.0)	2 (0.4)	0
Haemorrhagic Diathesis	0	3 (0.6)	0
Hypercoagulation	1 (0.2)	0	0
Increased Tendency To Bruise	0	1 (0.2)	0
Iron Deficiency Anaemia	0	1 (0 2)	0
Leukopenia	8 (1.3)	9 (1.7)	2 (3.4)
Lymphadenopathy	1 (0.2)	0	1 (1.7)
Microangiopathic Haemolytic Anaemia	0	1 (0 2)	0
Neutropenia	32 (5.3)	30 (5.6)	5 (8.6)
Pancytopenia	10 (1.7)	13 (2.4)	0
Thrombocytopenia	74 (12.2)	56 (10.4)	9 (15.5)
Thrombotic Microangiopathy	0	1 (0 2)	0
Thrombotic Thrombocytopenic Purpura	6 (1.0)	3 (0.6)	0
Cardiac Disorders	**53 (8.8)**	**58 (10 8)**	**4 (6.9)**
Acute Myocardial Infarction	2 (0.3)	0	0
Angina Pectoris	2 (0.3)	1 (0 2)	0
Arrhythmia	1 (0.2)	0	0
Atrial Fibrillation	5 (0.8)	9 (1.7)	2 (3.4)
Atrial Flutter	1 (0.2)	2 (0.4)	0
Bradycardia	1 (0.2)	2 (0.4)	0
Bundle Branch Block	0	1 (0 2)	0
Bundle Branch Block Left	1 (0.2)	1 (0 2)	0
Bundle Branch Block Right	0	1 (0 2)	0
Cardiac Arrest	10 (1.7)	8 (1 5)	1 (1.7)
Cardiac Failure	5 (0.8)	4 (0.7)	0
Cardiac Failure Congestive	5 (0.8)	3 (0.6)	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Cardiac Flutter	0	1 (0 2)	0
Cardiac Tamponade	1 (0.2)	3 (0.6)	0
Cardio-Respiratory Arrest	5 (0.8)	9 (1.7)	1 (1.7)
Cardiomegaly	1 (0.2)	0	0
Cardiomyopathy	1 (0.2)	0	0
Cardiopulmonary Failure	1 (0.2)	0	0
Cardiotoxicity	0	1 (0 2)	0
Cardiovascular Disorder	0	1 (0 2)	0
Cardiovascular Insufficiency	3 (0.5)	1 (0 2)	0
Endocarditis Noninfective	0	1 (0 2)	0
Intracardiac Mass	0	1 (0 2)	0
Left Atrial Dilatation	1 (0.2)	0	0
Left Ventricular Hypertrophy	2 (0.3)	0	0
Mitral Valve Incompetence	1 (0.2)	0	0
Myocardial Infarction	5 (0.8)	2 (0.4)	1 (1.7)
Myocardial Ischaemia	0	1 (0 2)	0
Myocarditis	1 (0.2)	1 (0 2)	0
Palpitations	1 (0.2)	1 (0 2)	0
Pericardial Effusion	2 (0.3)	4 (0.7)	0
Pericardial Mass	0	1 (0 2)	0
Pericarditis	1 (0.2)	0	0
Sinus Tachycardia	2 (0.3)	3 (0.6)	0
Subendocardial Ischaemia	0	1 (0 2)	0
Supraventricular Tachycardia	3 (0.5)	5 (0 9)	1 (1.7)
Tachycardia	4 (0.7)	4 (0.7)	1 (1.7)
Torsade De Pointes	1 (0.2)	1 (0 2)	0
Ventricular Extrasystoles	1 (0.2)	1 (0 2)	0
Ventricular Fibrillation	1 (0.2)	1 (0.2)	0
Ventricular Hypertrophy	0	1 (0 2)	0
Ventricular Hypokinesia	1 (0.2)	0	0
Ventricular Tachycardia	1 (0.2)	2 (0.4)	0
Ear And Labyrinth Disorders	**4 (0.7)**	**1 (0.2)**	**0**
Deafness	0	1 (0 2)	0
Ear Discomfort	1 (0.2)	0	0
Ear Haemorrhage	1 (0.2)	0	0
Hypoacusis	2 (0.3)	0	0
Vertigo	1 (0.2)	0	0
Endocrine Disorders	**0**	**2 (0.4)**	**1 (1.7)**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Adrenal Insufficiency	0	0	1 (1.7)
Inappropriate Antidiuretic Hormone Secretion	0	2 (0.4)	0
Eye Disorders	**6 (1.0)**	**11 (2.0)**	**1 (1.7)**
Blindness	0	0	1 (1.7)
Choroiditis	0	1 (0 2)	0
Corneal Degeneration	0	1 (0 2)	0
Diplopia	1 (0.2)	1 (0 2)	0
Dry Eye	0	1 (0 2)	0
Eye Pain	0	1 (0 2)	0
Eye Pruritus	1 (0.2)	0	0
Glaucoma	1 (0.2)	0	0
Mydriasis	0	2 (0.4)	0
Photophobia	0	1 (0 2)	0
Pupils Unequal	1 (0.2)	1 (0 2)	0
Retinal Haemorrhage	0	1 (0 2)	0
Scleral Haemorrhage	0	1 (0 2)	0
Vision Blurred	1 (0.2)	0	0
Visual Acuity Reduced	0	1 (0 2)	0
Visual Impairment	2 (0.3)	0	0
Gastrointestinal Disorders	**95 (15.7)**	**83 (15.4)**	**9 (15.5)**
Abdominal Compartment Syndrome	0	1 (0 2)	0
Abdominal Distension	0	1 (0 2)	0
Abdominal Pain	19 (3.1)	19 (3.5)	0
Abdominal Pain Upper	2 (0.3)	2 (0.4)	2 (3.4)
Acute Abdomen	1 (0.2)	1 (0 2)	0
Anal Fissure	1 (0.2)	0	0
Anal Fistula	0	0	1 (1.7)
Ascites	3 (0.5)	8 (1 5)	0
Colitis	1 (0.2)	3 (0.6)	0
Constipation	0	1 (0 2)	0
Diarrhoea	27 (4.5)	22 (4.1)	0
Diarrhoea Haemorrhagic	2 (0.3)	4 (0.7)	0
Duodenal Perforation	1 (0.2)	0	0
Duodenitis	0	1 (0.2)	1 (1.7)
Duodenitis Haemorrhagic	0	1 (0.2)	0
Dysphagia	2 (0.3)	3 (0.6)	0
Enterocolitis	1 (0.2)	0	0
Faecaloma	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Food Poisoning	0	1 (0 2)	0
Gastric Haemorrhage	2 (0.3)	0	0
Gastric Ulcer	1 (0.2)	0	0
Gastric Ulcer Haemorrhage	2 (0.3)	1 (0 2)	0
Gastric Varices	1 (0.2)	0	0
Gastritis	0	1 (0 2)	0
Gastritis Erosive	1 (0.2)	0	0
Gastritis Haemorrhagic	1 (0.2)	0	0
Gastroenteritis Eosinophilic	0	1 (0 2)	0
Gastrointestinal Haemorrhage	17 (2.8)	17 (3.2)	1 (1.7)
Gastrointestinal Obstruction	1 (0.2)	0	0
Gastrointestinal Pain	0	1 (0 2)	0
Gastrointestinal Sounds Abnormal	0	1 (0.2)	0
Gastrointestinal Ulcer Haemorrhage	2 (0.3)	0	0
Gingival Bleeding	1 (0.2)	1 (0 2)	0
Haematemesis	6 (1.0)	5 (0 9)	0
Haematochezia	2 (0.3)	1 (0 2)	0
Haemorrhoids	2 (0.3)	0	0
Ileus	3 (0.5)	5 (0 9)	0
Ileus Paralytic	1 (0.2)	2 (0.4)	0
Impaired Gastric Emptying	0	1 (0 2)	0
Inguinal Hernia	0	1 (0 2)	0
Intestinal Haemorrhage	1 (0.2)	1 (0 2)	0
Intestinal Infarction	1 (0.2)	0	0
Intestinal Ischaemia	1 (0.2)	0	0
Intestinal Mass	0	1 (0 2)	0
Intestinal Obstruction	2 (0.3)	1 (0 2)	0
Intestinal Ulcer	2 (0.3)	1 (0 2)	0
Intra-Abdominal Fluid Collection	0	1 (0 2)	0
Intra-Abdominal Haemorrhage	1 (0.2)	0	0
Large Intestinal Ulcer	1 (0.2)	0	0
Malabsorption	1 (0.2)	0	0
Megacolon	1 (0.2)	0	0
Melaena	5 (0.8)	2 (0.4)	1 (1.7)
Mouth Haemorrhage	1 (0.2)	1 (0 2)	0
Nausea	23 (3.8)	6 (1 1)	3 (5.2)
Neutropenic Colitis	4 (0.7)	1 (0 2)	1 (1.7)
Oesophagitis	1 (0.2)	0	0
Oral Mucosal Exfoliation	0	1 (0 2)	0
Oral Pain	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Pancreatitis	1 (0.2)	0	0
Parotid Gland Enlargement	0	0	1 (1.7)
Pneumoperitoneum	2 (0.3)	0	0
Proctalgia	0	1 (0 2)	0
Rectal Haemorrhage	2 (0.3)	1 (0 2)	0
Rectal Tenesmus	1 (0.2)	0	0
Retroperitoneal Haemorrhage	1 (0.2)	0	0
Small Intestinal Obstruction	2 (0.3)	2 (0.4)	0
Subileus	1 (0.2)	0	0
Tongue Discomfort	1 (0.2)	0	0
Upper Gastrointestinal Haemorrhage	2 (0.3)	0	0
Vomiting	22 (3.6)	12 (2.2)	1 (1.7)
General Disorders And Administration Site Conditions	**132 (21.8)**	**111 (20.6)**	**11 (19.0)**
Asthenia	9 (1.5)	14 (2.6)	0
Catheter Site Haemorrhage	1 (0.2)	0	0
Chest Discomfort	1 (0.2)	0	0
Chest Pain	6 (1.0)	6 (1 1)	0
Chills	11 (1.8)	10 (1.9)	2 (3.4)
Death	0	1 (0 2)	0
Device Related Thrombosis	1 (0.2)	0	0
Disease Progression	3 (0.5)	4 (0.7)	0
Drug Interaction	2 (0.3)	1 (0 2)	0
Drug Intolerance	0	1 (0 2)	0
Face Oedema	0	1 (0 2)	0
Fatigue	7 (1.2)	6 (1 1)	0
Gait Disturbance	0	2 (0.4)	0
General Physical Health Deterioration	2 (0.3)	1 (0.2)	0
Generalised Oedema	1 (0.2)	2 (0.4)	0
Hyperpyrexia	1 (0.2)	0	1 (1.7)
Hypothermia	1 (0.2)	0	0
Malaise	3 (0.5)	0	1 (1.7)
Mucosal Haemorrhage	0	1 (0 2)	0
Mucosal Inflammation	5 (0.8)	2 (0.4)	0
Multi-Organ Disorder	1 (0.2)	0	0
Multiple Organ Dysfunction Syndrome	21 (3.5)	13 (2.4)	2 (3.4)
Necrosis	1 (0.2)	0	0
Oedema	0	1 (0 2)	0
Oedema Peripheral	3 (0.5)	1 (0 2)	0
Pain	1 (0.2)	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Performance Status Decreased	1 (0.2)	0	0
Pyrexia	78 (12.9)	75 (13 9)	9 (15.5)
Sudden Death	0	1 (0 2)	0
Therapy Non-Responder	4 (0.7)	3 (0.6)	0
Ulcer	0	1 (0 2)	0
Hepatobiliary Disorders	**34 (5.6)**	**23 (4.3)**	**0**
Acute Hepatic Failure	1 (0.2)	0	0
Cholecystitis	0	1 (0 2)	0
Cholestasis	3 (0.5)	0	0
Drug-Induced Liver Injury	0	2 (0.4)	0
Hepatic Failure	9 (1.5)	5 (0 9)	0
Hepatic Function Abnormal	1 (0.2)	0	0
Hepatic Necrosis	1 (0.2)	0	0
Hepatitis	1 (0.2)	3 (0.6)	0
Hepatitis Acute	1 (0.2)	0	0
Hepatocellular Injury	3 (0.5)	0	0
Hepatotoxicity	3 (0.5)	1 (0 2)	0
Hyperbilirubinaemia	12 (2.0)	9 (1.7)	0
Jaundice	4 (0.7)	3 (0.6)	0
Liver Disorder	0	1 (0 2)	0
Liver Injury	1 (0.2)	0	0
Immune System Disorders	**66 (10.9)**	**60 (11 1)**	**1 (1.7)**
Acute Graft Versus Host Disease In Liver	0	1 (0.2)	0
Anaphylactic Reaction	1 (0.2)	2 (0.4)	0
Bone Marrow Transplant Rejection	0	1 (0 2)	0
Chronic Graft Versus Host Disease	1 (0.2)	2 (0.4)	0
Drug Hypersensitivity	2 (0.3)	0	1 (1.7)
Graft Versus Host Disease	47 (7.8)	33 (6.1)	0
Graft Versus Host Disease In Gastrointestinal Tract	19 (3.1)	14 (2.6)	0
Graft Versus Host Disease In Liver	8 (1.3)	3 (0.6)	0
Graft Versus Host Disease In Lung	0	5 (0.9)	0
Graft Versus Host Disease In Skin	7 (1.2)	5 (0.9)	0
Transplant Rejection	3 (0.5)	0	0
Infections And Infestations	**202 (33.4)**	**203 (37.7)**	**18 (31.0)**
Abdominal Abscess	0	1 (0 2)	0
Abscess Fungal	0	1 (0 2)	0
Abscess Limb	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Acinetobacter Bacteraemia	0	1 (0 2)	0
Acinetobacter Infection	0	2 (0.4)	0
Acute Sinusitis	3 (0.5)	0	0
Alpha Haemolytic Streptococcal Infection	1 (0.2)	0	0
Anal Abscess	1 (0.2)	2 (0.4)	0
Anorectal Infection	1 (0.2)	0	0
Appendicitis	0	1 (0 2)	0
Aspergilloma	0	1 (0 2)	0
Aspergillus Infection	2 (0.3)	16 (3.0)	1 (1.7)
Bacteraemia	21 (3.5)	13 (2.4)	1 (1.7)
Bacterial Infection	5 (0.8)	4 (0.7)	0
Bacterial Sepsis	9 (1.5)	5 (0 9)	0
Bk Virus Infection	1 (0.2)	0	0
Brain Abscess	0	1 (0 2)	0
Bronchiolitis	1 (0.2)	1 (0 2)	0
Bronchitis	2 (0.3)	2 (0.4)	0
Bronchopulmonary Aspergillosis	6 (1.0)	14 (2.6)	2 (3.4)
Candida Infection	2 (0.3)	3 (0.6)	0
Catheter Site Cellulitis	1 (0.2)	0	0
Catheter Site Infection	1 (0.2)	1 (0 2)	0
Cavernous Sinus Thrombosis	0	1 (0 2)	0
Cellulitis	4 (0.7)	4 (0.7)	0
Cerebral Fungal Infection	0	1 (0 2)	0
Cerebral Toxoplasmosis	1 (0.2)	3 (0.6)	0
Chronic Sinusitis	1 (0.2)	0	0
Citrobacter Infection	1 (0.2)	0	0
Clostridial Infection	2 (0.3)	0	0
Clostridium Difficile Colitis	0	3 (0.6)	0
Clostridium Difficile Infection	1 (0.2)	3 (0.6)	0
Corynebacterium Bacteraemia	0	1 (0 2)	0
Corynebacterium Infection	1 (0.2)	1 (0 2)	0
Corynebacterium Sepsis	1 (0.2)	0	0
Cystitis	2 (0.3)	0	0
Cystitis Escherichia	0	1 (0 2)	0
Cytomegalovirus Colitis	3 (0.5)	1 (0 2)	0
Cytomegalovirus Enteritis	1 (0.2)	0	0
Cytomegalovirus Enterocolitis	0	1 (0 2)	0
Cytomegalovirus Gastritis	1 (0.2)	0	0
Cytomegalovirus Gastroenteritis	1 (0.2)	2 (0.4)	0
Cytomegalovirus Infection	22 (3.6)	20 (3.7)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Cytomegalovirus Viraemia	2 (0.3)	1 (0 2)	0
Device Related Infection	6 (1.0)	11 (2.0)	2 (3.4)
Device Related Sepsis	2 (0.3)	1 (0 2)	1 (1.7)
Encephalitis	4 (0.7)	1 (0 2)	0
Encephalitis Viral	0	1 (0 2)	0
Endophthalmitis	0	1 (0 2)	0
Enterobacter Bacteraemia	1 (0.2)	1 (0 2)	0
Enterobacter Infection	1 (0.2)	0	0
Enterobacter Sepsis	1 (0.2)	1 (0 2)	0
Enterococcal Bacteraemia	2 (0.3)	1 (0 2)	1 (1.7)
Enterococcal Infection	1 (0.2)	5 (0 9)	0
Enterococcal Sepsis	1 (0.2)	1 (0 2)	0
Epstein-Barr Virus Infection	1 (0.2)	3 (0.6)	0
Erysipelas	0	0	1 (1.7)
Escherichia Bacteraemia	2 (0.3)	2 (0.4)	0
Escherichia Sepsis	1 (0.2)	1 (0 2)	0
Eye Infection	0	1 (0 2)	0
Eye Infection Fungal	1 (0.2)	0	0
Folliculitis	0	1 (0 2)	0
Fungaemia	1 (0.2)	1 (0 2)	0
Fungal Infection	6 (1.0)	6 (1 1)	0
Fungal Oesophagitis	1 (0.2)	0	0
Fungal Rhinitis	0	1 (0 2)	0
Fungal Sepsis	2 (0.3)	1 (0 2)	0
Fungal Skin Infection	1 (0.2)	0	0
Fusobacterium Infection	0	1 (0 2)	0
Gastroenteritis	2 (0.3)	2 (0.4)	0
Gastroenteritis Viral	1 (0.2)	0	0
Gastrointestinal Infection	1 (0.2)	0	0
Herpes Simplex	3 (0.5)	1 (0 2)	0
Herpes Virus Infection	0	1 (0 2)	0
Herpes Zoster	5 (0.8)	6 (1 1)	0
Herpes Zoster Disseminated	0	1 (0.2)	0
Human Herpesvirus 6 Infection	1 (0.2)	1 (0.2)	0
Infection	2 (0.3)	0	0
Influenza	0	2 (0.4)	0
Klebsiella Bacteraemia	1 (0.2)	7 (1 3)	0
Klebsiella Infection	0	1 (0 2)	0
Klebsiella Sepsis	1 (0.2)	0	0
Lactobacillus Infection	0	1 (0 2)	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Liver Abscess	0	1 (0 2)	0
Localised Infection	0	1 (0 2)	0
Lower Respiratory Tract Infection	2 (0.3)	4 (0.7)	0
Lung Abscess	1 (0.2)	0	0
Mastoiditis	2 (0.3)	1 (0 2)	0
Meningitis Listeria	0	1 (0 2)	0
Meningitis Pneumococcal	0	1 (0 2)	0
Meningococcal Infection	0	1 (0 2)	0
Micrococcus Infection	1 (0.2)	0	0
Mucormycosis	0	0	1 (1.7)
Neutropenic Sepsis	4 (0.7)	1 (0 2)	2 (3.4)
Nocardia Sepsis	0	1 (0 2)	0
Nocardiosis	1 (0.2)	1 (0 2)	0
Oesophageal Candidiasis	0	2 (0.4)	0
Oral Candidiasis	1 (0.2)	0	0
Oral Herpes	0	2 (0.4)	0
Otitis Media	1 (0.2)	0	0
Perirectal Abscess	1 (0.2)	1 (0.2)	0
Peritonitis	0	2 (0.4)	0
Peritonitis Bacterial	0	2 (0.4)	0
Pharyngitis	1 (0.2)	2 (0.4)	0
Pneumocystis Jirovecii Pneumonia	3 (0.5)	2 (0.4)	0
Pneumonia	29 (4.8)	36 (6.7)	2 (3.4)
Pneumonia Bacterial	4 (0.7)	1 (0 2)	0
Pneumonia Cytomegaloviral	4 (0.7)	2 (0.4)	0
Pneumonia Escherichia	1 (0.2)	0	0
Pneumonia Fungal	5 (0.8)	2 (0.4)	1 (1.7)
Pneumonia Klebsiella	0	3 (0.6)	0
Pneumonia Necrotising	0	1 (0 2)	0
Pneumonia Pseudomonal	1 (0.2)	2 (0.4)	0
Pneumonia Staphylococcal	3 (0.5)	2 (0.4)	0
Pneumonia Streptococcal	0	1 (0 2)	0
Pneumonia Viral	1 (0.2)	0	0
Pseudomembranous Colitis	1 (0.2)	0	0
Pseudomonal Bacteraemia	1 (0.2)	5 (0 9)	0
Pseudomonal Sepsis	3 (0.5)	2 (0.4)	0
Pseudomonas Infection	2 (0.3)	1 (0 2)	0
Pulmonary Mycosis	3 (0.5)	0	0
Pyelonephritis	0	1 (0 2)	0
Respiratory Syncytial Virus Infection	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Respiratory Tract Infection	1 (0.2)	0	0
Respiratory Tract Infection Fungal	1 (0.2)	0	0
Sepsis	23 (3.8)	30 (5.6)	2 (3.4)
Sepsis Syndrome	1 (0.2)	0	0
Septic Embolus	1 (0.2)	0	0
Septic Shock	20 (3.3)	20 (3.7)	6 (10.3)
Sinusitis	8 (1.3)	6 (1 1)	0
Sinusitis Bacterial	1 (0.2)	0	0
Sinusitis Fungal	0	0	1 (1.7)
Spinal Cord Infection	1 (0.2)	0	0
Staphylococcal Bacteraemia	7 (1.2)	6 (1 1)	1 (1.7)
Staphylococcal Infection	5 (0.8)	3 (0.6)	1 (1.7)
Staphylococcal Sepsis	0	3 (0.6)	0
Streptococcal Bacteraemia	2 (0.3)	5 (0 9)	1 (1.7)
Streptococcal Sepsis	1 (0.2)	2 (0.4)	0
Subcutaneous Abscess	0	1 (0.2)	0
Systemic Candida	2 (0.3)	2 (0.4)	0
Systemic Mycosis	0	3 (0.6)	0
Tooth Abscess	2 (0.3)	0	0
Tracheobronchitis	1 (0.2)	0	0
Tuberculosis	0	1 (0 2)	0
Upper Respiratory Tract Infection	7 (1.2)	2 (0.4)	0
Urinary Tract Infection	4 (0.7)	4 (0.7)	0
Urinary Tract Infection Viral	0	1 (0 2)	0
Varicella	0	1 (0 2)	0
Varicella Zoster Pneumonia	1 (0.2)	0	0
Varicella Zoster Virus Infection	3 (0.5)	0	0
Viral Haemorrhagic Cystitis	0	1 (0 2)	0
Viral Infection	2 (0.3)	3 (0.6)	0
Injury, Poisoning And Procedural Complications	**25 (4.1)**	**20 (3.7)**	**1 (1.7)**
Accidental Overdose	0	1 (0 2)	0
Brain Herniation	0	0	1 (1.7)
Complications Of Transplant Surgery	1 (0.2)	0	0
Compression Fracture	1 (0.2)	0	0
Fall	5 (0.8)	1 (0 2)	0
Femoral Neck Fracture	1 (0.2)	1 (0 2)	0
Head Injury	0	1 (0 2)	0
Hip Fracture	1 (0.2)	2 (0.4)	0
Infusion Related Reaction	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Lumbar Vertebral Fracture	1 (0.2)	0	0
Overdose	0	1 (0 2)	0
Post Procedural Complication	1 (0.2)	0	0
Post Procedural Haemorrhage	2 (0.3)	0	0
Spinal Fracture	1 (0.2)	0	0
Subarachnoid Haemorrhage	2 (0.3)	1 (0.2)	0
Subdural Haematoma	2 (0.3)	3 (0.6)	0
Subdural Haemorrhage	1 (0.2)	0	0
Toxicity To Various Agents	4 (0.7)	2 (0.4)	0
Transfusion Reaction	2 (0.3)	3 (0.6)	0
Transplant Failure	2 (0.3)	4 (0.7)	0
Investigations	**70 (11.6)**	**71 (13 2)**	**3 (5.2)**
Activated Partial Thromboplastin Time Prolonged	0	1 (0.2)	0
Alanine Aminotransferase Increased	6 (1.0)	10 (1.9)	1 (1.7)
Aspartate Aminotransferase Increased	2 (0.3)	3 (0.6)	0
Bacterial Test Positive	4 (0.7)	6 (1 1)	0
Band Neutrophil Count Increased	0	1 (0 2)	0
Bilirubin Conjugated Increased	1 (0.2)	0	0
Blood Alkaline Phosphatase Increased	4 (0.7)	1 (0 2)	0
Blood Bicarbonate Decreased	1 (0.2)	0	0
Blood Bilirubin Increased	5 (0.8)	8 (1 5)	1 (1.7)
Blood Creatine Phosphokinase Abnormal	1 (0.2)	0	0
Blood Creatinine Increased	4 (0.7)	6 (1 1)	0
Blood Culture Positive	4 (0.7)	6 (1 1)	1 (1.7)
Blood Electrolytes Abnormal	0	1 (0 2)	0
Blood Glucose Increased	0	1 (0 2)	0
Blood Lactate Dehydrogenase Increased	4 (0.7)	0	0
Blood Pressure Decreased	0	1 (0.2)	0
Blood Pressure Increased	1 (0.2)	1 (0.2)	0
Blood Pressure Orthostatic	1 (0.2)	0	0
Blood Urea Increased	1 (0.2)	1 (0 2)	0
Blood Urine Present	1 (0.2)	0	0
Body Temperature	1 (0.2)	0	0
Body Temperature Increased	1 (0.2)	0	0
C-Reactive Protein Increased	1 (0.2)	1 (0 2)	0
Cardiac Murmur	1 (0.2)	0	0
Clostridium Test Positive	1 (0.2)	0	0
Coagulation Test Abnormal	0	1 (0 2)	0
Computerised Tomogram Abnormal	0	2 (0.4)	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Creatinine Renal Clearance Decreased	1 (0.2)	0	0
Culture	1 (0.2)	0	0
Culture Positive	1 (0.2)	0	0
Cytomegalovirus Test	0	2 (0.4)	0
Cytomegalovirus Test Positive	4 (0.7)	4 (0.7)	0
Drug Level Increased	2 (0.3)	1 (0 2)	0
Ejection Fraction Decreased	2 (0.3)	0	0
Electrocardiogram Abnormal	1 (0.2)	0	0
Electrocardiogram Qt Prolonged	1 (0.2)	2 (0.4)	0
Electrocardiogram T Wave Abnormal	1 (0.2)	0	0
Fungal Test Positive	2 (0.3)	0	0
Gamma-Glutamyltransferase Abnormal	0	1 (0 2)	0
Gamma-Glutamyltransferase Increased	10 (1.7)	14 (2.6)	0
Haematocrit Decreased	1 (0.2)	1 (0 2)	0
Haemoglobin Decreased	2 (0.3)	2 (0.4)	0
Hepatic Enzyme Abnormal	1 (0.2)	1 (0 2)	0
Hepatic Enzyme Increased	4 (0.7)	2 (0.4)	0
Immunosuppressant Drug Level Decreased	0	1 (0.2)	0
Karnofsky Scale Worsened	0	1 (0.2)	0
Liver Function Test Abnormal	1 (0.2)	2 (0.4)	0
Liver Function Test Increased	2 (0.3)	5 (0 9)	0
Lymphocyte Count Increased	0	2 (0.4)	0
Nuclear Magnetic Resonance Imaging Brain Abnormal	0	1 (0.2)	0
Occult Blood Positive	1 (0.2)	0	0
Oxygen Saturation Decreased	2 (0.3)	2 (0.4)	0
Pco2 Increased	1 (0.2)	0	0
Platelet Count Decreased	1 (0.2)	0	0
Prothrombin Time Prolonged	0	1 (0 2)	0
Pulse Absent	0	1 (0 2)	0
Red Blood Cell Count Decreased	1 (0.2)	0	0
Romberg Test Positive	0	1 (0 2)	0
Salmonella Test Positive	1 (0.2)	0	0
Transaminases Increased	7 (1.2)	3 (0.6)	0
Troponin I Increased	0	1 (0 2)	0
Troponin Increased	0	1 (0 2)	0
Weight Decreased	4 (0.7)	4 (0.7)	0
White Blood Cell Count Increased	0	1 (0 2)	0
Metabolism And Nutrition Disorders	**55 (9.1)**	**43 (8.0)**	**0**
Acidosis	6 (1.0)	2 (0.4)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Cachexia	1 (0.2)	1 (0 2)	0
Decreased Appetite	4 (0.7)	7 (1 3)	0
Dehydration	11 (1.8)	9 (1.7)	0
Diabetes Mellitus	4 (0.7)	1 (0.2)	0
Electrolyte Depletion	1 (0.2)	0	0
Electrolyte Imbalance	1 (0.2)	1 (0 2)	0
Failure To Thrive	1 (0.2)	2 (0.4)	0
Feeding Disorder	0	1 (0 2)	0
Fluid Overload	1 (0.2)	3 (0.6)	0
Gout	1 (0.2)	1 (0 2)	0
Haemosiderosis	0	1 (0 2)	0
Hyperglycaemia	6 (1.0)	7 (1 3)	0
Hyperkalaemia	5 (0.8)	5 (0 9)	0
Hyperphosphataemia	0	1 (0 2)	0
Hyperuricaemia	1 (0.2)	0	0
Hypervolaemia	0	1 (0 2)	0
Hypoalbuminaemia	2 (0.3)	0	0
Hypocalcaemia	1 (0.2)	0	0
Hypoglycaemia	2 (0.3)	0	0
Hypokalaemia	4 (0.7)	1 (0 2)	0
Hypomagnesaemia	3 (0.5)	0	0
Hyponatraemia	2 (0.3)	2 (0.4)	0
Hypophagia	0	1 (0 2)	0
Hypoproteinaemia	1 (0.2)	0	0
Hypovolaemia	1 (0.2)	2 (0.4)	0
Lactic Acidosis	0	1 (0 2)	0
Malnutrition	2 (0.3)	1 (0 2)	0
Metabolic Acidosis	4 (0.7)	4 (0.7)	0
Polydipsia	1 (0.2)	0	0
Tumour Lysis Syndrome	1 (0.2)	0	0
Musculoskeletal And Connective Tissue Disorders	**22 (3.6)**	**15 (2.8)**	**0**
Arthralgia	4 (0.7)	5 (0 9)	0
Back Pain	3 (0.5)	2 (0.4)	0
Bone Pain	3 (0.5)	0	0
Intervertebral Disc Protrusion	0	1 (0 2)	0
Muscle Atrophy	0	2 (0.4)	0
Muscle Contracture	1 (0.2)	0	0
Muscle Twitching	1 (0.2)	0	0
Muscular Weakness	5 (0.8)	4 (0.7)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Musculoskeletal Chest Pain	0	1 (0 2)	0
Musculoskeletal Pain	1 (0.2)	0	0
Myalgia	2 (0.3)	2 (0.4)	0
Myopathy	3 (0.5)	0	0
Osteonecrosis	0	2 (0.4)	0
Pain In Extremity	2 (0.3)	0	0
Pathological Fracture	0	1 (0 2)	0
Polymyositis	1 (0.2)	0	0
Torticollis	1 (0.2)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**51 (8.4)**	**48 (8.9)**	**2 (3.4)**
Acute Lymphocytic Leukaemia Recurrent	0	6 (1.1)	0
Acute Myeloid Leukaemia	11 (1.8)	13 (2.4)	2 (3.4)
Acute Myeloid Leukaemia Recurrent	14 (2.3)	6 (1 1)	0
Adult T-Cell Lymphoma/Leukaemia	0	1 (0 2)	0
B-Cell Lymphoma	0	1 (0 2)	0
Blast Cell Crisis	0	1 (0 2)	0
Central Nervous System Leukaemia	1 (0.2)	0	0
Chloroma	1 (0.2)	0	0
Chronic Myeloid Leukaemia	2 (0.3)	0	0
Hodgkin's Disease	0	1 (0 2)	0
Hodgkin's Disease Refractory	1 (0.2)	0	0
Leukaemia	3 (0.5)	1 (0 2)	0
Leukaemia Recurrent	6 (1.0)	5 (0 9)	0
Lymphoma	5 (0.8)	2 (0.4)	0
Metastases To Kidney	0	1 (0.2)	0
Metastases To Liver	0	1 (0.2)	0
Metastatic Neoplasm	1 (0.2)	0	0
Myelodysplastic Syndrome	1 (0.2)	2 (0.4)	0
Neoplasm Malignant	1 (0.2)	3 (0.6)	0
Non-Hodgkin's Lymphoma	1 (0.2)	4 (0.7)	0
Non-Hodgkin's Lymphoma Recurrent	0	1 (0 2)	0
Plasma Cell Myeloma	0	1 (0 2)	0
Post Transplant Lymphoproliferative Disorder	1 (0.2)	1 (0 2)	0
Renal Cancer	1 (0.2)	0	0
Squamous Cell Carcinoma	1 (0.2)	1 (0 2)	0
Tumour Pain	1 (0.2)	0	0
Uterine Leiomyoma	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Nervous System Disorders	**58 (9.6)**	**71 (13 2)**	**2 (3.4)**
Ataxia	1 (0.2)	0	0
Balance Disorder	1 (0.2)	1 (0 2)	0
Brain Compression	0	0	1 (1.7)
Brain Oedema	3 (0.5)	4 (0.7)	0
Brain Stem Haemorrhage	1 (0.2)	0	0
Cauda Equina Syndrome	1 (0.2)	0	0
Central Nervous System Lesion	2 (0.3)	2 (0.4)	0
Cerebellar Haemorrhage	2 (0.3)	0	1 (1.7)
Cerebellar Syndrome	1 (0.2)	0	0
Cerebral Haemorrhage	7 (1.2)	5 (0 9)	0
Cerebral Hypoperfusion	0	1 (0.2)	0
Cerebral Infarction	1 (0.2)	2 (0.4)	0
Cerebrovascular Accident	1 (0.2)	2 (0.4)	0
Cognitive Disorder	2 (0.3)	1 (0 2)	0
Coma	4 (0.7)	6 (1 1)	0
Demyelination	2 (0.3)	0	0
Depressed Level Of Consciousness	2 (0.3)	4 (0.7)	0
Disturbance In Attention	1 (0.2)	1 (0 2)	0
Dizziness	2 (0.3)	2 (0.4)	0
Dysarthria	0	1 (0 2)	0
Encephalopathy	4 (0.7)	1 (0 2)	0
Facial Paralysis	1 (0.2)	0	0
Generalised Tonic-Clonic Seizure	0	2 (0.4)	0
Guillain-Barre Syndrome	0	1 (0 2)	0
Haemorrhage Intracranial	3 (0.5)	7 (1 3)	0
Haemorrhagic Stroke	1 (0.2)	1 (0 2)	0
Headache	10 (1.7)	9 (1.7)	2 (3.4)
Hemiparesis	1 (0.2)	7 (1 3)	0
Hemiplegia	0	1 (0 2)	0
Hydrocephalus	0	0	1 (1.7)
Hypoaesthesia	0	1 (0 2)	0
Hypoglycaemic Coma	1 (0.2)	0	0
Hypokinesia	0	1 (0 2)	0
Hyporeflexia	1 (0.2)	0	0
Hypotonia	1 (0.2)	0	0
Lethargy	2 (0.3)	1 (0 2)	0
Leukoencephalopathy	1 (0.2)	1 (0.2)	0
Loss Of Consciousness	5 (0.8)	8 (1 5)	1 (1.7)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Meningism	1 (0.2)	0	0
Metabolic Encephalopathy	3 (0.5)	0	0
Migraine	1 (0.2)	0	0
Nervous System Disorder	1 (0.2)	0	0
Neuralgia	0	1 (0 2)	0
Neuropathy Peripheral	1 (0.2)	1 (0 2)	0
Neurotoxicity	0	1 (0 2)	0
Nystagmus	0	0	1 (1.7)
Paraesthesia	0	1 (0 2)	0
Paralysis	1 (0.2)	1 (0 2)	0
Paraparesis	1 (0.2)	0	0
Paresis	0	1 (0 2)	0
Partial Seizures	0	1 (0 2)	0
Polyneuropathy	1 (0.2)	0	0
Pyramidal Tract Syndrome	1 (0.2)	0	0
Seizure	8 (1.3)	7 (1 3)	0
Sensory Loss	1 (0.2)	0	0
Simple Partial Seizures	1 (0.2)	0	0
Somnolence	1 (0.2)	3 (0.6)	0
Stupor	2 (0.3)	1 (0 2)	0
Syncope	5 (0.8)	4 (0.7)	0
Tonic Convulsion	1 (0.2)	0	0
Transient Ischaemic Attack	1 (0.2)	0	0
Tremor	2 (0.3)	3 (0.6)	0
Trigeminal Neuralgia	0	1 (0 2)	0
Unresponsive To Stimuli	3 (0.5)	3 (0.6)	0
Visual Field Defect	0	1 (0 2)	0
Psychiatric Disorders	**18 (3.0)**	**20 (3.7)**	**0**
Abnormal Behaviour	0	1 (0 2)	0
Affect Lability	1 (0.2)	0	0
Aggression	1 (0.2)	0	0
Agitation	1 (0.2)	0	0
Anxiety	0	1 (0 2)	0
Confusional State	7 (1.2)	6 (1 1)	0
Delirium	0	1 (0 2)	0
Depression	2 (0.3)	5 (0 9)	0
Depression Suicidal	0	1 (0 2)	0
Disorientation	1 (0.2)	0	0
Disturbance In Social Behaviour	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Insomnia	0	1 (0 2)	0
Mental Status Changes	7 (1.2)	8 (1 5)	0
Obsessive-Compulsive Disorder	1 (0.2)	0	0
Psychotic Disorder	1 (0.2)	0	0
Restlessness	0	1 (0 2)	0
Stress	0	1 (0 2)	0
Substance-Induced Psychotic Disorder	0	1 (0.2)	0
Suicidal Ideation	3 (0.5)	2 (0.4)	0
Renal And Urinary Disorders	**46 (7.6)**	**45 (8.3)**	**1 (1.7)**
Acute Kidney Injury	10 (1.7)	8 (1 5)	1 (1.7)
Acute Prerenal Failure	1 (0.2)	0	0
Anuria	3 (0.5)	1 (0 2)	0
Azotaemia	1 (0.2)	0	0
Cystitis Haemorrhagic	6 (1.0)	5 (0 9)	0
Dysuria	3 (0.5)	1 (0 2)	0
Haematuria	8 (1.3)	4 (0.7)	0
Nephrolithiasis	1 (0.2)	0	0
Obstructive Nephropathy	0	1 (0 2)	0
Oliguria	1 (0.2)	2 (0.4)	0
Pollakiuria	1 (0.2)	0	0
Polyuria	2 (0.3)	0	0
Renal Failure	19 (3.1)	29 (5.4)	0
Renal Haematoma	1 (0.2)	0	0
Renal Impairment	2 (0.3)	2 (0.4)	0
Renal Tubular Necrosis	0	1 (0 2)	0
Tubulointerstitial Nephritis	0	1 (0.2)	0
Urinary Retention	0	1 (0 2)	0
Reproductive System And Breast Disorders	**6 (1.0)**	**6 (1.1)**	**0**
Menorrhagia	0	2 (0.4)	0
Pelvic Pain	0	1 (0 2)	0
Prostatitis	1 (0.2)	0	0
Testicular Swelling	1 (0.2)	0	0
Uterine Haemorrhage	0	1 (0 2)	0
Vaginal Haemorrhage	4 (0.7)	2 (0.4)	0
Respiratory, Thoracic And Mediastinal Disorders	**113 (18.7)**	**109 (20.2)**	**13 (22.4)**
Acute Promyelocytic Leukaemia Differentiation Syndrome	1 (0.2)	0	0
Acute Pulmonary Oedema	2 (0.3)	2 (0.4)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Acute Respiratory Distress Syndrome	6 (1.0)	7 (1.3)	1 (1.7)
Acute Respiratory Failure	5 (0.8)	1 (0 2)	0
Apnoea	2 (0.3)	0	0
Asthma	0	1 (0 2)	0
Atelectasis	3 (0.5)	3 (0.6)	0
Bronchial Hyperreactivity	0	1 (0 2)	0
Bronchopneumopathy	1 (0.2)	0	0
Cough	12 (2.0)	10 (1.9)	0
Diffuse Alveolar Damage	0	1 (0 2)	0
Dyspnoea	29 (4.8)	24 (4.5)	2 (3.4)
Dyspnoea Exertional	1 (0.2)	1 (0 2)	0
Epiglottis Ulcer	1 (0.2)	0	0
Epistaxis	1 (0.2)	3 (0.6)	1 (1.7)
Haemoptysis	5 (0.8)	6 (1 1)	0
Haemothorax	0	2 (0.4)	0
Hydrothorax	1 (0.2)	1 (0 2)	0
Hypercapnia	1 (0.2)	0	0
Hypoxia	14 (2.3)	18 (3.3)	4 (6.9)
Interstitial Lung Disease	4 (0.7)	1 (0 2)	0
Laryngeal Oedema	0	0	1 (1.7)
Lung Consolidation	0	0	1 (1.7)
Lung Disorder	1 (0.2)	2 (0.4)	0
Lung Infiltration	6 (1.0)	12 (2.2)	0
Nasal Congestion	1 (0.2)	0	0
Nasal Necrosis	0	1 (0 2)	0
Nocturnal Dyspnoea	1 (0.2)	0	0
Obliterative Bronchiolitis	1 (0.2)	2 (0.4)	0
Obstructive Airways Disorder	1 (0.2)	0	0
Organising Pneumonia	3 (0.5)	0	0
Oropharyngeal Pain	1 (0.2)	1 (0 2)	1 (1.7)
Orthopnoea	1 (0.2)	0	0
Pleural Effusion	14 (2.3)	6 (1 1)	0
Pleuritic Pain	3 (0.5)	1 (0 2)	0
Pneumomediastinum	0	1 (0 2)	0
Pneumonia Aspiration	3 (0.5)	3 (0.6)	0
Pneumonitis	5 (0.8)	3 (0.6)	0
Pneumothorax	1 (0.2)	2 (0.4)	0
Productive Cough	5 (0.8)	4 (0.7)	0
Pulmonary Alveolar Haemorrhage	3 (0.5)	3 (0.6)	1 (1.7)
Pulmonary Embolism	7 (1.2)	1 (0 2)	1 (1.7)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Pulmonary Fibrosis	0	1 (0 2)	0
Pulmonary Haemorrhage	7 (1.2)	4 (0.7)	0
Pulmonary Hypertension	1 (0.2)	0	0
Pulmonary Mass	3 (0.5)	4 (0.7)	0
Pulmonary Oedema	13 (2.1)	13 (2.4)	1 (1.7)
Rales	1 (0.2)	0	0
Respiratory Acidosis	1 (0.2)	1 (0 2)	0
Respiratory Arrest	1 (0.2)	0	0
Respiratory Disorder	1 (0.2)	1 (0 2)	1 (1.7)
Respiratory Distress	8 (1.3)	8 (1 5)	2 (3.4)
Respiratory Failure	28 (4.6)	46 (8.5)	2 (3.4)
Respiratory Tract Haemorrhage	1 (0.2)	0	0
Restrictive Pulmonary Disease	1 (0.2)	0	0
Rhinorrhoea	2 (0.3)	0	0
Sinus Congestion	0	1 (0 2)	0
Sinus Disorder	1 (0.2)	0	0
Sinus Pain	0	1 (0 2)	0
Sputum Discoloured	1 (0.2)	0	0
Tachypnoea	3 (0.5)	8 (1 5)	0
Tonsillar Disorder	1 (0.2)	0	0
Skin And Subcutaneous Tissue Disorders	**7 (1.2)**	**7 (1.3)**	**0**
Blood Blister	1 (0.2)	0	0
Dermatitis Bullous	0	1 (0 2)	0
Erythema	1 (0.2)	0	0
Night Sweats	1 (0.2)	0	0
Petechiae	0	1 (0 2)	0
Pruritus	1 (0.2)	0	0
Rash	1 (0.2)	1 (0 2)	0
Rash Erythematous	1 (0.2)	0	0
Rash Maculo-Papular	1 (0.2)	0	0
Rash Pruritic	1 (0.2)	0	0
Rash Vesicular	1 (0.2)	0	0
Skin Burning Sensation	0	1 (0 2)	0
Skin Hyperpigmentation	0	1 (0 2)	0
Skin Lesion	0	2 (0.4)	0
Skin Oedema	1 (0.2)	0	0
Surgical And Medical Procedures	**6 (1.0)**	**4 (0.7)**	**1 (1.7)**
Analgesic Therapy	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Bone Marrow Transplant	3 (0.5)	0	0
Central Venous Catheterisation	0	1 (0 2)	0
Chemotherapy	2 (0.3)	2 (0.4)	0
Stem Cell Transplant	1 (0.2)	0	0
Surgery	0	0	1 (1.7)
Vascular Disorders	**52 (8.6)**	**66 (12 2)**	**5 (8.6)**
Circulatory Collapse	1 (0.2)	4 (0.7)	0
Deep Vein Thrombosis	3 (0.5)	2 (0.4)	0
Embolism Arterial	0	1 (0 2)	0
Flushing	0	1 (0 2)	0
Haematoma	1 (0.2)	0	0
Haemodynamic Instability	2 (0.3)	0	0
Haemorrhage	2 (0.3)	5 (0 9)	0
Haemorrhagic Infarction	0	1 (0 2)	0
Hypertension	7 (1.2)	2 (0.4)	1 (1.7)
Hypotension	34 (5.6)	44 (8.2)	4 (6.9)
Hypovolaemic Shock	3 (0.5)	3 (0.6)	0
Ischaemia	0	1 (0 2)	0
Microangiopathy	1 (0.2)	0	0
Orthostatic Hypotension	2 (0.3)	1 (0 2)	0
Peripheral Circulatory Failure	1 (0.2)	0	0
Shock	0	3 (0.6)	0
Subclavian Vein Thrombosis	1 (0.2)	0	0
Thrombosis	0	1 (0 2)	0
Vasodilatation	0	1 (0 2)	0
Vena Cava Embolism	0	1 (0 2)	0
Venoocclusive Disease	0	1 (0 2)	0
Venous Thrombosis	0	1 (0 2)	0

Every subject is counted a single time for each applicable row and column.
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付録 2.7.4-33 重篤な副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**59 (9.8)**	**33 (6.1)**	**2 (3.4)**
Blood And Lymphatic System Disorders	**5 (0.8)**	**4 (0.7)**	**0**
Anaemia	2 (0.3)	1 (0 2)	0
Bone Marrow Failure	1 (0.2)	0	0
Coagulopathy	0	1 (0 2)	0
Haemolytic Uraemic Syndrome	1 (0.2)	0	0
Neutropenia	0	1 (0 2)	0
Pancytopenia	0	1 (0 2)	0
Thrombocytopenia	2 (0.3)	0	0
Thrombotic Thrombocytopenic Purpura	1 (0.2)	0	0
Cardiac Disorders	**4 (0.7)**	**1 (0.2)**	**0**
Atrial Fibrillation	2 (0.3)	1 (0.2)	0
Bundle Branch Block Left	1 (0.2)	0	0
Torsade De Pointes	1 (0.2)	0	0
Eye Disorders	**1 (0.2)**	**1 (0.2)**	**0**
Diplopia	0	1 (0 2)	0
Vision Blurred	1 (0.2)	0	0
Gastrointestinal Disorders	**8 (1.3)**	**5 (0.9)**	**0**
Abdominal Pain Upper	1 (0.2)	0	0
Diarrhoea	2 (0.3)	1 (0 2)	0
Duodenitis	0	1 (0.2)	0
Dysphagia	1 (0.2)	1 (0 2)	0
Gastritis	0	1 (0 2)	0
Gastritis Haemorrhagic	1 (0.2)	0	0
Gastrointestinal Haemorrhage	0	1 (0 2)	0
Ileus	0	1 (0 2)	0
Intestinal Ulcer	0	1 (0 2)	0
Melaena	1 (0.2)	0	0
Nausea	4 (0.7)	0	0
Tongue Discomfort	1 (0.2)	0	0
Vomiting	4 (0.7)	1 (0 2)	0
General Disorders And Administration Site Conditions	**3 (0.5)**	**3 (0.6)**	**0**
Asthenia	0	1 (0 2)	0
Drug Interaction	2 (0.3)	1 (0 2)	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Mucosal Inflammation	1 (0.2)	0	0
Pyrexia	0	1 (0 2)	0
Hepatobiliary Disorders	**15 (2.5)**	**4 (0.7)**	**0**
Cholestasis	1 (0.2)	0	0
Hepatic Failure	1 (0.2)	1 (0 2)	0
Hepatitis	1 (0.2)	0	0
Hepatitis Acute	1 (0.2)	0	0
Hepatocellular Injury	3 (0.5)	0	0
Hepatotoxicity	2 (0.3)	0	0
Hyperbilirubinaemia	5 (0.8)	2 (0.4)	0
Jaundice	2 (0.3)	0	0
Liver Disorder	0	1 (0 2)	0
Immune System Disorders	**3 (0.5)**	**0**	**0**
Drug Hypersensitivity	1 (0.2)	0	0
Graft Versus Host Disease	2 (0.3)	0	0
Infections And Infestations	**1 (0.2)**	**2 (0.4)**	**0**
Candida Infection	0	1 (0 2)	0
Cavernous Sinus Thrombosis	0	1 (0 2)	0
Encephalitis	1 (0.2)	0	0
Injury, Poisoning And Procedural Complications	**3 (0.5)**	**1 (0.2)**	**0**
Accidental Overdose	0	1 (0 2)	0
Fall	1 (0.2)	0	0
Toxicity To Various Agents	2 (0.3)	0	0
Investigations	**22 (3.6)**	**11 (2.0)**	**2 (3.4)**
Alanine Aminotransferase Increased	3 (0.5)	1 (0.2)	1 (1.7)
Aspartate Aminotransferase Increased	2 (0.3)	1 (0.2)	0
Bilirubin Conjugated Increased	1 (0.2)	0	0
Blood Alkaline Phosphatase Increased	1 (0.2)	0	0
Blood Bilirubin Increased	3 (0.5)	3 (0.6)	1 (1.7)
Blood Creatinine Increased	1 (0.2)	1 (0 2)	0
Creatinine Renal Clearance Decreased	1 (0.2)	0	0
Drug Level Increased	2 (0.3)	1 (0 2)	0
Ejection Fraction Decreased	1 (0.2)	0	0
Electrocardiogram Qt Prolonged	1 (0.2)	0	0
Electrocardiogram T Wave Abnormal	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Gamma-Glutamyltransferase Increased	5 (0.8)	3 (0.6)	0
Hepatic Enzyme Abnormal	0	1 (0.2)	0
Hepatic Enzyme Increased	2 (0.3)	0	0
Liver Function Test Abnormal	1 (0.2)	0	0
Liver Function Test Increased	2 (0.3)	1 (0 2)	0
Transaminases Increased	4 (0.7)	2 (0.4)	0
Metabolism And Nutrition Disorders	**3 (0.5)**	**1 (0.2)**	**0**
Decreased Appetite	1 (0.2)	0	0
Hyperkalaemia	1 (0.2)	1 (0 2)	0
Hypomagnesaemia	1 (0.2)	0	0
Musculoskeletal And Connective Tissue Disorders	**2 (0.3)**	**1 (0.2)**	**0**
Muscle Twitching	1 (0.2)	0	0
Muscular Weakness	1 (0.2)	1 (0 2)	0
Torticollis	1 (0.2)	0	0
Nervous System Disorders	**7 (1.2)**	**2 (0.4)**	**0**
Ataxia	1 (0.2)	0	0
Dizziness	1 (0.2)	0	0
Dysarthria	0	1 (0 2)	0
Encephalopathy	2 (0.3)	0	0
Hyporeflexia	1 (0.2)	0	0
Lethargy	0	1 (0 2)	0
Meningism	1 (0.2)	0	0
Migraine	1 (0.2)	0	0
Neuropathy Peripheral	1 (0.2)	0	0
Seizure	1 (0.2)	0	0
Sensory Loss	1 (0.2)	0	0
Somnolence	0	2 (0.4)	0
Stupor	1 (0.2)	0	0
Syncope	2 (0.3)	0	0
Tremor	1 (0.2)	0	0
Psychiatric Disorders	**1 (0.2)**	**1 (0.2)**	**0**
Confusional State	0	1 (0 2)	0
Mental Status Changes	1 (0.2)	0	0
Psychotic Disorder	1 (0.2)	0	0
Renal And Urinary Disorders	**4 (0.7)**	**3 (0.6)**	**0**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Acute Kidney Injury	1 (0.2)	0	0
Haematuria	1 (0.2)	0	0
Nephrolithiasis	1 (0.2)	0	0
Renal Failure	1 (0.2)	3 (0.6)	0
Renal Impairment	1 (0.2)	0	0
Respiratory, Thoracic And Mediastinal Disorders	**4 (0.7)**	**2 (0.4)**	**0**
Cough	1 (0.2)	1 (0.2)	0
Hypoxia	1 (0.2)	0	0
Interstitial Lung Disease	1 (0.2)	0	0
Oropharyngeal Pain	0	1 (0 2)	0
Pneumonitis	1 (0.2)	0	0
Productive Cough	0	1 (0 2)	0
Pulmonary Embolism	1 (0.2)	0	0
Rales	1 (0.2)	0	0
Skin And Subcutaneous Tissue Disorders	**1 (0.2)**	**0**	**0**
Pruritus	1 (0.2)	0	0
Rash Maculo-Papular	1 (0.2)	0	0
Vascular Disorders	**1 (0.2)**	**3 (0.6)**	**0**
Deep Vein Thrombosis	1 (0.2)	0	0
Embolism Arterial	0	1 (0 2)	0
Flushing	0	1 (0 2)	0
Hypotension	0	1 (0 2)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-34 重篤な有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**97 (84 3)**	**100 (80.6)**	**178 (63.1)**	**189 (62.2)**	**275 (69.3)**	**289 (67.5)**
Blood And Lymphatic System Disorders	**27 (23 5)**	**28 (22.6)**	**48 (17.0)**	**52 (17.1)**	**75 (18.9)**	**80 (18.7)**
Anaemia	4 (3.5)	5 (4.0)	11 (3 9)	12 (3.9)	15 (3.8)	17 (4.0)
Aplastic Anaemia	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Autoimmune Haemolytic Anaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Coagulopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Disseminated Intravascular Coagulation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Eosinophilia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Febrile Neutropenia	4 (3.5)	4 (3.2)	13 (4.6)	16 (5.3)	17 (4 3)	20 (4.7)
Haemolysis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemolytic Anaemia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Haemolytic Uraemic Syndrome	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Hypercoagulation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Leukocytosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Leukopenia	1 (0 9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Lymphadenopathy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Neutropenia	6 (5.2)	6 (4.8)	10 (3.5)	10 (3.3)	16 (4.0)	16 (3.7)
Pancytopenia	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Splenic Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Splenomegaly	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Thrombocytopenia	11 (9.6)	11 (8.9)	14 (5.0)	15 (4.9)	25 (6 3)	26 (6.1)
Thrombotic Thrombocytopenic Purpura	5 (4.3)	5 (4.0)	1 (0.4)	1 (0.3)	6 (1.5)	6 (1.4)
Cardiac Disorders	**25 (21.7)**	**26 (21.0)**	**38 (13.5)**	**39 (12.8)**	**63 (15.9)**	**65 (15.2)**
Arrhythmia Supraventricular	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Atrial Fibrillation	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Atrial Flutter	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Atrioventricular Block First Degree	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bradycardia	2 (1.7)	2 (1.6)	4 (1.4)	4 (1.3)	6 (1.5)	6 (1.4)
Cardiac Arrest	2 (1.7)	2 (1.6)	6 (2.1)	6 (2.0)	8 (2.0)	8 (1.9)
Cardiac Failure	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Cardiac Failure Congestive	0	0	8 (2.8)	8 (2.6)	8 (2.0)	8 (1.9)
Cardiac Valve Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	7 (6.1)	8 (6.5)	8 (2.8)	9 (3.0)	15 (3.8)	17 (4.0)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Cardiogenic Shock	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiopulmonary Failure	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Coronary Artery Occlusion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myocardial Infarction	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Palpitations	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pericardial Effusion	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pericarditis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pulseless Electrical Activity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sinus Tachycardia	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Supraventricular Tachycardia	4 (3.5)	4 (3.2)	5 (1.8)	5 (1.6)	9 (2.3)	9 (2.1)
Tachycardia	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Ventricular Extrasystoles	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Ventricular Fibrillation	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Tachycardia	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Congenital, Familial And Genetic Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Aplasia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ear And Labyrinth Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Vertigo Labyrinthine	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Endocrine Disorders	**1 (0.9)**	**1 (0.8)**	**2 (0.7)**	**2 (0.7)**	**3 (0.8)**	**3 (0.7)**
Adrenal Insufficiency	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Eye Disorders	**0**	**0**	**5 (1.8)**	**5 (1.6)**	**5 (1.3)**	**5 (1.2)**
Blindness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Conjunctivitis Allergic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Corneal Perforation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diplopia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal Disorders	**23 (20.0)**	**25 (20.2)**	**39 (13.8)**	**41 (13.5)**	**62 (15.6)**	**66 (15.4)**
Abdominal Distension	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Abdominal Pain	4 (3.5)	4 (3.2)	6 (2.1)	6 (2.0)	10 (2 5)	10 (2.3)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Abdominal Pain Lower	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Abdominal Pain Upper	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Abdominal Tenderness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ascites	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Colitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diarrhoea	10 (8.7)	10 (8.1)	14 (5.0)	14 (4.6)	24 (6.0)	24 (5.6)
Duodenal Ulcer	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Duodenitis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Dysphagia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Enteritis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Food Poisoning	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastric Haemorrhage	0	0	0	1 (0.3)	0	1 (0.2)
Gastric Perforation	0	1 (0.8)	0	0	0	1 (0.2)
Gastritis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gastrointestinal Haemorrhage	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Gingival Bleeding	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haematemesis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haematochezia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ileus	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ileus Paralytic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intestinal Ischaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intestinal Obstruction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intestinal Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mallory-Weiss Syndrome	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Melaena	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nausea	5 (4.3)	6 (4.8)	14 (5.0)	14 (4.6)	19 (4.8)	20 (4.7)
Neutropenic Colitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oesophageal Ulcer	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pancreatitis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Pancreatitis Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Stomatitis	0	0	0	1 (0.3)	0	1 (0.2)
Upper Gastrointestinal Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vomiting	6 (5.2)	7 (5.6)	18 (6.4)	18 (5.9)	24 (6.0)	25 (5.8)
General Disorders And Administration Site Conditions	**51 (44 3)**	**52 (41.9)**	**74 (26.2)**	**80 (26.3)**	**125 (31.5)**	**132 (30.8)**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Asthenia	4 (3.5)	4 (3.2)	14 (5.0)	15 (4.9)	18 (4 5)	19 (4.4)
Brain Death	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chest Pain	2 (1.7)	3 (2.4)	6 (2.1)	6 (2.0)	8 (2.0)	9 (2.1)
Chills	5 (4.3)	5 (4.0)	5 (1.8)	5 (1.6)	10 (2 5)	10 (2.3)
Death	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Disease Progression	14 (12 2)	14 (11.3)	16 (5.7)	16 (5.3)	30 (7.6)	30 (7.0)
Drug Interaction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Facial Pain	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Fatigue	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Gait Disturbance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Generalised Oedema	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Malaise	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mucosal Inflammation	0	0	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.7)
Multi-Organ Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Multiple Organ Dysfunction Syndrome	9 (7.8)	9 (7.3)	5 (1.8)	6 (2.0)	14 (3 5)	15 (3.5)
Oedema Peripheral	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pyrexia	27 (23 5)	27 (21.8)	41 (14.5)	44 (14.5)	68 (17.1)	71 (16.6)
Hepatobiliary Disorders	**8 (7.0)**	**8 (6.5)**	**9 (3.2)**	**9 (3.0)**	**17 (4 3)**	**17 (4.0)**
Cholecystitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cholelithiasis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Hepatic Failure	2 (1.7)	2 (1.6)	5 (1.8)	5 (1.6)	7 (1.8)	7 (1.6)
Hepatic Function Abnormal	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hepatic Necrosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Hepatitis Acute	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Jaundice	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Immune System Disorders	**23 (20.0)**	**25 (20.2)**	**6 (2.1)**	**6 (2.0)**	**29 (7 3)**	**31 (7.2)**
Chronic Graft Versus Host Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Drug Hypersensitivity	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Graft Versus Host Disease	10 (8.7)	11 (8.9)	1 (0.4)	1 (0.3)	11 (2.8)	12 (2.8)
Graft Versus Host Disease In Gastrointestinal Tract	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Graft Versus Host Disease In Liver	4 (3.5)	4 (3.2)	0	0	4 (1.0)	4 (0.9)

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Graft Versus Host Disease In Lung	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Graft Versus Host Disease In Skin	4 (3.5)	5 (4.0)	1 (0.4)	1 (0.3)	5 (1.3)	6 (1.4)
Kidney Transplant Rejection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Transplant Rejection	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Infections And Infestations	**59 (51 3)**	**61 (49.2)**	**94 (33.3)**	**99 (32.6)**	**153 (38.5)**	**160 (37.4)**
Abdominal Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abscess Limb	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Abscess Neck	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Acquired Immunodeficiency Syndrome	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Acute Sinusitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Anal Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Arthritis Bacterial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Aspergilloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Aspergillus Infection	2 (1.7)	2 (1.6)	1 (0.4)	2 (0.7)	3 (0.8)	4 (0.9)
Atypical Pneumonia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bacteraemia	6 (5.2)	6 (4.8)	4 (1.4)	4 (1.3)	10 (2 5)	10 (2.3)
Bacterial Infection	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Brain Abscess	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bronchiolitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bronchitis Viral	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bronchopulmonary Aspergillosis	0	1 (0.8)	2 (0.7)	2 (0.7)	2 (0.5)	3 (0.7)
Catheter Site Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cellulitis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Cellulitis Of Male External Genital Organ	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cellulitis Orbital	1 (0.9)	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.5)
Cerebral Aspergillosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Clostridium Difficile Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Conjunctivitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Chorioretinitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Duodenitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cytomegalovirus Infection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Device Related Infection	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Disseminated Tuberculosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Empyema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Encephalitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
End Stage Aids	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Enterobacter Infection	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Enterococcal Bacteraemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Enterococcal Infection	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Enterococcal Sepsis	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Escherichia Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fungaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fungal Infection	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Fungal Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Furuncle	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Fusarium Infection	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatic Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatosplenic Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Herpes Zoster	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Infection Parasitic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Klebsiella Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Klebsiella Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Meningitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Meningitis Cryptococcal	0	0	8 (2.8)	8 (2.6)	8 (2.0)	8 (1.9)
Mucormycosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Mycobacterial Infection	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Mycobacterium Avium Complex Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nocardiosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oesophageal Candidiasis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Oral Herpes	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Osteomyelitis	0	0	0	1 (0.3)	0	1 (0.2)
Pelvic Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Perirectal Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Peritonitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumocystis Jirovecii Pneumonia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pneumonia	14 (12 2)	14 (11.3)	22 (7.8)	24 (7.9)	36 (9 1)	38 (8.9)
Pneumonia Bacterial	4 (3.5)	4 (3.2)	0	0	4 (1.0)	4 (0.9)

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Pneumonia Fungal	5 (4.3)	6 (4.8)	5 (1.8)	6 (2.0)	10 (2 5)	12 (2.8)
Pneumonia Klebsiella	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pneumonia Pseudomonal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumonia Staphylococcal	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pseudallescheria Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pseudomonas Infection	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary Mycosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pulmonary Tuberculosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pyelonephritis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Syncytial Virus Infection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Respiratory Tract Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Retinitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rhinitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Salmonella Sepsis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sepsis	7 (6.1)	7 (5.6)	11 (3 9)	11 (3.6)	18 (4 5)	18 (4.2)
Septic Embolus	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Septic Shock	4 (3.5)	5 (4.0)	2 (0.7)	2 (0.7)	6 (1.5)	7 (1.6)
Sinusitis	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Sinusitis Bacterial	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Staphylococcal Bacteraemia	4 (3.5)	4 (3.2)	5 (1.8)	5 (1.6)	9 (2.3)	9 (2.1)
Staphylococcal Infection	3 (2.6)	3 (2.4)	3 (1.1)	3 (1.0)	6 (1.5)	6 (1.4)
Staphylococcal Sepsis	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Stenotrophomonas Sepsis	0	0	0	1 (0.3)	0	1 (0.2)
Subcutaneous Abscess	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tuberculosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Upper Respiratory Tract Infection	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Urinary Tract Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Viral Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Viral Sinusitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Wound Infection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Injury, Poisoning And Procedural Complications	**4 (3.5)**	**4 (3.2)**	**10 (3 5)**	**10 (3.3)**	**14 (3 5)**	**14 (3.3)**
Contusion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fall	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Femur Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Foot Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Head Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hip Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Limb Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Overdose	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Post Procedural Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Procedural Complication	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Subarachnoid Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Toxicity To Various Agents	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Investigations	**18 (15.7)**	**18 (14.5)**	**32 (11.3)**	**32 (10.5)**	**50 (12.6)**	**50 (11.7)**
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Anticoagulation Drug Level Above Therapeutic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bacterial Test Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Biopsy Brain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blast Cell Count Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Bilirubin Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Creatinine Increased	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Blood Culture Positive	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Blood Lactate Dehydrogenase Increased	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Blood Pressure Decreased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Blood Urea Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Body Temperature Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardioactive Drug Level Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cytomegalovirus Test	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Cytomegalovirus Test Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Level Increased	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Ejection Fraction Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram Qt Prolonged	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Electrocardiogram St Segment Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrocardiogram T Wave Peaked	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Eosinophil Count Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Fungal Test Positive	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gamma-Glutamyltransferase Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Haemoglobin Abnormal	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hepatic Enzyme Increased	1 (0 9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Liver Function Test Increased	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Oxygen Saturation Decreased	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pancreatic Enzymes Increased	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Platelet Count Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Prothrombin Level Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pupillary Light Reflex Tests Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Troponin Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Weight Decreased	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Metabolism And Nutrition Disorders	**21 (18 3)**	**22 (17.7)**	**28 (9 9)**	**31 (10.2)**	**49 (12.3)**	**53 (12.4)**
Acidosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cachexia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Decreased Appetite	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Dehydration	7 (6.1)	7 (5.6)	10 (3 5)	10 (3.3)	17 (4 3)	17 (4.0)
Diabetes Mellitus Inadequate Control	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrolyte Imbalance	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Failure To Thrive	0	0	1 (0.4)	2 (0.7)	1 (0.3)	2 (0.5)
Fluid Overload	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Fluid Retention	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hypercalcaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypercreatininaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Hyperglycaemia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hyperkalaemia	5 (4.3)	6 (4.8)	6 (2.1)	6 (2.0)	11 (2.8)	12 (2.8)
Hypervolaemia	0	0	0	1 (0.3)	0	1 (0.2)
Hypoalbuminaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypocalcaemia	1 (0.9)	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.5)
Hypoglycaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypokalaemia	0	0	5 (1.8)	6 (2.0)	5 (1.3)	6 (1.4)
Hypomagnesaemia	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Hyponatraemia	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Hypovolaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lactic Acidosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

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Malnutrition	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Metabolic Acidosis	4 (3.5)	4 (3.2)	3 (1.1)	3 (1.0)	7 (1.8)	7 (1.6)
Tumour Lysis Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Musculoskeletal And Connective Tissue Disorders	**8 (7.0)**	**8 (6.5)**	**8 (2.8)**	**10 (3.3)**	**16 (4.0)**	**18 (4.2)**
Arthralgia	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Back Pain	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Bone Pain	0	0	0	1 (0.3)	0	1 (0.2)
Compartment Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Flank Pain	1 (0.9)	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.5)
Muscle Spasms	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Muscular Weakness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Musculoskeletal Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Myalgia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myopathy	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Nuchal Rigidity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Osteonecrosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pain In Extremity	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pathological Fracture	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Soft Tissue Mass	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Systemic Lupus Erythematosus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**24 (20 9)**	**24 (19.4)**	**41 (14.5)**	**43 (14.1)**	**65 (16.4)**	**67 (15.7)**
Acute Lymphocytic Leukaemia Recurrent	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Acute Myeloid Leukaemia	11 (9.6)	11 (8.9)	21 (7.4)	22 (7.2)	32 (8 1)	33 (7.7)
Acute Myeloid Leukaemia Recurrent	2 (1.7)	2 (1.6)	8 (2.8)	8 (2.6)	10 (2 5)	10 (2.3)
Blast Cell Crisis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blast Crisis In Myelogenous Leukaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Central Nervous System Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Chronic Lymphocytic Leukaemia Recurrent	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Chronic Myeloid Leukaemia	3 (2.6)	3 (2.4)	2 (0.7)	3 (1.0)	5 (1.3)	6 (1.4)
Hepatic Cancer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Number (%) of Subjects

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Hodgkin's Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Kaposi's Sarcoma	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Leukaemia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lymphoma	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Metastases To Meninges	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Myelodysplastic Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neoplasm Malignant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Non-Hodgkin's Lymphoma	3 (2.6)	3 (2.4)	0	0	3 (0.8)	3 (0.7)
Plasma Cell Myeloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Respiratory Tract Neoplasm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
T-Cell Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorders	**32 (27 8)**	**33 (26.6)**	**46 (16.3)**	**47 (15.5)**	**78 (19.6)**	**80 (18.7)**
Amnesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Arachnoiditis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Asterixis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ataxia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Balance Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Brain Oedema	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Cauda Equina Syndrome	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Central Nervous System Lesion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cerebral Atrophy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cerebral Haemorrhage	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Cerebral Infarction	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Cerebrovascular Accident	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Coma	5 (4.3)	6 (4.8)	1 (0.4)	1 (0.3)	6 (1.5)	7 (1.6)
Demyelination	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Depressed Level Of Consciousness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Dizziness	1 (0.9)	1 (0.8)	5 (1.8)	5 (1.6)	6 (1.5)	6 (1.4)
Dysarthria	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Dyskinesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dystonia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Embolic Stroke	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Encephalomalacia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Encephalopathy	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)

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Facial Paralysis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Haemorrhage Intracranial	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haemorrhagic Cerebral Infarction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Headache	4 (3.5)	4 (3.2)	11 (3 9)	11 (3.6)	15 (3.8)	15 (3.5)
Hemiparesis	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Hemiplegia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypoaesthesia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Intracranial Pressure Increased	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Intraventricular Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ischaemic Stroke	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lethargy	2 (1.7)	2 (1.6)	0	1 (0.3)	2 (0.5)	3 (0.7)
Loss Of Consciousness	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mental Impairment	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Metabolic Encephalopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Myoclonus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nervous System Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Occipital Neuralgia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Presyncope	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sedation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Seizure	6 (5.2)	6 (4.8)	10 (3 5)	10 (3.3)	16 (4.0)	16 (3.7)
Somnolence	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Speech Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Syncope	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tremor	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Unresponsive To Stimuli	6 (5.2)	7 (5.6)	4 (1.4)	4 (1.3)	10 (2 5)	11 (2.6)
Psychiatric Disorders	**11 (9.6)**	**11 (8.9)**	**13 (4.6)**	**14 (4.6)**	**24 (6.0)**	**25 (5.8)**
Anxiety	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Confusional State	7 (6.1)	7 (5.6)	1 (0.4)	2 (0.7)	8 (2.0)	9 (2.1)
Delirium	1 (0.9)	1 (0.8)	1 (0.4)	2 (0.7)	2 (0.5)	3 (0.7)
Delusion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Depression	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Disorientation	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Echolalia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hallucination	1 (0.9)	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.5)

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Mental Status Changes	5 (4.3)	5 (4.0)	7 (2.5)	7 (2.3)	12 (3.0)	12 (2.8)
Perseveration	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Restlessness	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Renal And Urinary Disorders	**26 (22.6)**	**27 (21.8)**	**21 (7.4)**	**22 (7.2)**	**47 (11.8)**	**49 (11.4)**
Acute Kidney Injury	4 (3.5)	4 (3.2)	4 (1.4)	5 (1.6)	8 (2.0)	9 (2.1)
Anuria	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Bladder Spasm	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Kidney Disease	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Cystitis Haemorrhagic	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Dysuria	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
End Stage Renal Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nephrolithiasis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nephropathy Toxic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Colic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal Failure	15 (13.0)	16 (12.9)	11 (3 9)	11 (3.6)	26 (6 5)	27 (6.3)
Renal Impairment	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Renal Tubular Acidosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Urinary Retention	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Reproductive System And Breast Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Vaginal Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**52 (45 2)**	**54 (43.5)**	**57 (20.2)**	**62 (20.4)**	**109 (27.5)**	**116 (27.1)**
Acute Respiratory Distress Syndrome	5 (4.3)	5 (4.0)	1 (0.4)	1 (0.3)	6 (1.5)	6 (1.4)
Acute Respiratory Failure	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Apnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Asthma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Atelectasis	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Bronchiectasis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Bronchospasm	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cheyne-Stokes Respiration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Chronic Obstructive Pulmonary Disease	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Cough	3 (2.6)	3 (2.4)	2 (0.7)	2 (0.7)	5 (1.3)	5 (1.2)
Dyspnoea	15 (13.0)	15 (12.1)	21 (7.4)	23 (7.6)	36 (9 1)	38 (8.9)
Emphysema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Epistaxis	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Haemoptysis	6 (5.2)	6 (4.8)	3 (1.1)	3 (1.0)	9 (2.3)	9 (2.1)
Haemothorax	2 (1.7)	3 (2.4)	0	0	2 (0.5)	3 (0.7)
Hypoxia	3 (2.6)	3 (2.4)	6 (2.1)	8 (2.6)	9 (2.3)	11 (2.6)
Interstitial Lung Disease	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Infiltration	6 (5.2)	6 (4.8)	5 (1.8)	5 (1.6)	11 (2.8)	11 (2.6)
Obliterative Bronchiolitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Organising Pneumonia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pleural Effusion	5 (4.3)	5 (4.0)	5 (1.8)	5 (1.6)	10 (2 5)	10 (2.3)
Pleuritic Pain	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pneumonia Aspiration	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Pneumonitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumothorax	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Pulmonary Alveolar Haemorrhage	2 (1.7)	2 (1.6)	2 (0.7)	2 (0.7)	4 (1.0)	4 (0.9)
Pulmonary Haemorrhage	4 (3.5)	4 (3.2)	2 (0.7)	2 (0.7)	6 (1.5)	6 (1.4)
Pulmonary Hypertension	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Oedema	3 (2.6)	3 (2.4)	4 (1.4)	5 (1.6)	7 (1.8)	8 (1.9)
Rales	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory Acidosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory Arrest	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Disorder	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Respiratory Distress	7 (6.1)	7 (5.6)	9 (3.2)	10 (3.3)	16 (4.0)	17 (4.0)
Respiratory Failure	22 (19 1)	24 (19.4)	20 (7 1)	21 (6.9)	42 (10.6)	45 (10.5)
Respiratory Tract Congestion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sinus Congestion	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Tachypnoea	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Wheezing	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin And Subcutaneous Tissue Disorders	**2 (1.7)**	**2 (1.6)**	**10 (3 5)**	**10 (3.3)**	**12 (3.0)**	**12 (2.8)**
Decubitus Ulcer	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Hyperhidrosis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Rash	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Rash Maculo-Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Pruritic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Vesicular	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Skin Lesion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Stevens-Johnson Syndrome	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Swelling Face	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Surgical And Medical Procedures	**10 (8.7)**	**10 (8.1)**	**20 (7 1)**	**20 (6.6)**	**30 (7.6)**	**30 (7.0)**
Bone Marrow Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cataract Operation	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Catheter Removal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chemotherapy	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Corneal Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Debridement	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Endotracheal Intubation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Laparotomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lung Lobectomy	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Lung Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Maxillofacial Operation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Omentectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Orthopaedic Procedure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Plastic Surgery To The Face	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pneumonectomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Polypectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary Resection	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Skin Graft	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Splenectomy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Stem Cell Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Surgery	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Therapeutic Procedure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thoracotomy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Tooth Extraction	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Transfusion	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Vascular Disorders	**19 (16 5)**	**21 (16.9)**	**23 (8 2)**	**25 (8.2)**	**42 (10.6)**	**46 (10.7)**
Aneurysm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Angiopathy	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Aortic Aneurysm	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Circulatory Collapse	0	1 (0.8)	0	0	0	1 (0.2)
Deep Vein Thrombosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haematoma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Haemorrhage	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Hypertension	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Hypoperfusion	0	1 (0.8)	0	0	0	1 (0.2)
Hypotension	14 (12 2)	15 (12.1)	14 (5.0)	16 (5.3)	28 (7 1)	31 (7.2)
Hypovolaemic Shock	0	1 (0.8)	0	0	0	1 (0.2)
Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ischaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pallor	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Peripheral Artery Thrombosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Phlebitis	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Shock Haemorrhagic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Thrombophlebitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-35 重篤な副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
by Risk Group
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**9 (7.8)**	**9 (7.3)**	**26 (9 2)**	**26 (8.6)**	**35 (8 8)**	**35 (8.2)**
Blood And Lymphatic System Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Eosinophilia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pancytopenia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiac Disorders	**2 (1.7)**	**2 (1.6)**	**6 (2.1)**	**6 (2.0)**	**8 (2.0)**	**8 (1.9)**
Atrial Fibrillation	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Atrial Flutter	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardio-Respiratory Arrest	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Myocardial Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Supraventricular Tachycardia	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ventricular Extrasystoles	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Ventricular Hypertrophy	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Tachycardia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Endocrine Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Adrenal Insufficiency	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Eye Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Eye Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal Disorders	**3 (2.6)**	**3 (2.4)**	**2 (0.7)**	**2 (0.7)**	**5 (1.3)**	**5 (1.2)**
Abdominal Distension	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Abdominal Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Diarrhoea	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gastrointestinal Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Ileus	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nausea	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
Pancreatitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vomiting	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)
General Disorders And Administration Site Conditions	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Death	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
by Risk Group
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Hepatobiliary Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Hepatic Failure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic Function Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Jaundice	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Immune System Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Drug Hypersensitivity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Infections And Infestations	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Meningitis Cryptococcal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Oesophageal Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Injury, Poisoning And Procedural Complications	**0**	**0**	**3 (1.1)**	**3 (1.0)**	**3 (0.8)**	**3 (0.7)**
Overdose	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Toxicity To Various Agents	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Investigations	**4 (3.5)**	**4 (3.2)**	**9 (3.2)**	**9 (3.0)**	**13 (3 3)**	**13 (3.0)**
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Bilirubin Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Blood Creatinine Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardioactive Drug Level Decreased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Drug Level Increased	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Electrocardiogram Qt Prolonged	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gamma-Glutamyltransferase Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatic Enzyme Increased	1 (0 9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Liver Function Test Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pancreatic Enzymes Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolism And Nutrition Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Electrolyte Imbalance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nervous System Disorders	**2 (1.7)**	**2 (1.6)**	**5 (1.8)**	**5 (1.6)**	**7 (1.8)**	**7 (1.6)**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Treatment Related Adverse Events
by Risk Group
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Balance Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dizziness	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Headache	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mental Impairment	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Seizure	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Psychiatric Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Delirium	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mental Status Changes	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Renal And Urinary Disorders	**1 (0.9)**	**1 (0.8)**	**3 (1.1)**	**3 (1.0)**	**4 (1.0)**	**4 (0.9)**
Acute Kidney Injury	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Kidney Disease	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nephropathy Toxic	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Renal Tubular Acidosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Dyspnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin And Subcutaneous Tissue Disorders	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**4 (1.0)**	**4 (0.9)**
Rash	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Rash Maculo-Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Pruritic	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vascular Disorders	**1 (0.9)**	**1 (0.8)**	**0**	**0**	**1 (0.3)**	**1 (0.2)**
Hypotension	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-36 投与中止に至った有害事象の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**202 (33.4)**	**208 (38.6)**	**26 (44.8)**
Blood And Lymphatic System Disorders	**14 (2.3)**	**16 (3.0)**	**3 (5.2)**
Anaemia	1 (0.2)	2 (0.4)	0
Disseminated Intravascular Coagulation	1 (0.2)	0	0
Febrile Neutropenia	9 (1.5)	11 (2.0)	3 (5.2)
Haemolytic Uraemic Syndrome	1 (0.2)	0	0
Leukopenia	0	1 (0.2)	0
Neutropenia	0	3 (0.6)	0
Pancytopenia	0	1 (0 2)	0
Thrombocytopenia	2 (0.3)	3 (0.6)	0
Thrombotic Microangiopathy	0	1 (0 2)	0
Thrombotic Thrombocytopenic Purpura	1 (0.2)	0	0
Cardiac Disorders	**8 (1.3)**	**6 (1.1)**	**2 (3.4)**
Atrial Fibrillation	1 (0.2)	4 (0.7)	0
Bradycardia	1 (0.2)	0	1 (1.7)
Cardiac Arrest	2 (0.3)	0	0
Cardiac Failure	2 (0.3)	0	0
Cardiac Failure Congestive	0	1 (0 2)	0
Cardio-Respiratory Arrest	0	1 (0 2)	0
Cardiopulmonary Failure	1 (0.2)	0	0
Sinus Bradycardia	0	0	1 (1.7)
Supraventricular Tachycardia	0	1 (0 2)	0
Torsade De Pointes	1 (0.2)	0	0
Ventricular Extrasystoles	1 (0.2)	0	0
Endocrine Disorders	**0**	**1 (0.2)**	**0**
Cushingoid	0	1 (0 2)	0
Eye Disorders	**2 (0.3)**	**0**	**0**
Photophobia	1 (0.2)	0	0
Vision Blurred	1 (0.2)	0	0
Gastrointestinal Disorders	**43 (7.1)**	**34 (6.3)**	**6 (10.3)**
Abdominal Distension	0	2 (0.4)	0
Abdominal Pain	3 (0.5)	3 (0.6)	0
Abdominal Pain Upper	2 (0.3)	1 (0 2)	0
Abdominal Rigidity	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Acute Abdomen	1 (0.2)	0	0
Aptyalism	1 (0.2)	0	0
Ascites	1 (0.2)	1 (0 2)	0
Diarrhoea	5 (0.8)	3 (0.6)	4 (6.9)
Duodenitis	0	1 (0.2)	0
Dyspepsia	2 (0.3)	0	0
Dysphagia	2 (0.3)	1 (0 2)	0
Gastritis	0	2 (0.4)	0
Gastrointestinal Haemorrhage	3 (0.5)	1 (0 2)	0
Ileus	0	1 (0 2)	0
Melaena	1 (0.2)	0	0
Nausea	19 (3.1)	13 (2.4)	1 (1.7)
Neutropenic Colitis	1 (0.2)	0	1 (1.7)
Tongue Discomfort	1 (0.2)	0	0
Trichoglossia	1 (0.2)	0	0
Upper Gastrointestinal Haemorrhage	1 (0.2)	0	0
Vomiting	15 (2.5)	17 (3.2)	0
General Disorders And Administration Site Conditions	**24 (4.0)**	**24 (4.5)**	**3 (5.2)**
Asthenia	2 (0.3)	1 (0 2)	0
Chest Pain	0	1 (0 2)	0
Chills	1 (0.2)	0	0
Device Related Thrombosis	1 (0.2)	0	0
Disease Progression	1 (0.2)	2 (0.4)	0
Drug Interaction	0	1 (0 2)	0
Drug Intolerance	0	1 (0 2)	0
Fatigue	1 (0.2)	1 (0 2)	0
Feeling Jittery	1 (0.2)	0	0
General Physical Health Deterioration	1 (0.2)	0	0
Hyperthermia	1 (0.2)	0	1 (1.7)
Mucosal Inflammation	4 (0.7)	2 (0.4)	0
Multi-Organ Disorder	1 (0.2)	0	0
Multiple Organ Dysfunction Syndrome	1 (0.2)	0	0
Pyrexia	9 (1.5)	13 (2.4)	2 (3.4)
Therapy Non-Responder	1 (0.2)	2 (0.4)	0
Hepatobiliary Disorders	**10 (1.7)**	**10 (1.9)**	**0**
Hepatic Failure	0	2 (0.4)	0
Hepatic Function Abnormal	0	1 (0 2)	0
Hepatic Steatosis	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Hepatitis Acute	1 (0.2)	0	0
Hepatocellular Injury	2 (0.3)	0	0
Hepatotoxicity	2 (0.3)	0	0
Hyperbilirubinaemia	4 (0.7)	4 (0.7)	0
Jaundice	2 (0.3)	1 (0 2)	0
Liver Disorder	0	1 (0 2)	0
Ocular Icterus	1 (0.2)	0	0
Immune System Disorders	**9 (1.5)**	**7 (1.3)**	**0**
Drug Hypersensitivity	2 (0.3)	0	0
Graft Versus Host Disease	4 (0.7)	3 (0.6)	0
Graft Versus Host Disease In Gastrointestinal Tract	2 (0.3)	3 (0.6)	0
Graft Versus Host Disease In Liver	1 (0.2)	0	0
Graft Versus Host Disease In Lung	0	1 (0.2)	0
Hypersensitivity	0	1 (0 2)	0
Infections And Infestations	**41 (6.8)**	**65 (12 1)**	**6 (10.3)**
Acid Fast Bacilli Infection	1 (0.2)	0	0
Aspergillus Infection	1 (0.2)	10 (1.9)	1 (1.7)
Bacteraemia	1 (0.2)	2 (0.4)	0
Bronchopulmonary Aspergillosis	0	5 (0 9)	1 (1.7)
Candida Infection	1 (0.2)	3 (0.6)	0
Candida Sepsis	1 (0.2)	0	0
Clostridium Difficile Colitis	0	1 (0 2)	0
Conjunctivitis	0	1 (0 2)	0
Enterococcal Bacteraemia	0	0	1 (1.7)
Enterococcal Sepsis	1 (0.2)	0	0
Escherichia Sepsis	0	1 (0.2)	0
Fungaemia	0	1 (0 2)	0
Fungal Infection	6 (1.0)	11 (2.0)	0
Fungal Rhinitis	0	1 (0 2)	0
Lower Respiratory Tract Infection	0	1 (0.2)	0
Neutropenic Sepsis	1 (0.2)	1 (0 2)	0
Nocardiosis	0	1 (0 2)	0
Oesophageal Candidiasis	0	2 (0.4)	0
Oral Candidiasis	1 (0.2)	0	0
Oral Herpes	1 (0.2)	0	0
Periorbital Cellulitis	0	0	1 (1.7)
Pneumonia	10 (1.7)	4 (0.7)	0
Pneumonia Bacterial	2 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Pneumonia Fungal	2 (0.3)	5 (0 9)	0
Pulmonary Mycosis	2 (0.3)	5 (0 9)	0
Pulmonary Tuberculosis	1 (0.2)	0	0
Relapsing Fever	0	1 (0 2)	0
Scedosporium Infection	0	1 (0 2)	0
Sepsis	1 (0.2)	5 (0 9)	0
Septic Shock	4 (0.7)	3 (0.6)	1 (1.7)
Sinusitis	0	2 (0.4)	0
Staphylococcal Infection	2 (0.3)	0	0
Streptococcal Infection	0	1 (0 2)	0
Systemic Candida	2 (0.3)	0	0
Systemic Mycosis	1 (0.2)	2 (0.4)	1 (1.7)
Injury, Poisoning And Procedural Complications	**1 (0.2)**	**1 (0.2)**	**0**
Overdose	0	1 (0 2)	0
Subdural Haematoma	1 (0.2)	0	0
Investigations	**28 (4.6)**	**23 (4.3)**	**5 (8.6)**
Alanine Aminotransferase Increased	2 (0.3)	2 (0.4)	0
Aspartate Aminotransferase Increased	0	2 (0.4)	0
Aspergillus Test Positive	0	1 (0.2)	0
Blood Alkaline Phosphatase Increased	0	0	1 (1.7)
Blood Bilirubin Increased	4 (0.7)	4 (0.7)	1 (1.7)
Blood Creatinine Increased	1 (0.2)	0	0
Blood Lactate Dehydrogenase Increased	0	1 (0.2)	0
Blood Urea Increased	0	1 (0 2)	0
C-Reactive Protein Increased	1 (0.2)	0	0
Drug Level Increased	1 (0.2)	1 (0 2)	0
Electrocardiogram Qt Prolonged	8 (1.3)	4 (0.7)	2 (3.4)
Fungal Test	0	0	1 (1.7)
Gamma-Glutamyltransferase Increased	2 (0.3)	2 (0.4)	0
Hepatic Enzyme Abnormal	0	1 (0.2)	0
Hepatic Enzyme Increased	2 (0.3)	1 (0.2)	0
Liver Function Test Abnormal	1 (0.2)	0	0
Liver Function Test Increased	5 (0.8)	3 (0.6)	0
Transaminases Increased	5 (0.8)	4 (0.7)	0
Metabolism And Nutrition Disorders	**3 (0.5)**	**6 (1.1)**	**0**
Cachexia	1 (0.2)	0	0
Decreased Appetite	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Dehydration	0	3 (0.6)	0
Hyperkalaemia	0	1 (0 2)	0
Hyponatraemia	0	1 (0 2)	0
Hypophagia	1 (0.2)	0	0
Hypovolaemia	0	1 (0 2)	0
Metabolic Acidosis	1 (0.2)	1 (0 2)	0
Musculoskeletal And Connective Tissue Disorders	**1 (0.2)**	**2 (0.4)**	**0**
Arthritis	1 (0.2)	0	0
Myalgia	0	1 (0 2)	0
Pain In Extremity	0	1 (0 2)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**11 (1.8)**	**8 (1.5)**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	3 (0.6)	0
Acute Myeloid Leukaemia	3 (0.5)	0	0
Acute Myeloid Leukaemia Recurrent	3 (0.5)	0	0
Chronic Myeloid Leukaemia	1 (0.2)	0	0
Leukaemia	1 (0.2)	1 (0 2)	0
Leukaemia Recurrent	1 (0.2)	2 (0.4)	0
Lymphoma	0	1 (0 2)	0
Myelodysplastic Syndrome	1 (0.2)	0	0
Non-Hodgkin's Lymphoma Recurrent	0	1 (0 2)	0
Renal Cancer	1 (0.2)	0	0
Nervous System Disorders	**21 (3.5)**	**16 (3.0)**	**0**
Brain Oedema	1 (0.2)	0	0
Central Nervous System Lesion	1 (0.2)	0	0
Cerebral Haemorrhage	3 (0.5)	1 (0 2)	0
Coma	2 (0.3)	0	0
Demyelination	1 (0.2)	0	0
Depressed Level Of Consciousness	1 (0.2)	0	0
Dysgeusia	1 (0.2)	2 (0.4)	0
Encephalopathy	2 (0.3)	0	0
Facial Paresis	0	1 (0 2)	0
Guillain-Barre Syndrome	0	1 (0 2)	0
Haemorrhage Intracranial	1 (0.2)	2 (0.4)	0
Haemorrhagic Stroke	1 (0.2)	1 (0 2)	0
Headache	4 (0.7)	1 (0 2)	0
Hypoglycaemic Coma	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Loss Of Consciousness	0	2 (0.4)	0
Meningism	1 (0.2)	0	0
Metabolic Encephalopathy	1 (0.2)	0	0
Migraine	1 (0.2)	0	0
Neuropathy Peripheral	1 (0.2)	0	0
Seizure	3 (0.5)	3 (0.6)	0
Somnolence	0	2 (0.4)	0
Stupor	2 (0.3)	0	0
Tremor	2 (0.3)	0	0
Unresponsive To Stimuli	0	1 (0.2)	0
Psychiatric Disorders	**6 (1.0)**	**3 (0.6)**	**1 (1.7)**
Aversion	0	0	1 (1.7)
Confusional State	2 (0.3)	2 (0.4)	0
Depression	1 (0.2)	0	0
Hallucination, Visual	1 (0.2)	0	0
Irritability	0	1 (0.2)	0
Mental Status Changes	2 (0.3)	0	0
Renal And Urinary Disorders	**5 (0.8)**	**6 (1.1)**	**0**
Acute Kidney Injury	2 (0.3)	2 (0.4)	0
Haematuria	0	1 (0 2)	0
Renal Failure	3 (0.5)	3 (0.6)	0
Renal Impairment	1 (0.2)	0	0
Reproductive System And Breast Disorders	**0**	**1 (0.2)**	**0**
Erectile Dysfunction	0	1 (0 2)	0
Respiratory, Thoracic And Mediastinal Disorders	**22 (3.6)**	**18 (3.3)**	**2 (3.4)**
Acute Respiratory Distress Syndrome	1 (0.2)	1 (0.2)	0
Acute Respiratory Failure	1 (0.2)	0	0
Bronchospasm	1 (0.2)	0	0
Cough	2 (0.3)	0	1 (1.7)
Dyspnoea	1 (0.2)	7 (1 3)	0
Haemoptysis	1 (0.2)	1 (0 2)	0
Hypoxia	1 (0.2)	3 (0.6)	0
Interstitial Lung Disease	1 (0.2)	1 (0 2)	0
Lung Disorder	1 (0.2)	0	0
Lung Infiltration	4 (0.7)	5 (0.9)	0
Nasal Congestion	1 (0.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Pneumonitis	3 (0.5)	0	0
Pulmonary Haemorrhage	2 (0.3)	0	0
Pulmonary Mass	2 (0.3)	1 (0 2)	0
Pulmonary Oedema	1 (0.2)	0	0
Respiratory Disorder	0	0	1 (1.7)
Respiratory Distress	0	1 (0 2)	0
Respiratory Failure	2 (0.3)	3 (0.6)	0
Skin And Subcutaneous Tissue Disorders	**2 (0.3)**	**6 (1.1)**	**1 (1.7)**
Drug Eruption	0	1 (0 2)	0
Pruritus	1 (0.2)	0	0
Rash	2 (0.3)	2 (0.4)	1 (1.7)
Rash Pruritic	0	1 (0 2)	0
Skin Lesion	0	2 (0.4)	0
Vascular Disorders	**3 (0.5)**	**9 (1.7)**	**0**
Flushing	0	1 (0 2)	0
Haemorrhage	1 (0.2)	2 (0.4)	0
Hypotension	1 (0.2)	5 (0 9)	0
Hypovolaemic Shock	1 (0.2)	1 (0 2)	0
Shock	0	1 (0 2)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-37 投与中止に至った副作用の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899

All Randomized Subjects

Summary of Treatment-Related Adverse Events Leading to Study Drug Discontinuation

Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Subjects Reporting Any Adverse Event	**58 (9.6)**	**49 (9.1)**	**13 (22.4)**
Blood And Lymphatic System Disorders	**2 (0.3)**	**1 (0.2)**	**0**
Anaemia	1 (0.2)	0	0
Haemolytic Uraemic Syndrome	1 (0.2)	0	0
Neutropenia	0	1 (0 2)	0
Thrombotic Thrombocytopenic Purpura	1 (0.2)	0	0
Cardiac Disorders	**3 (0.5)**	**1 (0.2)**	**2 (3.4)**
Atrial Fibrillation	1 (0.2)	1 (0.2)	0
Bradycardia	1 (0.2)	0	1 (1.7)
Sinus Bradycardia	0	0	1 (1.7)
Torsade De Pointes	1 (0.2)	0	0
Eye Disorders	**2 (0.3)**	**0**	**0**
Photophobia	1 (0.2)	0	0
Vision Blurred	1 (0.2)	0	0
Gastrointestinal Disorders	**22 (3.6)**	**22 (4.1)**	**5 (8.6)**
Abdominal Distension	0	1 (0 2)	0
Abdominal Pain	1 (0.2)	1 (0 2)	0
Abdominal Pain Upper	1 (0.2)	1 (0 2)	0
Abdominal Rigidity	0	1 (0 2)	0
Aptyalism	1 (0.2)	0	0
Diarrhoea	3 (0.5)	1 (0 2)	4 (6.9)
Duodenitis	0	1 (0.2)	0
Dyspepsia	2 (0.3)	0	0
Dysphagia	1 (0.2)	0	0
Gastritis	0	2 (0.4)	0
Gastrointestinal Haemorrhage	0	1 (0 2)	0
Ileus	0	1 (0 2)	0
Nausea	13 (2.1)	9 (1.7)	1 (1.7)
Tongue Discomfort	1 (0.2)	0	0
Vomiting	10 (1.7)	11 (2.0)	0
General Disorders And Administration Site Conditions	**3 (0.5)**	**2 (0.4)**	**0**
Asthenia	1 (0.2)	0	0
Drug Interaction	0	1 (0 2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment-Related Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Fatigue	1 (0.2)	1 (0 2)	0
Mucosal Inflammation	1 (0.2)	0	0
Hepatobiliary Disorders	**8 (1.3)**	**6 (1.1)**	**0**
Hepatic Failure	0	1 (0 2)	0
Hepatic Function Abnormal	0	1 (0 2)	0
Hepatitis Acute	1 (0.2)	0	0
Hepatocellular Injury	2 (0.3)	0	0
Hepatotoxicity	1 (0.2)	0	0
Hyperbilirubinaemia	3 (0.5)	3 (0.6)	0
Jaundice	1 (0.2)	0	0
Liver Disorder	0	1 (0 2)	0
Immune System Disorders	**2 (0.3)**	**1 (0.2)**	**0**
Drug Hypersensitivity	1 (0.2)	0	0
Graft Versus Host Disease	1 (0.2)	0	0
Hypersensitivity	0	1 (0 2)	0
Infections And Infestations	**0**	**2 (0.4)**	**1 (1.7)**
Candida Infection	0	1 (0 2)	0
Conjunctivitis	0	1 (0 2)	0
Periorbital Cellulitis	0	0	1 (1.7)
Investigations	**21 (3.5)**	**12 (2.2)**	**3 (5.2)**
Alanine Aminotransferase Increased	2 (0.3)	2 (0.4)	0
Aspartate Aminotransferase Increased	0	2 (0.4)	0
Blood Alkaline Phosphatase Increased	0	0	1 (1.7)
Blood Bilirubin Increased	3 (0.5)	2 (0.4)	0
Blood Creatinine Increased	1 (0.2)	0	0
Blood Urea Increased	0	1 (0 2)	0
Drug Level Increased	1 (0.2)	1 (0 2)	0
Electrocardiogram Qt Prolonged	6 (1.0)	1 (0 2)	2 (3.4)
Gamma-Glutamyltransferase Increased	2 (0.3)	1 (0 2)	0
Hepatic Enzyme Abnormal	0	1 (0.2)	0
Hepatic Enzyme Increased	2 (0.3)	0	0
Liver Function Test Abnormal	1 (0.2)	0	0
Liver Function Test Increased	3 (0.5)	2 (0.4)	0
Transaminases Increased	4 (0.7)	3 (0.6)	0

C Confidential

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment-Related Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Musculoskeletal And Connective Tissue Disorders	**0**	**2 (0.4)**	**0**
Myalgia	0	1 (0 2)	0
Pain In Extremity	0	1 (0 2)	0
Nervous System Disorders	**4 (0.7)**	**3 (0.6)**	**0**
Dysgeusia	1 (0.2)	2 (0.4)	0
Encephalopathy	1 (0.2)	0	0
Headache	1 (0.2)	1 (0 2)	0
Meningism	1 (0.2)	0	0
Migraine	1 (0.2)	0	0
Neuropathy Peripheral	1 (0.2)	0	0
Seizure	1 (0.2)	0	0
Stupor	1 (0.2)	0	0
Tremor	2 (0.3)	0	0
Psychiatric Disorders	**1 (0.2)**	**0**	**1 (1.7)**
Aversion	0	0	1 (1.7)
Mental Status Changes	1 (0.2)	0	0
Renal And Urinary Disorders	**1 (0.2)**	**0**	**0**
Renal Impairment	1 (0.2)	0	0
Reproductive System And Breast Disorders	**0**	**1 (0.2)**	**0**
Erectile Dysfunction	0	1 (0 2)	0
Respiratory, Thoracic And Mediastinal Disorders	**2 (0.3)**	**0**	**1 (1.7)**
Cough	1 (0.2)	0	1 (1.7)
Interstitial Lung Disease	1 (0.2)	0	0
Pneumonitis	1 (0.2)	0	0
Skin And Subcutaneous Tissue Disorders	**2 (0.3)**	**3 (0.6)**	**1 (1.7)**
Drug Eruption	0	1 (0 2)	0
Pruritus	1 (0.2)	0	0
Rash	2 (0.3)	1 (0 2)	1 (1.7)
Rash Pruritic	0	1 (0 2)	0
Vascular Disorders	**0**	**1 (0.2)**	**0**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment-Related Adverse Events Leading to Study Drug Discontinuation
Number (%) of Subjects

	Posaconazole n = 605	Fluconazole n = 539	Itraconazole n = 58
Flushing	0	1 (0 2)	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-38 投与中止に至った有害事象の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Study Drug Discontinuation
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Subjects Reporting Any Adverse Event	**49 (42.6)**	**49 (39.5)**	**75 (26.6)**	**75 (24.7)**	**124 (31.2)**	**124 (29.0)**
Blood And Lymphatic System Disorders	**1 (0.9)**	**1 (0.8)**	**1 (0.4)**	**1 (0.3)**	**2 (0.5)**	**2 (0.5)**
Thrombocytopenia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Thrombotic Thrombocytopenic Purpura	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Cardiac Disorders	**3 (2.6)**	**3 (2.4)**	**8 (2.8)**	**8 (2.6)**	**11 (2 8)**	**11 (2.6)**
Bradycardia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cardiac Arrest	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
Cardiac Failure	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Cardio-Respiratory Arrest	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Myocardial Infarction	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Ventricular Tachycardia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Gastrointestinal Disorders	**4 (3.5)**	**4 (3.2)**	**10 (3 5)**	**10 (3.3)**	**14 (3 5)**	**14 (3.3)**
Abdominal Pain	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Diarrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dysphagia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Haematemesis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Intestinal Ischaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nausea	0	0	7 (2.5)	7 (2.3)	7 (1.8)	7 (1.6)
Pancreatitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Upper Gastrointestinal Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vomiting	0	0	7 (2.5)	7 (2.3)	7 (1.8)	7 (1.6)
General Disorders And Administration Site Conditions	**8 (7.0)**	**8 (6.5)**	**13 (4.6)**	**13 (4.3)**	**21 (5 3)**	**21 (4.9)**
Asthenia	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Chills	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Disease Progression	5 (4.3)	5 (4.0)	2 (0.7)	2 (0.7)	7 (1.8)	7 (1.6)
Fatigue	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gait Disturbance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Malaise	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Mucosal Inflammation	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Multiple Organ Dysfunction Syndrome	2 (1.7)	2 (1.6)	1 (0.4)	1 (0.3)	3 (0.8)	3 (0.7)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Study Drug Discontinuation
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Pyrexia	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Hepatobiliary Disorders	**1 (0.9)**	**1 (0.8)**	**2 (0.7)**	**2 (0.7)**	**3 (0.8)**	**3 (0.7)**
Hepatic Function Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Jaundice	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Immune System Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Drug Hypersensitivity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Transplant Rejection	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Infections And Infestations	**12 (10.4)**	**12 (9.7)**	**12 (4 3)**	**12 (3.9)**	**24 (6.0)**	**24 (5.6)**
Aspergillus Infection	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Bronchopulmonary Aspergillosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cerebral Aspergillosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
End Stage Aids	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Fungal Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Meningitis Cryptococcal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mucormycosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Oesophageal Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Pneumonia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Pneumonia Fungal	3 (2.6)	3 (2.4)	1 (0.4)	1 (0.3)	4 (1.0)	4 (0.9)
Pulmonary Tuberculosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Sepsis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Septic Embolus	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Septic Shock	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sinusitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Sinusitis Fungal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Tuberculosis	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Injury, Poisoning And Procedural Complications	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Hip Fracture	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Investigations	**5 (4.3)**	**5 (4.0)**	**5 (1.8)**	**5 (1.6)**	**10 (2 5)**	**10 (2.3)**
Alanine Aminotransferase Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Study Drug Discontinuation
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Creatinine Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Pressure Decreased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Drug Level Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Gamma-Glutamyltransferase Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatic Enzyme Increased	1 (0 9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Liver Function Test Increased	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pancreatic Enzymes Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolism And Nutrition Disorders	**1 (0.9)**	**1 (0.8)**	**3 (1.1)**	**3 (1.0)**	**4 (1.0)**	**4 (0.9)**
Cachexia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Decreased Appetite	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrolyte Imbalance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lactic Acidosis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Musculoskeletal And Connective Tissue Disorders	**1 (0.9)**	**1 (0.8)**	**2 (0.7)**	**2 (0.7)**	**3 (0.8)**	**3 (0.7)**
Back Pain	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Bone Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**5 (4.3)**	**5 (4.0)**	**8 (2.8)**	**8 (2.6)**	**13 (3 3)**	**13 (3.0)**
Acute Myeloid Leukaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Acute Myeloid Leukaemia Recurrent	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blast Crisis In Myelogenous Leukaemia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Chronic Lymphocytic Leukaemia	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Kaposi's Sarcoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lung Neoplasm	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lymphoma	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Neoplasm Malignant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Non-Hodgkin's Lymphoma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Plasma Cell Myeloma	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
T-Cell Lymphoma	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Study Drug Discontinuation
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Nervous System Disorders	**10 (8.7)**	**10 (8.1)**	**12 (4 3)**	**12 (3.9)**	**22 (5 5)**	**22 (5.1)**
Arachnoiditis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Balance Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Central Nervous System Lesion	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Cerebrovascular Accident	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Depressed Level Of Consciousness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Dizziness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Dysgeusia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Haemorrhage Intracranial	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Headache	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Hypoaesthesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Intraventricular Haemorrhage	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lethargy	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Loss Of Consciousness	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Nervous System Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Seizure	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Slow Response To Stimuli	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Psychiatric Disorders	**1 (0.9)**	**1 (0.8)**	**3 (1.1)**	**3 (1.0)**	**4 (1.0)**	**4 (0.9)**
Confusional State	1 (0.9)	1 (0.8)	2 (0.7)	2 (0.7)	3 (0.8)	3 (0.7)
Mental Status Changes	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal And Urinary Disorders	**1 (0.9)**	**1 (0.8)**	**4 (1.4)**	**4 (1.3)**	**5 (1.3)**	**5 (1.2)**
Acute Kidney Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal Failure	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Renal Tubular Acidosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**10 (8.7)**	**10 (8.1)**	**14 (5.0)**	**14 (4.6)**	**24 (6.0)**	**24 (5.6)**
Cough	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dyspnoea	1 (0.9)	1 (0.8)	3 (1.1)	3 (1.0)	4 (1.0)	4 (0.9)
Lung Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Adverse Events Resulting in Study Drug Discontinuation
by Risk Group, 800 mg/day vs. All Doses
Number (%) of Subjects

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Lung Infiltration	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Obliterative Bronchiolitis	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Obstructive Airways Disorder	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pulmonary Oedema	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory Distress	2 (1.7)	2 (1.6)	3 (1.1)	3 (1.0)	5 (1.3)	5 (1.2)
Respiratory Failure	4 (3.5)	4 (3.2)	5 (1.8)	5 (1.6)	9 (2.3)	9 (2.1)
Wheezing	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin And Subcutaneous Tissue Disorders	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**4 (1.0)**	**4 (0.9)**
Rash	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Rash Macular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Maculo-Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Surgical And Medical Procedures	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Lung Transplant	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Therapeutic Procedure	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vascular Disorders	**1 (0.9)**	**1 (0.8)**	**3 (1.1)**	**3 (1.0)**	**4 (1.0)**	**4 (0.9)**
Aortic Aneurysm	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Haemorrhage	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hypertension	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypotension	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-39 投与中止に至った副作用の発現例数（%）

（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Adverse Events
Resulting in Study Drug Discontinuation by Risk Group
Number (%) of Subjects

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Subjects Reporting Any Adverse Event	**6 (5.2)**	**6 (4.8)**	**17 (6.0)**	**17 (5.6)**	**23 (5 8)**	**23 (5.4)**
Cardiac Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Cardio-Respiratory Arrest	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal Disorders	**1 (0.9)**	**1 (0.8)**	**4 (1.4)**	**4 (1.3)**	**5 (1.3)**	**5 (1.2)**
Abdominal Pain	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Diarrhoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Nausea	0	0	4 (1.4)	4 (1.3)	4 (1.0)	4 (0.9)
Pancreatitis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Vomiting	0	0	3 (1.1)	3 (1.0)	3 (0.8)	3 (0.7)
General Disorders And Administration Site Conditions	**1 (0.9)**	**1 (0.8)**	**1 (0.4)**	**1 (0.3)**	**2 (0.5)**	**2 (0.5)**
Fatigue	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Malaise	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hepatobiliary Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Hepatic Function Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Jaundice	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Immune System Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Drug Hypersensitivity	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Infections And Infestations	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Oesophageal Candidiasis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Investigations	**2 (1.7)**	**2 (1.6)**	**5 (1.8)**	**5 (1.6)**	**7 (1.8)**	**7 (1.6)**
Alanine Aminotransferase Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Amylase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Blood Creatinine Increased	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Gamma-Glutamyltransferase Increased	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)
Hepatic Enzyme Increased	1 (0 9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Lipase	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Lipase Abnormal	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Adverse Events
Resulting in Study Drug Discontinuation by Risk Group
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Liver Function Test Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Pancreatic Enzymes Increased	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Metabolism And Nutrition Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Decreased Appetite	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Electrolyte Imbalance	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Musculoskeletal And Connective Tissue Disorders	**1 (0.9)**	**1 (0.8)**	**1 (0.4)**	**1 (0.3)**	**2 (0.5)**	**2 (0.5)**
Back Pain	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Bone Pain	1 (0.9)	1 (0.8)	0	0	1 (0.3)	1 (0.2)
Nervous System Disorders	**3 (2.6)**	**3 (2.4)**	**3 (1.1)**	**3 (1.0)**	**6 (1.5)**	**6 (1.4)**
Balance Disorder	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Dizziness	1 (0.9)	1 (0.8)	1 (0.4)	1 (0.3)	2 (0.5)	2 (0.5)
Dysgeusia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Hypoaesthesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Seizure	2 (1.7)	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Psychiatric Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Confusional State	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Mental Status Changes	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal And Urinary Disorders	**0**	**0**	**2 (0.7)**	**2 (0.7)**	**2 (0.5)**	**2 (0.5)**
Acute Kidney Injury	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Choluria	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Renal Tubular Acidosis	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.2)**
Dyspnoea	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Skin And Subcutaneous Tissue Disorders	**0**	**0**	**4 (1.4)**	**4 (1.3)**	**4 (1.0)**	**4 (0.9)**
Rash	0	0	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.5)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Adverse Events
Resulting in Study Drug Discontinuation by Risk Group
Number (%) of Subjects

	BMT 800 mg/day n = 115	BMT All Doses n = 124	Non-BMT 800 mg/day n = 282	Non-BMT ALL Doses n = 304	rIFI Pool 800 mg/day n = 397	rIFI Pool ALL Doses n = 428
Rash Macular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)
Rash Maculo-Papular	0	0	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-40 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する有害事象の発現例数（%）（発現割合 0%超）ポサコナゾール経口懸濁液を投与した海外試験併合（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**99**	**(9.6)**
Hepatobiliary Disorders	**83**	**(8.0)**
Acute Hepatic Failure	1	(0.1)
Hepatic Failure	12	(1.2)
Hepatic Function Abnormal	1	(0.1)
Hepatic Necrosis	3	(0.3)
Hepatitis	1	(0.1)
Hepatitis Acute	2	(0.2)
Hepatocellular Injury	1	(0.1)
Hepatotoxicity	4	(0.4)
Hyperbilirubinaemia	34	(3.3)
Jaundice	38	(3.7)
Jaundice Cholestatic	1	(0.1)
Liver Disorder	1	(0.1)
Ocular Icterus	2	(0.2)
Investigations	**21**	**(2.0)**
Alanine Aminotransferase Abnormal	1	(0.1)
Aspartate Aminotransferase Abnormal	1	(0.1)
Aspartate Aminotransferase Increased	1	(0.1)
Hepatic Enzyme Abnormal	1	(0.1)
Hepatic Enzyme Increased	2	(0.2)
Liver Function Test Abnormal	5	(0.5)
Transaminases Increased	11	(1.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-41 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する副作用の発現例数（%）（発現割合 0%超）ポサコナゾール経口懸濁液を投与した海外試験併合（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**21**	**(2.0)**
Hepatobiliary Disorders	**17**	**(1.6)**
Hepatic Failure	2	(0.2)
Hepatitis	1	(0.1)
Hepatitis Acute	1	(0.1)
Hepatocellular Injury	1	(0.1)
Hepatotoxicity	1	(0.1)
Hyperbilirubinaemia	8	(0.8)
Jaundice	7	(0.7)
Investigations	**6**	**(0.6)**
Aspartate Aminotransferase Abnormal	1	(0.1)
Liver Function Test Abnormal	3	(0.3)
Transaminases Increased	2	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-42 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis (P05615, P05520) All Treated Subjects Subjects With Treatment Emergent Adverse Events (Incidence >0%) for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**37**	**(7.3)**
Hepatobiliary Disorders	**23**	**(4.5)**
Acute Hepatic Failure	1	(0.2)
Hepatic Function Abnormal	1	(0.2)
Hepatitis	1	(0.2)
Hepatotoxicity	2	(0.4)
Hyperbilirubinaemia	14	(2.8)
Jaundice	4	(0.8)
Investigations	**18**	**(3.5)**
Alanine Aminotransferase Increased	9	(1.8)
Aspartate Aminotransferase Increased	3	(0.6)
Blood Bilirubin Increased	4	(0.8)
Hepatic Enzyme Increased	3	(0.6)
Liver Function Test Abnormal	1	(0.2)
Transaminases Increased	1	(0.2)
Nervous System Disorders	**1**	**(0.2)**
Hepatic Encephalopathy	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-43 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**18**	**(3.5)**
Hepatobiliary Disorders	**7**	**(1.4)**
Hepatotoxicity	2	(0.4)
Hyperbilirubinaemia	5	(1.0)
Investigations	**13**	**(2.6)**
Alanine Aminotransferase Increased	7	(1.4)
Aspartate Aminotransferase Increased	2	(0.4)
Blood Bilirubin Increased	2	(0.4)
Hepatic Enzyme Increased	3	(0.6)
Liver Function Test Abnormal	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-44 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events (Incidence >0% in One or More Treatment Groups) for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	15	(19.5)	6	(15.8)
with no adverse events	62	(80.5)	32	(84.2)
Hepatobiliary disorders	**5**	**(6.5)**	**2**	**(5.3)**
Hepatic function abnormal	5	(6.5)	2	(5.3)
Investigations	**10**	**(13.0)**	**4**	**(10.5)**
Alanine aminotransferase increased	9	(11.7)	2	(5.3)
Aspartate aminotransferase increased	10	(13.0)	4	(10.5)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-45 肝（肝酵素増加、肝毒性、肝不全、肝炎）に関連する副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events (Incidence >0% in One or More Treatment Groups) for Hepatobiliary Disorders - Elevated Liver Enzymes, Hepatotoxicity, Hepatic Failure, and Hepatitis Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	10	(13.0)	5	(13.2)
with no drug-related adverse events	67	(87.0)	33	(86.8)
Hepatobiliary disorders	**3**	**(3.9)**	**2**	**(5.3)**
Hepatic function abnormal	3	(3.9)	2	(5.3)
Investigations	**7**	**(9.1)**	**3**	**(7.9)**
Alanine aminotransferase increased	7	(9.1)	2	(5.3)
Aspartate aminotransferase increased	7	(9.1)	3	(7.9)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-46 血液（血栓性血小板減少性紫斑病、溶血性尿毒症症候群）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Blood and Lymphatic Disorders - Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**41**	**(4.0)**
Blood And Lymphatic System Disorders	**41**	**(4.0)**
Coagulopathy	15	(1.5)
Disseminated Intravascular Coagulation	5	(0.5)
Haemolytic Uraemic Syndrome	10	(1.0)
Haemorrhagic Diathesis	1	(0.1)
Hypercoagulation	2	(0.2)
Thrombotic Thrombocytopenic Purpura	15	(1.5)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-47 血液（血栓性血小板減少性紫斑病、溶血性尿毒症症候群）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Blood and Lymphatic Disorders - Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**1**	**(0.1)**
Blood And Lymphatic System Disorders	**1**	**(0.1)**
Haemolytic Uraemic Syndrome	1	(0.1)
Thrombotic Thrombocytopenic Purpura	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-48 血液（血栓性血小板減少性紫斑病、溶血性尿毒症症候群）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis (P05615, P05520) All Treated Subjects Subjects With Treatment Emergent Adverse Events (Incidence >0%) for Blood and Lymphatic Disorders - Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**5**	**(1.0)**
Blood And Lymphatic System Disorders	**5**	**(1.0)**
Coagulopathy	2	(0.4)
Haemorrhagic Diathesis	1	(0.2)
Microangiopathic Haemolytic Anaemia	1	(0.2)
Thrombotic Thrombocytopenic Purpura	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

Confidential

付録 2.7.4-49 心臓（トルサード ド ポアント、QT 延長）に関連する有害事象の発現例数（%）（発現割合 0%超）ポサコナゾール経口懸濁液を投与した海外試験併合（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Torsade de Pointes and QTc Prolongation

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**36**	**(3.5)**
Cardiac Disorders	**35**	**(3.4)**
Atrial Fibrillation	26	(2.5)
Torsade De Pointes	1	(0.1)
Ventricular Fibrillation	3	(0.3)
Ventricular Tachycardia	6	(0.6)
Investigations	**1**	**(0.1)**
Electrocardiogram Qt Interval Abnormal	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-50 心臓（トルサード ド ポアント、QT 延長）に関連する副作用の発現例数（%）（発現割合 0%超）ポサコナゾール経口懸濁液を投与した海外試験併合（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Torsade de Pointes and QTc Prolongation

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**6**	**(0.6)**
Cardiac Disorders	**6**	**(0.6)**
Atrial Fibrillation	4	(0.4)
Torsade De Pointes	1	(0.1)
Ventricular Tachycardia	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-51 心臓（トルサード ド ポアント、QT 延長）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis (P05615, P05520) All Treated Subjects Subjects With Treatment Emergent Adverse Events (Incidence >0%) for Cardiac Disorders - Torsade de Pointes and QTc Prolongation

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**6**	**(1.2)**
Cardiac Disorders	**3**	**(0.6)**
Atrial Fibrillation	3	(0.6)
Investigations	**3**	**(0.6)**
Electrocardiogram Qt Interval Abnormal	1	(0.2)
Electrocardiogram Qt Prolonged	2	(0.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-52 心臓（トルサード ド ポアント、QT 延長）に関連する副作用の発現例数（%）（発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Torsade de Pointes and QTc Prolongation

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**3**	**(0.6)**
Investigations	**3**	**(0.6)**
Electrocardiogram Qt Interval Abnormal	1	(0.2)
Electrocardiogram Qt Prolonged	2	(0.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-53 心臓（トルサード ド ポアント、QT 延長）に関連する有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Cardiac Disorders - Torsade de Pointes and QTc Prolongation
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	7	(9.1)	2	(5.3)
with no adverse events	70	(90.9)	36	(94.7)
Investigations	**7**	**(9.1)**	**2**	**(5.3)**
Electrocardiogram QT prolonged	7	(9.1)	2	(5.3)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-54 心臓（トルサード ド ポアント、QT 延長）に関連する副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events (Incidence >0% in One or More Treatment Groups) for Cardiac Disorders - Torsade de Pointes and QTc Prolongation Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	6	(7.8)	2	(5.3)
with no drug-related adverse events	71	(92.2)	36	(94.7)
Investigations	**6**	**(7.8)**	**2**	**(5.3)**
Electrocardiogram QT prolonged	6	(7.8)	2	(5.3)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-55 内分泌（副腎機能不全）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Endocrine Disorders - Adrenal Insufficiency

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**10**	**(1.0)**
Endocrine Disorders	**10**	**(1.0)**
Addison's Disease	1	(0.1)
Adrenal Insufficiency	9	(0.9)
Adrenocortical Insufficiency Acute	1	(0.1)
Investigations	**1**	**(0.1)**
Glucocorticoids Decreased	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-56 内分泌（副腎機能不全）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Endocrine Disorders - Adrenal Insufficiency

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**1**	**(0.1)**
Endocrine Disorders	**1**	**(0.1)**
Adrenal Insufficiency	1	(0.1)
Adrenocortical Insufficiency Acute	1	(0.1)
Investigations	**1**	**(0.1)**
Glucocorticoids Decreased	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-57 内分泌（副腎機能不全）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Endocrine Disorders - Adrenal Insufficiency

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**1**	**(0.2)**
Endocrine Disorders	**1**	**(0.2)**
Adrenal Insufficiency	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-58 代謝（低カリウム血症）に関連する
有害事象の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液を投与した海外試験併合
（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Metabolism and Nutritional Disorders - Hypokalemia

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**227**	**(22.0)**
Metabolism And Nutrition Disorders	**227**	**(22.0)**
Hypokalaemia	227	(22.0)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-59 代謝（低カリウム血症）に関連する
副作用の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液を投与した海外試験併合
（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Metabolism and Nutritional Disorders - Hypokalemia

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**11**	**(1.1)**
Metabolism And Nutrition Disorders	**11**	**(1.1)**
Hypokalaemia	11	(1.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-60 代謝（低カリウム血症）に関連する
有害事象の発現例数（%）（発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合
（P05615 及び P05520 試験）（All Treated Subjects）
Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Metabolism and Nutritional Disorders - Hypokalemia

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**124**	**(24.4)**
Metabolism And Nutrition Disorders	**124**	**(24.4)**
Hypokalaemia	124	(24.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-61 代謝（低カリウム血症）に関連する副作用の発現例数（%）（発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Metabolism and Nutritional Disorders - Hypokalemia

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**21**	**(4.1)**
Metabolism And Nutrition Disorders	**21**	**(4.1)**
Hypokalaemia	21	(4.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-62 代謝（低カリウム血症）に関連する
有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Metabolism and Nutritional Disorders - Hypokalemia
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	16	(20.8)	1	(2.6)
with no adverse events	61	(79.2)	37	(97.4)
Metabolism and nutrition disorders	**16**	**(20.8)**	**1**	**(2.6)**
Hypokalaemia	16	(20.8)	1	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-63 代謝（低カリウム血症）に関連する
副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Metabolism and Nutritional Disorders - Hypokalemia
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	10	(13.0)	0	(0.0)
with no drug-related adverse events	67	(87.0)	38	(100.0)
Metabolism and nutrition disorders	**10**	**(13.0)**	**0**	**(0.0)**
Hypokalaemia	10	(13.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-64 血液（無顆粒球症、再生不良性貧血）に関連する有害事象の発現例数（%）（発現割合 0%超）ポサコナゾール経口懸濁液を投与した海外試験併合（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Blood and Lymphatic Disorders - Agranulocytosis and Aplastic Anemia

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**1**	**(0.1)**
Blood And Lymphatic System Disorders	**1**	**(0.1)**
Aplastic Anaemia	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-65 血液（無顆粒球症、再生不良性貧血）に関連する有害事象の発現例数（%）（発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Blood and Lymphatic Disorders - Agranulocytosis and Aplastic Anemia

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**1**	**(0.2)**
Blood And Lymphatic System Disorders	**1**	**(0.2)**
Agranulocytosis	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-66 心臓（心不全）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Heart Failure

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**92**	**(8.9)**
Cardiac Disorders	**40**	**(3.9)**
Cardiac Failure	9	(0.9)
Cardiac Failure Congestive	12	(1.2)
Cardiogenic Shock	1	(0.1)
Cardiomegaly	9	(0.9)
Cardiomyopathy	6	(0.6)
Cardiopulmonary Failure	4	(0.4)
Congestive Cardiomyopathy	1	(0.1)
Left Ventricular Dysfunction	4	(0.4)
Metabolism And Nutrition Disorders	**38**	**(3.7)**
Fluid Overload	38	(3.7)
Respiratory, Thoracic And Mediastinal Disorders	**31**	**(3.0)**
Pulmonary Oedema	31	(3.0)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-67 心臓（心不全）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Heart Failure

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**1**	**(0.1)**
Cardiac Disorders	**1**	**(0.1)**
Cardiomegaly	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-68 心臓（心筋梗塞）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Myocardial Infarction

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**15**	**(1.5)**
Cardiac Disorders	**15**	**(1.5)**
Acute Myocardial Infarction	1	(0.1)
Angina Pectoris	7	(0.7)
Coronary Artery Occlusion	1	(0.1)
Myocardial Infarction	4	(0.4)
Myocardial Ischaemia	2	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-69 心臓（心不全）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Heart Failure

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**21**	**(4.1)**
Cardiac Disorders	**9**	**(1.8)**
Cardiac Failure	4	(0.8)
Cardiac Failure Congestive	4	(0.8)
Left Ventricular Failure	1	(0.2)
Metabolism And Nutrition Disorders	**9**	**(1.8)**
Fluid Overload	9	(1.8)
Respiratory, Thoracic And Mediastinal Disorders	**7**	**(1.4)**
Pulmonary Oedema	7	(1.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-70 心臓（心不全）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Heart Failure

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**2**	**(0.4)**
Metabolism And Nutrition Disorders	**2**	**(0.4)**
Fluid Overload	2	(0.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-71 心臓（心筋梗塞）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Cardiac Disorders - Myocardial Infarction

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**1**	**(0.2)**
Cardiac Disorders	**1**	**(0.2)**
Angina Pectoris	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-72 心臓（心不全）に関連する
有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Cardiac Disorders - Heart Failure
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	6	(7.8)	0	(0.0)
with no adverse events	71	(92.2)	38	(100.0)
Cardiac disorders	**6**	**(7.8)**	**0**	**(0.0)**
Cardiac failure	4	(5.2)	0	(0.0)
Cardiac failure congestive	2	(2.6)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-73 心臓（心不全）に関連する
副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Cardiac Disorders - Heart Failure
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	1	(1.3)	0	(0.0)
with no drug-related adverse events	76	(98.7)	38	(100.0)
Cardiac disorders	**1**	**(1.3)**	**0**	**(0.0)**
Cardiac failure	1	(1.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-74 中枢神経（痙攣）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Central Nervous System Disorders - Convulsion

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**4**	**(0.4)**
Nervous System Disorders	**4**	**(0.4)**
Seizure	3	(0.3)
Tonic Convulsion	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-75 中枢神経（脳虚血）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Central Nervous System Disorders - Cerebral Ischemia

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**12**	**(1.2)**
Nervous System Disorders	**12**	**(1.2)**
Cerebral Infarction	5	(0.5)
Cerebrovascular Accident	5	(0.5)
Embolic Stroke	1	(0.1)
Ischaemic Stroke	2	(0.2)
Transient Ischaemic Attack	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-76 中枢神経（脳出血）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Central Nervous System Disorders - Cerebral Haemorrhage

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**17**	**(1.6)**
Injury, Poisoning And Procedural Complications	**3**	**(0.3)**
Subarachnoid Haemorrhage	3	(0.3)
Nervous System Disorders	**15**	**(1.5)**
Cerebellar Haemorrhage	2	(0.2)
Cerebral Haemorrhage	7	(0.7)
Haemorrhage Intracranial	4	(0.4)
Haemorrhagic Cerebral Infarction	1	(0.1)
Haemorrhagic Stroke	1	(0.1)
Intraventricular Haemorrhage	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-77 中枢神経（痙攣）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Central Nervous System Disorders - Convulsion

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**1**	**(0.2)**
Nervous System Disorders	**1**	**(0.2)**
Epilepsy	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-78 中枢神経（脳出血）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Central Nervous System Disorders - Cerebral Haemorrhage

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**3**	**(0.6)**
Injury, Poisoning And Procedural Complications	**3**	**(0.6)**
Subarachnoid Haemorrhage	2	(0.4)
Subdural Haemorrhage	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

付録 2.7.4-79 呼吸器（肺出血）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Respiratory Disorders - Pulmonary Haemorrhage

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**20**	**(1.9)**
Respiratory, Thoracic And Mediastinal Disorders	**20**	**(1.9)**
Pulmonary Alveolar Haemorrhage	6	(0.6)
Pulmonary Haemorrhage	14	(1.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-80 呼吸器（肺出血）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Respiratory Disorders - Pulmonary Haemorrhage

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**3**	**(0.6)**
Respiratory, Thoracic And Mediastinal Disorders	**3**	**(0.6)**
Pulmonary Haemorrhage	3	(0.6)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-81 血管（高血圧）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Hypertension

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**148**	**(14.3)**
Investigations	**14**	**(1.4)**
Blood Pressure Increased	13	(1.3)
Blood Pressure Systolic Increased	1	(0.1)
Vascular Disorders	**137**	**(13.3)**
Hypertension	137	(13.3)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-82 血管（高血圧）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Hypertension

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**5**	**(0.5)**
Vascular Disorders	**5**	**(0.5)**
Hypertension	5	(0.5)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-83 血管（静脈血栓症）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Venous Thrombosis

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**25**	**(2.4)**
Respiratory, Thoracic And Mediastinal Disorders	**8**	**(0.8)**
Pulmonary Embolism	7	(0.7)
Pulmonary Infarction	1	(0.1)
Vascular Disorders	**19**	**(1.8)**
Deep Vein Thrombosis	7	(0.7)
Subclavian Vein Thrombosis	2	(0.2)
Thrombophlebitis	4	(0.4)
Thrombosis	1	(0.1)
Venous Thrombosis	4	(0.4)
Venous Thrombosis Limb	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-84 血管（静脈血栓症）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Venous Thrombosis

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**1**	**(0.1)**
Respiratory, Thoracic And Mediastinal Disorders	**1**	**(0.1)**
Pulmonary Embolism	1	(0.1)
Vascular Disorders	**1**	**(0.1)**
Deep Vein Thrombosis	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-85 血管（高血圧）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Hypertension

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**50**	**(9.8)**
Investigations	**3**	**(0.6)**
Blood Pressure Increased	3	(0.6)
Vascular Disorders	**48**	**(9.4)**
Hypertension	48	(9.4)
Hypertensive Crisis	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-86 血管（高血圧）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Hypertension

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**4**	**(0.8)**
Vascular Disorders	**4**	**(0.8)**
Hypertension	4	(0.8)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-87 血管（静脈血栓症）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Venous Thrombosis

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**14**	**(2.8)**
Respiratory, Thoracic And Mediastinal Disorders	**2**	**(0.4)**
Pulmonary Embolism	2	(0.4)
Vascular Disorders	**12**	**(2.4)**
Deep Vein Thrombosis	1	(0.2)
Jugular Vein Thrombosis	1	(0.2)
Subclavian Vein Thrombosis	1	(0.2)
Thrombophlebitis	3	(0.6)
Venoocclusive Disease	2	(0.4)
Venous Thrombosis	4	(0.8)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-88 血管（静脈血栓症）に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合

（P05615 及び P05520 試験）（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Vascular Disorders - Venous Thrombosis

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**1**	**(0.2)**
Vascular Disorders	**1**	**(0.2)**
Thrombophlebitis	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-89 血管（高血圧）に関連する
有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Vascular Disorders - Hypertension
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	12	(15.6)	1	(2.6)
with no adverse events	65	(84.4)	37	(97.4)
Investigations	**1**	**(1.3)**	**0**	**(0.0)**
Blood pressure increased	1	(1.3)	0	(0.0)
Vascular disorders	**11**	**(14.3)**	**1**	**(2.6)**
Hypertension	11	(14.3)	1	(2.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

付録 2.7.4-90 血管（高血圧）に関連する
副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Vascular Disorders - Hypertension
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	10	(13.0)	1	(2.6)
with no drug-related adverse events	67	(87.0)	37	(97.4)
Vascular disorders	**10**	**(13.0)**	**1**	**(2.6)**
Hypertension	10	(13.0)	1	(2.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-91 血管（静脈血栓症）に関連する
有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Vascular Disorders - Venous Thrombosis
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	0	(0.0)	1	(2.6)
with no adverse events	77	(100.0)	37	(97.4)
Vascular disorders	**0**	**(0.0)**	**1**	**(2.6)**
Thrombophlebitis	0	(0.0)	1	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-92 新生物

［新生物・悪性腫瘍の発現（特に、肝腺腫、肝新生物、副腎腺腫、副腎新生物、褐色細胞腫）］に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液を投与した海外試験併合

（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）

Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Neoplasm/Malignancy

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**2**	**(0.2)**
Endocrine Disorders	**1**	**(0.1)**
Adrenal Mass	1	(0.1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**1**	**(0.1)**
Hepatic Cancer	1	(0.1)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-93 視覚（光視症、視覚の明るさ、視覚障害）に関連する
有害事象の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液を投与した海外試験併合
（C/I98-316、P01899、P01893 及び P00041 試験）（All Randomized Subjects）
Pooled Posaconazole Oral Suspension Safety Analysis
(CI98-316, P01899, P01893, P00041)
All Randomized Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances

	Posaconazole n = 1033	
Subjects Reporting Any Adverse Event	**2**	**(0.2)**
Eye Disorders	**2**	**(0.2)**
Visual Impairment	2	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-94 視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液を投与した海外試験併合（P05615 及び P05520 試験）

（All Treated Subjects）

Pooled Posaconazole Tablet and IV Safety Analysis
(P05615, P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances

	Posaconazole n = 509	
Subjects Reporting Any Adverse Event	**3**	**(0.6)**
Eye Disorders	**3**	**(0.6)**
Visual Impairment	3	(0.6)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1
P05615: All Cohorts (Posaconazole tablet 200 mg Cohort and 300 mg Cohort) are included.
P05520: All Cohorts (Cohort 0, 1, 2, and 3) are included.

C Confidential

付録 2.7.4-95 視覚（光視症、視覚の明るさ、視覚障害）に関連する有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events (Incidence >0% in One or More Treatment Groups) for Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events	0	(0.0)	4	(10.5)
with no adverse events	77	(100.0)	34	(89.5)
Eye disorders	**0**	**(0.0)**	**4**	**(10.5)**
Visual impairment	0	(0.0)	4	(10.5)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-96 視覚（光視症、視覚の明るさ、視覚障害）に関連する副作用の発現例数（%）
（いずれかの投与群で発現割合 0%超）
ポサコナゾール新錠剤及び静注用溶液を投与した国内試験（P101 試験）
（コホート 1 及び 2 併合）（ASaT）
Subjects With Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
for Eye Disorders - Photopsia, Visual Brightness, and Visual Disturbances
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events	0	(0.0)	4	(10.5)
with no drug-related adverse events	77	(100.0)	34	(89.5)
Eye disorders	**0**	**(0.0)**	**4**	**(10.5)**
Visual impairment	0	(0.0)	4	(10.5)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-97 注入部位反応に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）（All Treated Subjects）

Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Infusion Site Reactions after Central Line Infusion of Intravenous Posaconazole

	Posaconazole n = 268	
Subjects Reporting Any Adverse Event	**32**	**(11.9)**
General Disorders And Administration Site Conditions	**32**	**(11.9)**
Catheter Site Discharge	2	(0.7)
Catheter Site Erythema	3	(1.1)
Catheter Site Haematoma	1	(0.4)
Catheter Site Inflammation	3	(1.1)
Catheter Site Pain	6	(2.2)
Catheter Site Pruritus	2	(0.7)
Catheter Site Rash	1	(0.4)
Catheter Site Related Reaction	1	(0.4)
Infusion Site Erythema	2	(0.7)
Infusion Site Inflammation	1	(0.4)
Infusion Site Pain	3	(1.1)
Infusion Site Phlebitis	2	(0.7)
Infusion Site Thrombosis	4	(1.5)
Injection Site Inflammation	1	(0.4)
Injection Site Irritation	1	(0.4)
Injection Site Reaction	1	(0.4)
Oedema Peripheral	2	(0.7)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

Confidential

付録 2.7.4-98 注入部位反応に関連する副作用の発現例数（%）（発現割合 0%超）
ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）（All Treated Subjects）
Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Infusion Site Reactions after Central Line Infusion of Intravenous Posaconazole

	Posaconazole n = 268	
Subjects Reporting Any Adverse Event	**3**	**(1.1)**
General Disorders And Administration Site Conditions	**3**	**(1.1)**
Infusion Site Phlebitis	1	(0.4)
Infusion Site Thrombosis	2	(0.7)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-99 腎機能障害に関連する有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）（All Treated Subjects）

Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Subjects With Treatment Emergent Adverse Events
(Incidence >0%)
for Renal Effects of Cyclodextrin with Intravenous Infusion of Posaconazole

	Posaconazole n = 268	
Subjects Reporting Any Adverse Event	**6**	**(2.2)**
Renal And Urinary Disorders	**6**	**(2.2)**
Acute Kidney Injury	4	(1.5)
Renal Failure	1	(0.4)
Renal Impairment	1	(0.4)
Every subject is counted a single time for each applicable row and column.		
MedDRA Version 20.1		

Confidential

付録 2.7.4-100　　腎機能障害に関連する副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール静注用溶液を投与した患者対象試験（P05520 試験）（All Treated Subjects）

Posaconazole IV Safety Analysis
(P05520)
All Treated Subjects
Subjects With Treatment Related Treatment Emergent Adverse Events
(Incidence >0%)
for Renal Effects of Cyclodextrin with Intravenous Infusion of Posaconazole

	Posaconazole n = 268	
Subjects Reporting Any Adverse Event	**1**	**(0.4)**
Renal And Urinary Disorders	**1**	**(0.4)**
Acute Kidney Injury	1	(0.4)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-101　　臨床検査項目の共通毒性基準（CTC）

Toxicity		CTC Grade				
		0	1	2	3	4
Hemoglobin (g/L)		≥LLN	100 - <LLN	80 - <100	65 - <80	<65
Hematocrit (V/V)	Males	≥0.42	0.30 - <0.42	0.24-<0.30	0.19-<0.24	<0.19
	Females	≥0.37	0.30 - <0.37	0.24-<0.30	0.19-<0.24	<0.19
WBC (x10^9/L)	Non BMT	≥LLN	3.0 - < LLN	2.0 - <3.0	1.0 - <2.0	<1.0
	BMT	≥3.0	2.0 - <3.0	1.0 - <2.0	0.5 - <1.0	<0.5
Platelets (x10^9/L)	Non BMT	≥LLN	75.0 - <LLN	50.0 - <75.0	10.0 - <50.0	<10.0
	BMT	≥75.0	50.0 - <75.0	20.0 - <50.0	10.0 - <20.0	<10.0
ANC (x 10^9/L)	Non BMT	≥2.0	1.5 - <2.0	1.0 - <1.5	0.5 - <1.0	<0.5
	BMT	≥1.5	1.0 - <1.5	0.5 - <1.0	0.1 - <0.5	<0.1
ALT (x ULN)		≤1	>1 - 2.5	>2.5 - 5	>5 - 20	>20
AST (x ULN)		≤1	>1 - 2.5	>2.5 - 5	>5 - 20	>20
Total Bilirubin (x ULN)		≤1	>1 - 1.5	>1.5 - 3	>3 - 10	>10
Alkaline Phosphatase (xULN)		≤1	>1 - 2.5	>2.5 - 5	>5 - 20	>20
Creatinine (x ULN)		≤1	>1 - 1.5	>1.5 - 3	>3 - 6	>6

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BMT = bone marrow transplant; CTC = Common Toxicity Criteria; LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cell count

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付録 2.7.4-102　　臨床検査項目の有害事象共通用語基準（CTCAE）

Adverse Event	CTCAE Grade				
	1	2	3	4	5
ALT increased (x ULN)	>1 - 3	>3 - 5	>5 - 20	>20	-
AST increased (x ULN)	>1 - 3	>3 - 5	>5 - 20	>20	-
Total Bilirubin increased (x ULN)	>1 - 1.5	>1.5 - 3	>3 - 10	>10	-
Alkaline Phosphatase increased (xULN)	>1 - 2.5	>2.5 - 5	>5 - 20	>20	-
Creatinine increased (x ULN)	>1 - 1.5	>1.5 - 3	>3 - 6	>6	-

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

付録 2.7.4-103　　臨床検査項目のベースラインから
Treatment Phase で測定した最終時点までの値の変動
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

		Posaconazole n=605				Fluconazole n=539			
Lab Test		n	Mean	SD	Median	n	Mean	SD	Median
K (mmol/L)	Baseline Value	560	4.08	0.50	4.10	507	4.06	0.52	4.10
	Endpoint Value	560	3.95	0.58	4.00	507	3.98	0.62	4.00
	Change from Baseline	560	-0.14	0.72	-0.10	507	-0.08	0.74	-0.10
	% Change from Baseline	560	-2.1	17.6	-2.7	507	-0.7	19.1	-2.6
CREAT (umol/L)	Baseline Value	575	80.7	29.5	77.0	515	83.6	30.0	79.6
	Endpoint Value	575	95.7	57.8	80.0	515	102.9	60.9	88.0
	Change from Baseline	575	15.0	53.0	7.8	515	19.3	54.0	8.8
	% Change from Baseline	575	22.7	64.4	10.0	515	26.0	62.6	9.3
AST (U/L)	Baseline Value	552	37.5	41.5	24.0	490	39.4	35.5	27.0
	Endpoint Value	552	60.7	349.8	26.0	490	121.8	1150.7	26.0
	Change from Baseline	552	23.2	349.7	1.0	490	82.4	1151.2	-1.6
	% Change from Baseline	552	90.8	616.5	5.0	490	345.4	4189.3	-5.1
ALT (U/L)	Baseline Value	560	69.0	90.7	37.5	502	74.8	97.0	39.0
	Endpoint Value	560	84.5	311.9	37.0	502	95.5	545.6	38.0
	Change from Baseline	560	15.4	316.6	-1.0	502	20.7	552.1	-4.0
	% Change from Baseline	560	126.6	655.1	-4.2	502	240.0	3910.9	-14.3
ALP (U/L)	Baseline Value	552	134.2	144.8	85.5	491	126.0	137.8	87.0
	Endpoint Value	552	167.9	231.2	101.0	491	146.1	151.2	100.0
	Change from Baseline	552	33.7	215.7	14.5	491	20.1	129.6	12.0
	% Change from Baseline	552	48.5	143.2	18.9	491	42.5	112.3	16.9
TBILI (umol/L)	Baseline Value	561	20.0	26.5	13.7	505	18.4	21.4	13.0
	Endpoint Value	561	24.4	57.0	12.0	505	25.0	58.4	10.3
	Change from Baseline	561	4.4	55.0	-1.7	505	6.6	54.5	-1.7
	% Change from Baseline	561	55.2	442.7	-13.0	505	74.1	515.3	-14.3

K = kalium/potassium, CREAT = Creatinine, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, TBILI = total bilirubin

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付録 2.7.4-104　　臨床検査項目のベースライン値の CTC Grade から試験期間中の最も重い Grade への変動

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine							
Posaconazole (n = 605)	Grade 0	375 (62)	102 (17)	25 (4)	4 (1)	0	16 (3)
	Grade 1	9 (1)	26 (4)	19 (3)	4 (1)	1 (<1)	3 (<1)
	Grade 2	0	3 (<1)	6 (1)	1 (<1)	0	1 (<1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	3 (<1)	6 (1)	1 (<1)	0	0	0
Fluconazole (n = 539)	Grade 0	298 (55)	96 (18)	50 (9)	5 (1)	0	10 (2)
	Grade 1	6 (1)	26 (5)	24 (4)	2 (<1)	0	2 (<1)
	Grade 2	1 (<1)	1 (<1)	5 (1)	0	1 (<1)	1 (<1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	6 (1)	2 (<1)	1 (<1)	0	0	2 (<1)
Itraconazole (n = 58)	Grade 0	51 (88)	3 (5)	2 (3)	1 (2)	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	1 (2)	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hyperkalemia							
Posaconazole (n = 605)	Grade 0	473 (78)	49 (8)	13 (2)	4 (1)	1 (<1)	20 (3)
	Grade 1	10 (2)	5 (1)	0	1 (<1)	0	0
	Grade 2	3 (<1)	0	0	0	0	0
	Grade 3	1 (<1)	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	15 (2)	0	1 (<1)	1 (<1)	0	8 (1)
Fluconazole (n = 539)	Grade 0	404 (75)	60 (11)	21 (4)	6 (1)	1 (<1)	14 (3)
	Grade 1	7 (1)	3 (1)	0	0	0	1 (<1)
	Grade 2	2 (<1)	0	1 (<1)	1 (<1)	0	0
	Grade 3	0	1 (<1)	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	12 (2)	1 (<1)	1 (<1)	0	0	3 (1)
Itraconazole (n = 58)	Grade 0	54 (93)	2 (3)	0	0	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	2 (3)	0	0	0	0	0
Hypokalemia							
Posaconazole (n = 605)	Grade 0	286 (47)	150 (25)	0	57 (9)	6 (1)	18 (3)
	Grade 1	16 (3)	31 (5)	0	9 (1)	1 (<1)	2 (<1)
	Grade 2	0	0	0	0	0	0
	Grade 3	0	1 (<1)	0	3 (<1)	0	0
	Grade 4	0	0	0	0	0	0
	Missing	7 (1)	6 (1)	0	2 (<1)	2 (<1)	8 (1)

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	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Fluconazole (n = 539)	Grade 0	277 (51)	124 (23)	0	41 (8)	2 (<1)	14 (3)
	Grade 1	23 (4)	24 (4)	0	7 (1)	2 (<1)	1 (<1)
	Grade 2	0	0	0	0	0	0
	Grade 3	4 (1)	1 (<1)	0	1 (<1)	0	0
	Grade 4	0	1 (<1)	0	0	0	0
	Missing	10 (2)	3 (1)	0	1 (<1)	0	3 (1)
Itraconazole (n = 58)	Grade 0	13 (22)	24 (41)	0	11 (19)	2 (3)	0
	Grade 1	3 (5)	2 (3)	0	0	1 (2)	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	1 (2)	0	0	0	1 (2)	0
Alkaline Phosphatase							
Posaconazole (n = 605)	Grade 0	293 (48)	100 (17)	14 (2)	6 (1)	0	25 (4)
	Grade 1	23 (4)	60 (10)	18 (3)	2 (<1)	0	4 (1)
	Grade 2	0	9 (1)	12 (2)	5 (1)	0	1 (<1)
	Grade 3	0	0	5 (1)	5 (1)	0	0
	Grade 4	0	0	0	0	0	0
	Missing	11 (2)	9 (1)	0	2 (<1)	0	1 (<1)
Fluconazole (n = 539)	Grade 0	260 (48)	82 (15)	15 (3)	3 (1)	0	19 (4)
	Grade 1	24 (4)	62 (12)	16 (3)	4 (1)	0	6 (1)
	Grade 2	0	9 (2)	13 (2)	2 (<1)	0	3 (1)
	Grade 3	0	0	0	1 (<1)	0	1 (<1)
	Grade 4	0	0	0	0	0	0
	Missing	9 (2)	6 (1)	1 (<1)	0	0	3 (1)
Itraconazole (n = 58)	Grade 0	33 (57)	18 (31)	1 (2)	1 (2)	0	1 (2)
	Grade 1	1 (2)	3 (5)	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Alanine Aminotransferase (ALT)							
Posaconazole (n = 605)	Grade 0	165 (27)	108 (18)	26 (4)	14 (2)	2 (<1)	12 (2)
	Grade 1	23 (4)	60 (10)	31 (5)	24 (4)	4 (1)	6 (1)
	Grade 2	3 (<1)	22 (4)	19 (3)	21 (3)	0	3 (<1)
	Grade 3	0	7 (1)	9 (1)	18 (3)	2 (<1)	1 (<1)
	Grade 4	0	0	1 (<1)	0	1 (<1)	0
	Missing	6 (1)	5 (1)	6 (1)	1 (<1)	0	5 (1)
Fluconazole (n = 539)	Grade 0	139 (26)	94 (17)	20 (4)	11 (2)	3 (1)	11 (2)
	Grade 1	27 (5)	53 (10)	25 (5)	19 (4)	1 (<1)	7 (1)
	Grade 2	2 (<1)	25 (5)	23 (4)	20 (4)	0	4 (1)
	Grade 3	2 (<1)	3 (1)	14 (3)	19 (4)	1 (<1)	1 (<1)
	Grade 4	0	0	1 (<1)	0	0	0
	Missing	3 (1)	5 (1)	0	2 (<1)	2 (<1)	2 (<1)
Itraconazole (n = 58)	Grade 0	32 (55)	10 (17)	3 (5)	1 (2)	0	0
	Grade 1	4 (7)	5 (9)	0	0	0	0
	Grade 2	0	0	1 (2)	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	2 (3)	0	0	0	0
Aspartate Aminotransferase (AST)							
Posaconazole (n = 605)	Grade 0	261 (43)	103 (17)	24 (4)	12 (2)	0	16 (3)
	Grade 1	32 (5)	52 (9)	28 (5)	3 (<1)	2 (<1)	4 (1)
	Grade 2	2 (<1)	10 (2)	10 (2)	3 (<1)	1 (<1)	4 (1)
	Grade 3	2 (<1)	4 (1)	1 (<1)	2 (<1)	0	0
	Grade 4	0	0	0	0	0	0
	Missing	5 (1)	6 (1)	2 (<1)	2 (<1)	0	14 (2)

	Baseline CTC Grade	Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Fluconazole (n = 539)	Grade 0	208 (39)	97 (18)	23 (4)	2 (<1)	2 (<1)	18 (3)
	Grade 1	32 (6)	59 (11)	20 (4)	10 (2)	1 (<1)	6 (1)
	Grade 2	6 (1)	13 (2)	12 (2)	2 (<1)	0	0
	Grade 3	0	1 (<1)	2 (<1)	0	0	1 (<1)
	Grade 4	0	0	0	0	0	0
	Missing	4 (1)	3 (1)	3 (1)	2 (<1)	0	12 (2)
Itraconazole (n = 58)	Grade 0	38 (66)	12 (21)	0	1 (2)	1 (2)	0
	Grade 1	1 (2)	2 (3)	1 (2)	0	0	0
	Grade 2	1 (2)	1 (2)	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Total Bilirubin							
Posaconazole (n = 605)	Grade 0	279 (46)	79 (13)	46 (8)	13 (2)	4 (1)	16 (3)
	Grade 1	24 (4)	18 (3)	19 (3)	11 (2)	2 (<1)	3 (<1)
	Grade 2	4 (1)	9 (1)	22 (4)	11 (2)	3 (<1)	2 (<1)
	Grade 3	0	0	4 (1)	8 (1)	2 (<1)	0
	Grade 4	0	0	0	2 (<1)	1 (<1)	2 (<1)
	Missing	6 (1)	3 (<1)	6 (1)	2 (<1)	2 (<1)	2 (<1)
Fluconazole (n = 539)	Grade 0	283 (53)	50 (9)	26 (5)	18 (3)	2 (<1)	15 (3)
	Grade 1	18 (3)	24 (4)	17 (3)	11 (2)	1 (<1)	4 (1)
	Grade 2	9 (2)	15 (3)	9 (2)	4 (1)	3 (1)	2 (<1)
	Grade 3	0	0	2 (<1)	8 (1)	3 (1)	1 (<1)
	Grade 4	0	0	0	0	2 (<1)	1 (<1)
	Missing	4 (1)	3 (1)	0	2 (<1)	0	2 (<1)
Itraconazole (n = 58)	Grade 0	20 (34)	13 (22)	6 (10)	2 (3)	1 (2)	1 (2)
	Grade 1	3 (5)	4 (7)	2 (3)	2 (3)	0	0
	Grade 2	1 (2)	0	1 (2)	2 (3)	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

CTC = Common Toxicity Criteria

付録 2.7.4-105　　肝機能関連の臨床検査項目のベースライン値が異常であり、その後値が上昇した被験者数
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

Parameter	Posaconazole N = 359 n (%)	Fluconazole N = 328 n (%)	Itraconazole N = 25 n (%)
AST	141/338 (42)	126/312 (40)	8/25 (32)
ALT	152/345 (44)	138/317 (44)	9/23 (39)
Alkaline Phosphatase	121/341 (35)	115/315 (37)	7/25 (28)
Total Bilirubin	137/344 (40)	89/320 (28)	12/25 (48)

AST = aspartate aminotransferase, ALT = alanine aminotransferase

付録 2.7.4-106　　臨床検査項目のベースライン値の CTC Grade から試験期間中の最も重い Grade への変動
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

		Worst CTC Grade During Treatment					
Risk Group	Baseline CTC Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	N/A
ALKALINE PHOSPHATASE							
BMT (n = 124)	Grade 0	26 (21)	19 (15)	2 (2)	1 (1)	0	4 (3)
	Grade 1	5 (4)	24 (19)	8 (6)	0	0	4 (3)
	Grade 2	1 (1)	3 (2)	6 (5)	10 (8)	0	2 (2)
	Grade 3	0	0	0	2 (2)	0	1 (1)
	Grade 4	0	0	0	0	0	0
	N/A	1 (1)	1 (1)	1 (1)	0	0	3 (2)
Non-BMT (n = 304)	Grade 0	103 (34)	52 (17)	5 (2)	2 (1)	0	11 (4)
	Grade 1	6 (2)	56 (18)	7 (2)	2 (1)	0	4 (1)
	Grade 2	0	4 (1)	10 (3)	1 (<1)	0	4 (1)
	Grade 3	0	0	3 (1)	4 (1)	0	0
	Grade 4	0	0	0	0	0	0
	N/A	10 (3)	13 (4)	1 (<1)	2 (1)	0	4 (1)
Overall (n = 428)	Grade 0	129 (30)	71 (17)	7 (2)	3 (1)	0	15 (4)
	Grade 1	11 (3)	80 (19)	15 (4)	2 (<1)	0	8 (2)
	Grade 2	1 (<1)	7 (2)	16 (4)	11 (3)	0	6 (1)
	Grade 3	0	0	3 (1)	6 (1)	0	1 (<1)
	Grade 4	0	0	0	0	0	0
	N/A	11 (3)	14 (3)	2 (<1)	2 (<1)	0	7 (2)
CREATININE							
BMT (n = 124)	Grade 0	37 (30)	13 (10)	8 (6)	0	0	4 (3)
	Grade 1	5 (4)	13 (10)	17 (14)	1 (1)	0	2 (2)
	Grade 2	4 (3)	3 (2)	11 (9)	2 (2)	0	2 (2)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	N/A	0	1 (1)	0	0	0	1 (1)
Non-BMT (n = 304)	Grade 0	167 (55)	21 (7)	9 (3)	0	0	13 (4)
	Grade 1	20 (7)	22 (7)	6 (2)	3 (1)	0	3 (1)
	Grade 2	5 (2)	2 (1)	9 (3)	1 (<1)	1 (<1)	2 (1)
	Grade 3	0	1 (<1)	2 (1)	1 (<1)	0	0
	Grade 4	0	0	0	0	0	0
	N/A	11 (4)	1 (<1)	2 (1)	0	0	2 (1)
Overall (n = 428)	Grade 0	204 (48)	34 (8)	17 (4)	0	0	17 (4)
	Grade 1	25 (6)	35 (8)	23 (5)	4 (1)	0	5 (1)
	Grade 2	9 (2)	5 (1)	20 (5)	3 (1)	1 (<1)	4 (1)
	Grade 3	0	1 (<1)	2 (<1)	1 (<1)	0	0
	Grade 4	0	0	0	0	0	0
	N/A	11 (3)	2 (<1)	2 (<1)	0	0	3 (1)
ASPARTATE AMINOTRANSFERASE (AST)							
BMT (n = 124)	Grade 0	30 (24)	22 (18)	4 (3)	2 (2)	0	7 (6)
	Grade 1	4 (3)	6 (5)	3 (2)	3 (2)	1 (1)	3 (2)
	Grade 2	1 (1)	1 (1)	2 (2)	0	0	1 (1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	N/A	14 (11)	6 (5)	0	0	0	14 (11)

		Worst CTC Grade During Treatment					
Risk Group	Baseline CTC Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	N/A
Non-BMT (n = 304)	Grade 0	106 (35)	61 (20)	9 (3)	4 (1)	0	11 (4)
	Grade 1	9 (3)	21 (7)	8 (3)	2 (1)	1 (<1)	1 (<1)
	Grade 2	0	3 (1)	2 (1)	2 (1)	0	2 (1)
	Grade 3	1 (<1)	3 (1)	0	0	1 (<1)	0
	Grade 4	0	0	0	0	0	0
	N/A	24 (8)	9 (3)	4 (1)	1 (<1)	0	19 (6)
Overall (n = 428)	Grade 0	136 (32)	83 (19)	13 (3)	6 (1)	0	18 (4)
	Grade 1	13 (3)	27 (6)	11 (3)	5 (1)	2 (<1)	4 (1)
	Grade 2	1 (<1)	4 (1)	4 (1)	2 (<1)	0	3 (1)
	Grade 3	1 (<1)	3 (1)	0	0	1 (<1)	0
	Grade 4	0	0	0	0	0	0
	N/A	38 (9)	15 (4)	4 (1)	1 (<1)	0	33 (8)
ALANINE AMINOTRANSFERASE (ALT)							
BMT (n = 124)	Grade 0	41 (33)	24 (19)	5 (4)	3 (2)	1 (1)	7 (6)
	Grade 1	6 (5)	7 (6)	5 (4)	3 (2)	0	4 (3)
	Grade 2	0	1 (1)	2 (2)	2 (2)	0	2 (2)
	Grade 3	1 (1)	0	0	1 (1)	0	1 (1)
	Grade 4	0	0	0	0	0	0
	N/A	5 (4)	2 (2)	0	0	0	1 (1)
Non-BMT (n = 304)	Grade 0	107 (35)	70 (23)	8 (3)	4 (1)	1 (<1)	12 (4)
	Grade 1	9 (3)	36 (12)	5 (2)	5 (2)	0	5 (2)
	Grade 2	2 (1)	2 (1)	4 (1)	2 (1)	0	2 (1)
	Grade 3	0	4 (1)	2 (1)	1 (<1)	0	0
	Grade 4	0	0	0	0	0	0
	N/A	13 (4)	5 (2)	1 (<1)	1 (<1)	0	3 (1)
Overall (n = 428)	Grade 0	148 (35)	94 (22)	13 (3)	7 (2)	2 (<1)	19 (4)
	Grade 1	15 (4)	43 (10)	10 (2)	8 (2)	0	9 (2)
	Grade 2	2 (<1)	3 (1)	6 (1)	4 (1)	0	4 (1)
	Grade 3	1 (<1)	4 (1)	2 (<1)	2 (<1)	0	1 (<1)
	Grade 4	0	0	0	0	0	0
	N/A	18 (4)	7 (2)	1 (<1)	1 (<1)	0	4 (1)
TOTAL BILIRUBIN							
BMT (n = 124)	Grade 0	43 (35)	10 (8)	14 (11)	1 (1)	1 (1)	5 (4)
	Grade 1	6 (5)	5 (4)	4 (3)	0	0	2 (2)
	Grade 2	1 (1)	4 (3)	3 (2)	4 (3)	1 (1)	2 (2)
	Grade 3	0	0	3 (2)	6 (5)	0	1 (1)
	Grade 4	0	0	0	0	2 (2)	1 (1)
	N/A	1 (1)	1 (1)	1 (1)	0	0	2 (2)
Non-BMT (n = 304)	Grade 0	159 (52)	29 (10)	16 (5)	3 (1)	0	9 (3)
	Grade 1	8 (3)	9 (3)	2 (1)	2 (1)	1 (<1)	2 (1)
	Grade 2	4 (1)	6 (2)	6 (2)	3 (1)	0	5 (2)
	Grade 3	0	0	3 (1)	7 (2)	0	3 (1)
	Grade 4	0	0	0	0	0	0
	N/A	21 (7)	0	2 (1)	0	1 (<1)	3 (1)
Overall (n = 428)	Grade 0	202 (47)	39 (9)	30 (7)	4 (1)	1 (<1)	14 (3)
	Grade 1	14 (3)	14 (3)	6 (1)	2 (<1)	1 (<1)	4 (1)
	Grade 2	5 (1)	10 (2)	9 (2)	7 (2)	1 (<1)	7 (2)
	Grade 3	0	0	6 (1)	13 (3)	0	4 (1)
	Grade 4	0	0	0	0	2 (<1)	1 (<1)
	N/A	22 (5)	1 (<1)	3 (1)	0	1 (<1)	5 (1)

		Worst CTC Grade During Treatment					
Risk Group	Baseline CTC Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	N/A
HEMATOCRIT							
BMT (n = 124)	Grade 0	0	0	0	0	0	0
	Grade 1	0	6 (5)	11 (9)	10 (8)	1 (1)	1 (1)
	Grade 2	0	4 (3)	35 (28)	22 (18)	3 (2)	5 (4)
	Grade 3	0	1 (1)	6 (5)	9 (7)	0	3 (2)
	Grade 4	0	0	2 (2)	0	0	0
	N/A	0	0	2 (2)	2 (2)	0	1 (1)
Non-BMT (n = 304)	Grade 0	13 (4)	10 (3)	1 (<1)	0	0	1 (<1)
	Grade 1	0	48 (16)	32 (11)	11 (4)	1 (<1)	3 (1)
	Grade 2	0	18 (6)	57 (19)	35 (12)	6 (2)	10 (3)
	Grade 3	0	1 (<1)	10 (3)	24 (8)	3 (1)	5 (2)
	Grade 4	0	0	0	1 (<1)	0	0
	N/A	2 (1)	2 (1)	5 (2)	2 (1)	1 (<1)	2 (1)
Overall (n = 428)	Grade 0	13 (3)	10 (2)	1 (<1)	0	0	1 (<1)
	Grade 1	0	54 (13)	43 (10)	21 (5)	2 (<1)	4 (1)
	Grade 2	0	22 (5)	92 (21)	57 (13)	9 (2)	15 (4)
	Grade 3	0	2 (<1)	16 (4)	33 (8)	3 (1)	8 (2)
	Grade 4	0	0	2 (<1)	1 (<1)	0	0
	N/A	2 (<1)	2 (<1)	7 (2)	4 (1)	1 (<1)	3 (1)
HEMOGLOBIN							
BMT (n = 124)	Grade 0	1 (1)	2 (2)	2 (2)	0	0	0
	Grade 1	0	5 (4)	17 (14)	8 (6)	1 (1)	1 (1)
	Grade 2	0	5 (4)	35 (28)	21 (17)	3 (2)	6 (5)
	Grade 3	0	2 (2)	1 (1)	5 (4)	0	2 (2)
	Grade 4	0	0	2 (2)	0	0	0
	N/A	0	0	3 (2)	1 (1)	0	1 (1)
Non-BMT (n = 304)	Grade 0	17 (6)	17 (6)	3 (1)	0	0	1 (<1)
	Grade 1	2 (1)	33 (11)	38 (13)	13 (4)	3 (1)	4 (1)
	Grade 2	0	19 (6)	61 (20)	32 (11)	5 (2)	13 (4)
	Grade 3	0	1 (<1)	9 (3)	16 (5)	2 (1)	1 (<1)
	Grade 4	0	0	0	1 (<1)	0	0
	N/A	1 (<1)	2 (1)	6 (2)	1 (<1)	1 (<1)	2 (1)
Overall (n = 428)	Grade 0	18 (4)	19 (4)	5 (1)	0	0	1 (<1)
	Grade 1	2 (<1)	38 (9)	55 (13)	21 (5)	4 (1)	5 (1)
	Grade 2	0	24 (6)	96 (22)	53 (12)	8 (2)	19 (4)
	Grade 3	0	3 (1)	10 (2)	21 (5)	2 (<1)	3 (1)
	Grade 4	0	0	2 (<1)	1 (<1)	0	0
	N/A	1 (<1)	2 (<1)	9 (2)	2 (<1)	1 (<1)	3 (1)
NEUTROPHILS							
BMT (n = 124)	Grade 0	32 (26)	11 (9)	11 (9)	4 (3)	6 (5)	5 (4)
	Grade 1	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	0
	Grade 2	0	0	2 (2)	1 (1)	0	0
	Grade 3	4 (3)	1 (1)	1 (1)	7 (6)	2 (2)	2 (2)
	Grade 4	3 (2)	1 (1)	2 (2)	3 (2)	4 (3)	2 (2)
	N/A	3 (2)	2 (2)	1 (1)	4 (3)	2 (2)	3 (2)
Non-BMT (n = 304)	Grade 0	103 (34)	23 (8)	14 (5)	10 (3)	11 (4)	9 (3)
	Grade 1	3 (1)	4 (1)	4 (1)	0	0	0
	Grade 2	1 (<1)	2 (1)	4 (1)	1 (<1)	4 (1)	1 (<1)
	Grade 3	2 (1)	0	0	2 (1)	7 (2)	1 (<1)
	Grade 4	1 (<1)	0	0	5 (2)	49 (16)	8 (3)
	N/A	9 (3)	6 (2)	2 (1)	1 (<1)	9 (3)	8 (3)

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		Worst CTC Grade During Treatment					
Risk Group	Baseline CTC Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	N/A
Overall (n = 428)	Grade 0	135 (32)	34 (8)	25 (6)	14 (3)	17 (4)	14 (3)
	Grade 1	4 (1)	5 (1)	5 (1)	1 (<1)	1 (<1)	0
	Grade 2	1 (<1)	2 (<1)	6 (1)	2 (<1)	4 (1)	1 (<1)
	Grade 3	6 (1)	1 (<1)	1 (<1)	9 (2)	9 (2)	3 (1)
	Grade 4	4 (1)	1 (<1)	2 (<1)	8 (2)	53 (12)	10 (2)
	N/A	12 (3)	8 (2)	3 (1)	5 (1)	11 (3)	11 (3)
PLATELET COUNT							
BMT (n = 124)	Grade 0	5 (4)	2 (2)	0	2 (2)	0	0
	Grade 1	0	4 (3)	3 (2)	7 (6)	0	0
	Grade 2	1 (1)	5 (4)	6 (5)	11 (9)	4 (3)	3 (2)
	Grade 3	0	4 (3)	5 (4)	31 (25)	10 (8)	5 (4)
	Grade 4	0	0	0	4 (3)	5 (4)	1 (1)
	N/A	0	0	1 (1)	4 (3)	0	1 (1)
Non-BMT (n = 304)	Grade 0	103 (34)	23 (8)	4 (1)	5 (2)	2 (1)	5 (2)
	Grade 1	8 (3)	10 (3)	7 (2)	11 (4)	3 (1)	3 (1)
	Grade 2	1 (<1)	0	4 (1)	9 (3)	1 (<1)	1 (<1)
	Grade 3	1 (<1)	1 (<1)	3 (1)	43 (14)	14 (5)	8 (3)
	Grade 4	0	1 (<1)	0	8 (3)	9 (3)	2 (1)
	N/A	6 (2)	1 (<1)	0	4 (1)	1 (<1)	2 (1)
Overall (n = 428)	Grade 0	108 (25)	25 (6)	4 (1)	7 (2)	2 (<1)	5 (1)
	Grade 1	8 (2)	14 (3)	10 (2)	18 (4)	3 (1)	3 (1)
	Grade 2	2 (<1)	5 (1)	10 (2)	20 (5)	5 (1)	4 (1)
	Grade 3	1 (<1)	5 (1)	8 (2)	74 (17)	24 (6)	13 (3)
	Grade 4	0	1 (<1)	0	12 (3)	14 (3)	3 (1)
	N/A	6 (1)	1 (<1)	1 (<1)	8 (2)	1 (<1)	3 (1)
LEUKOCYTE COUNT							
BMT (n = 124)	Grade 0	27 (22)	6 (5)	13 (10)	11 (9)	2 (2)	3 (2)
	Grade 1	5 (4)	0	2 (2)	1 (1)	1 (1)	0
	Grade 2	2 (2)	0	3 (2)	0	0	1 (1)
	Grade 3	1 (1)	2 (2)	2 (2)	4 (3)	3 (2)	2 (2)
	Grade 4	6 (5)	1 (1)	4 (3)	5 (4)	9 (7)	3 (2)
	N/A	0	0	1 (1)	1 (1)	2 (2)	1 (1)
Non-BMT (n = 304)	Grade 0	96 (32)	22 (7)	15 (5)	6 (2)	9 (3)	8 (3)
	Grade 1	5 (2)	10 (3)	7 (2)	3 (1)	1 (<1)	1 (<1)
	Grade 2	1 (<1)	1 (<1)	9 (3)	3 (1)	4 (1)	1 (<1)
	Grade 3	0	2 (1)	3 (1)	6 (2)	7 (2)	3 (1)
	Grade 4	1 (<1)	0	5 (2)	11 (4)	44 (14)	6 (2)
	N/A	4 (1)	1 (<1)	2 (1)	0	5 (2)	2 (1)
Overall (n = 428)	Grade 0	123 (29)	28 (7)	28 (7)	17 (4)	11 (3)	11 (3)
	Grade 1	10 (2)	10 (2)	9 (2)	4 (1)	2 (<1)	1 (<1)
	Grade 2	3 (1)	1 (<1)	12 (3)	3 (1)	4 (1)	2 (<1)
	Grade 3	1 (<1)	4 (1)	5 (1)	10 (2)	10 (2)	5 (1)
	Grade 4	7 (2)	1 (<1)	9 (2)	16 (4)	53 (12)	9 (2)
	N/A	4 (1)	1 (<1)	3 (1)	1 (<1)	7 (2)	3 (1)

CTC = Common Toxicity Criteria, BMT = Bone Marrow Transplant, Overall = Overall rIFI Pool, rIFI = refractory Invasive Fungal Infection

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付録 2.7.4-107　　臨床検査項目のベースラインからの中央値の変動
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）

Risk Group	Interval	Observed Value		Change from Baseline	
		n	Med	n	Med
ALKALINE PHOSPHATASE (U/L)					
Overall (n = 428)	Baseline	392	123.5	*	*
	Month 1	390	147	361	13
	Month 2	212	117	194	-1.5
	Month 3	165	120	152	3
	Month 4	154	112	141	-3
	Month 5	136	104.5	127	-1
	Month 6	117	111	106	-5.5
	Month 7	68	106.5	62	-6
	Month 8	49	112	46	-9.7
	Month 9	39	115	34	-6
	Month 10	37	98	33	-16
	Month 11	30	98	26	-13.5
	Month 12	23	100	20	-5.5
	Month 13	17	102	16	-20
	Month 14	10	117	10	-18.5
	Month 15	10	116.5	10	-30.5
	Month 16	8	117.5	8	-11.5
	Month 17	6	118.5	6	-20
	>17 Month	4	165	4	-103
	EOT	391	125	362	0.5
CREATININE (umol/L)					
Overall (n = 428)	Baseline	410	97.2	*	*
	Month 1	398	97.2	383	3
	Month 2	215	97.2	206	-8.8
	Month 3	169	97.2	162	-6.2
	Month 4	157	97.2	151	0
	Month 5	137	102	132	0
	Month 6	119	97.2	113	0
	Month 7	71	97.2	69	0
	Month 8	53	88.4	51	0
	Month 9	38	96.6	36	0.9
	Month 10	37	88.4	35	0
	Month 11	31	89.3	29	0
	Month 12	24	95.6	22	7.1
	Month 13	16	88.4	14	0
	Month 14	9	97.2	8	-8.8
	Month 15	10	88.4	9	0
	Month 16	8	88.4	8	0
	Month 17	7	102	6	8.8
	>17 Month	4	178.3	4	13.3
	EOT	399	88.4	384	0

Risk Group	Interval	Observed Value		Change from Baseline	
		n	Med	n	Med
ASPARTATE AMINOTRANSFERASE (AST) (U/L)					
Overall (n = 428)	Baseline	337	25	*	*
	Month 1	360	32	310	6
	Month 2	199	28	172	2
	Month 3	157	28	137	3
	Month 4	150	28	129	2
	Month 5	124	27	114	2
	Month 6	110	24	95	2
	Month 7	67	25	59	-1
	Month 8	51	27	49	0
	Month 9	39	26	36	-4.5
	Month 10	37	22	35	-6
	Month 11	31	26	29	0
	Month 12	25	25	22	-4
	Month 13	16	23	16	-4
	Month 14	10	31	10	-10.5
	Month 15	9	26	9	-6
	Month 16	8	32	7	-8
	Month 17	5	35	5	-10
	>17 Month	3	24	3	-9
	EOT	370	27	312	4
ALANINE AMINOTRANSFERASE (ALT) (U/L)					
Overall (n = 428)	Baseline	397	28	*	*
	Month 1	388	38.5	361	6
	Month 2	213	29	201	0
	Month 3	166	30	156	2
	Month 4	158	27.5	148	2
	Month 5	135	30	129	2
	Month 6	118	26	109	2
	Month 7	70	26.5	66	3
	Month 8	52	25	51	1
	Month 9	39	23	37	-1
	Month 10	37	23	36	-5
	Month 11	31	27	29	-1
	Month 12	26	22.5	24	-3.5
	Month 13	17	22	17	-5
	Month 14	10	31.5	10	-17
	Month 15	10	31	10	-17.5
	Month 16	8	30.5	8	-10.5
	Month 17	6	48.5	6	-9
	>17 Month	4	53.5	4	6.5
	EOT	391	28	364	1

Risk Group	Interval	Observed Value		Change from Baseline	
		n	Med	n	Med
TOTAL BILIRUBIN (umol/L)					
Overall (n = 428)	Baseline	396	12	*	*
	Month 1	392	13.7	365	1.7
	Month 2	215	11.1	198	1.7
	Month 3	166	10.3	151	0
	Month 4	156	10.3	142	0.9
	Month 5	137	10.3	127	0
	Month 6	115	10.3	104	0
	Month 7	71	10.3	63	0
	Month 8	51	8.6	47	0
	Month 9	37	8.8	32	0
	Month 10	36	9.6	31	0
	Month 11	31	10.3	26	0.9
	Month 12	25	8.6	21	-1.7
	Month 13	17	12	16	0.9
	Month 14	10	7.4	10	0
	Month 15	10	6.8	10	-2.2
	Month 16	8	6.6	8	-3.4
	Month 17	6	7.4	6	0
	>17 Month	4	6	4	-8.6
	EOT	393	12	366	0
HEMATOCRIT (V/V)					
Overall (n = 428)	Baseline	409	0.28	*	*
	Month 1	396	0.269	381	-0.01
	Month 2	215	0.315	207	0.005
	Month 3	174	0.34	167	0.012
	Month 4	156	0.354	151	0.03
	Month 5	140	0.346	135	0.019
	Month 6	119	0.35	114	0.023
	Month 7	69	0.362	68	0.032
	Month 8	55	0.383	53	0.023
	Month 9	41	0.38	40	0.015
	Month 10	37	0.399	35	0.015
	Month 11	31	0.385	30	0.011
	Month 12	28	0.395	25	0.026
	Month 13	17	0.379	17	0.019
	Month 14	10	0.386	9	0.042
	Month 15	10	0.379	9	0.004
	Month 16	8	0.402	7	0.045
	Month 17	8	0.396	7	0.036
	>17 Month	5	0.38	4	0.022
	EOT	397	0.3	381	0.011

Risk Group	Interval	Observed Value		Change from Baseline	
		n	Med	n	Med
HEMOGLOBIN (g/L)					
Overall (n = 428)	Baseline	410	95	*	*
	Month 1	396	92	382	-4
	Month 2	215	105	208	0.5
	Month 3	175	114	169	4
	Month 4	156	119	152	9
	Month 5	140	117	135	7
	Month 6	119	117	114	6
	Month 7	69	122	68	8
	Month 8	55	127	54	8
	Month 9	41	125	40	5
	Month 10	37	133	35	5
	Month 11	31	126	30	5.5
	Month 12	28	132.5	25	9
	Month 13	17	126	17	5
	Month 14	10	126	9	13
	Month 15	10	127	9	5
	Month 16	8	134.5	7	16
	Month 17	8	135.5	7	19
	>17 Month	5	122	4	7
	EOT	397	102	382	3
NEUTROPHILS (10^9/L)					
Overall (n = 428)	Baseline	378	2.939	*	*
	Month 1	387	2.156	350	-0.348
	Month 2	215	3.06	197	-0.244
	Month 3	168	3.383	152	-0.682
	Month 4	151	3.13	137	-0.766
	Month 5	139	3.647	125	-0.366
	Month 6	118	3.292	106	-0.814
	Month 7	68	3.882	64	-0.145
	Month 8	55	3.666	51	-0.726
	Month 9	41	3.514	36	-0.358
	Month 10	37	3.635	32	-0.712
	Month 11	31	3.15	27	-1.278
	Month 12	27	4.209	21	-0.852
	Month 13	16	4.458	15	-0.98
	Month 14	9	3.227	8	-0.781
	Month 15	10	4.883	9	-1.19
	Month 16	7	5.18	6	0.739
	Month 17	7	6.138	6	1.207
	>17 Month	4	5.394	3	-3.153
	EOT	389	2.99	350	0

Risk Group	Interval	Observed Value		Change from Baseline	
		n	Med	n	Med
PLATELET COUNT (10^9/L)					
Overall (n = 428)	Baseline	408	76	*	*
	Month 1	395	66	379	-7
	Month 2	213	168	206	-7
	Month 3	175	181	169	-5
	Month 4	155	188	151	-12
	Month 5	139	182	134	-11.5
	Month 6	119	199	114	-11.5
	Month 7	67	199	66	-4.5
	Month 8	55	211	54	-27
	Month 9	41	248	40	-4.5
	Month 10	37	238	35	5
	Month 11	31	238	30	-24
	Month 12	28	257.5	25	-17
	Month 13	16	233.5	16	-36.5
	Month 14	10	228	9	-34
	Month 15	10	210	9	-40
	Month 16	8	171	7	-23
	Month 17	8	171	7	-14
	>17 Month	5	216	4	0
	EOT	397	95	380	2
LEUKOCYTE COUNT (10^9/L)					
Overall (n = 428)	Baseline	409	4.6	*	*
	Month 1	396	3.6	381	-0.4
	Month 2	215	5.24	208	-0.35
	Month 3	175	5.7	169	-0.6
	Month 4	156	5.45	152	-0.56
	Month 5	140	5.85	135	-0.4
	Month 6	119	5.74	114	-0.47
	Month 7	69	6.3	68	0
	Month 8	55	6.4	54	-1.11
	Month 9	41	6.3	40	-0.38
	Month 10	37	5.9	35	-1.2
	Month 11	31	5.4	30	-1.25
	Month 12	28	6.9	25	-0.6
	Month 13	17	6	17	-0.8
	Month 14	10	6.65	9	-1.4
	Month 15	10	6.3	9	-1.2
	Month 16	8	6.25	7	0.9
	Month 17	8	7.85	7	-0.3
	>17 Month	5	7.3	4	-3
	EOT	397	4.8	381	0.2
Overall = Overall rIFI Pool, rIFI = refractory Invasive Fungal Infection, EOT = End of Trial					

付録 2.7.4-108　　肝機能関連の臨床検査項目のベースライン値の CTC Grade から
試験期間中の最も重い Grade への変動
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ポサコナゾール群（ASaT）

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Liver Function Tests
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Aspartate aminotransferase increased (IU/L)	0	25 (32.5)	38 (49.4)	5 (6.5)	2 (2.6)	0	1 (1.3)
	1	0	4 (5.2)	1 (1.3)	0	0	0
	2	0	1 (1.3)	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Alanine aminotransferase increased (IU/L)	0	41 (53.2)	26 (33.8)	2 (2.6)	4 (5.2)	0	1 (1.3)
	1	0	2 (2.6)	0	0	0	0
	2	0	0	0	1 (1.3)	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Alkaline phosphatase increased (IU/L)	0	38 (49.4)	25 (32.5)	0	0	0	1 (1.3)
	1	0	12 (15.6)	1 (1.3)	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Blood bilirubin increased (mg/dL)	0	63 (81.8)	7 (9.1)	1 (1.3)	1 (1.3)	0	1 (1.3)
	1	1 (1.3)	1 (1.3)	2 (2.6)	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0

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Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Liver Function Tests in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Blood bilirubin increased (mg/dL)	Missing	0	0	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Source:　[P101MK5592: adam-adsl; adlb]

C Confidential

付録 2.7.4-109　　肝機能関連の臨床検査項目のベースライン値の CTC Grade から
試験期間中の最も重い Grade への変動
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ボリコナゾール群（ASaT）

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Liver Function Tests
in Voriconazole Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Aspartate aminotransferase increased (IU/L)	0	16 (42.1)	16 (42.1)	3 (7.9)	0	0	1 (2.6)
	1	0	0	2 (5.3)	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Alanine aminotransferase increased (IU/L)	0	26 (68.4)	9 (23.7)	0	0	0	1 (2.6)
	1	0	1 (2.6)	1 (2.6)	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Alkaline phosphatase increased (IU/L)	0	17 (44.7)	16 (42.1)	2 (5.3)	0	0	1 (2.6)
	1	0	2 (5.3)	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Blood bilirubin increased (mg/dL)	0	35 (92.1)	1 (2.6)	0	0	0	1 (2.6)
	1	0	1 (2.6)	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0

C Confidential

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Liver Function Tests in Voriconazole Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Blood bilirubin increased (mg/dL)	Missing	0	0	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Source:　[P101MK5592: adam-adsl; adlb]

Confidential

付録 2.7.4-110　　代謝機能関連の臨床検査項目のベースライン値の CTC Grade から
試験期間中の最も重い Grade への変動
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ポサコナゾール群（ASaT）

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Electrolytes
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Hyperkalemia (mmol/L)	0	70 (90.9)	4 (5.2)	0	0	0	1 (1.3)
	1	2 (2.6)	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hypokalemia (mmol/L)	0	28 (36.4)	34 (44.2)	0	6 (7.8)	2 (2.6)	1 (1.3)
	1	0	2 (2.6)	0	1 (1.3)	2 (2.6)	0
	2	0	0	0	0	0	0
	3	0	0	0	1 (1.3)	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hypernatremia (mmol/L)	0	74 (96.1)	2 (2.6)	0	0	0	1 (1.3)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hyponatremia (mmol/L)	0	36 (46.8)	12 (15.6)	0	0	0	1 (1.3)
	1	2 (2.6)	25 (32.5)	0	1 (1.3)	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0

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Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Electrolytes in MK-5592 Treatment Group Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Hyponatremia (mmol/L)	Missing	0	0	0	0	0	0
CTC=Common Terminology Criteria CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).							

Source:　[P101MK5592: adam-adsl; adlb]

Confidential

付録 2.7.4-111　　代謝機能関連の臨床検査項目のベースライン値の CTC Grade から
試験期間中の最も重い Grade への変動
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ボリコナゾール群（ASaT）

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Electrolytes
in Voriconazole Treatment Group
Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Hyperkalemia (mmol/L)	0	22 (57.9)	11 (28.9)	2 (5.3)	1 (2.6)	0	1 (2.6)
	1	0	1 (2.6)	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hypokalemia (mmol/L)	0	33 (86.8)	2 (5.3)	0	1 (2.6)	0	1 (2.6)
	1	0	1 (2.6)	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hypernatremia (mmol/L)	0	36 (94.7)	1 (2.6)	0	0	0	1 (2.6)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Hyponatremia (mmol/L)	0	19 (50.0)	5 (13.2)	0	0	0	1 (2.6)
	1	1 (2.6)	12 (31.6)	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0

C Confidential

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Selected Electrolytes in Voriconazole Treatment Group Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Hyponatremia (mmol/L)	Missing	0	0	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Source:　[P101MK5592: adam-adsl; adlb]

Confidential

付録 2.7.4-112　　腎機能関連の臨床検査項目のベースライン値の CTC Grade から試験期間中の最も重い Grade への変動

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）

ポサコナゾール群（ASaT）

Summary of Laboratory CTC Grade Changes from Baseline to Worst in Creatinine in MK-5592 Treatment Group Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine increased (mg/dL)	0	61 (79.2)	8 (10.4)	0	0	0	1 (1.3)
	1	0	5 (6.5)	0	0	0	0
	2	0	0	2 (2.6)	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Source:　[P101MK5592: adam-adsl; adlb]

C Confidential

付録 2.7.4-113　　腎機能関連の臨床検査項目のベースライン値の CTC Grade から試験期間中の最も重い Grade への変動
ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）
ボリコナゾール群（ASaT）
Summary of Laboratory CTC Grade Changes from Baseline to Worst in Creatinine in Voriconazole Treatment Group Cohort 1 and 2 (ASaT)

Laboratory Test	Baseline CTC Grade	Worst CTC Grade During Treatment Number (%) of Subjects					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine increased (mg/dL)	0	27 (71.1)	6 (15.8)	1 (2.6)	0	0	1 (2.6)
	1	0	1 (2.6)	1 (2.6)	0	0	0
	2	0	1 (2.6)	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

CTC=Common Terminology Criteria
CTC Grade based on: Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Source:　[P101MK5592: adam-adsl; adlb]

C Confidential

付録 2.7.4-114　　血圧変動の要約

健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験

（P02489、P02810、P02811、P02812 及び P02862 試験）

Mean (SD) Systolic Blood Pressure - mm Hg					
Study	Screening	Postdose	Difference	Min	Max
Placebo (n=17)	123 (14.5)	117 (20)	-6 (15)	-34	28
P02489 (n=12)	113 (5.7)	116 (7.3)	2.3 (7.3)	-8	16
P02810 (n=53)	122 (15.8)	120 (16.6)	-2.2 (16.7)	-40	40
P02811 (n=56)	130 (8.0)	130 (8.7)	0 (12)	-25	25
P02812 (n=23)	112 (9.5)	107 (8.1)	-5 (10)	-22	14
P02862 (n=35)	115 (11.5)	107 (8.9)	-8 (9.7)	-30	10
Mean (SD) Diastolic Blood Pressure - mm Hg					
Study	Screening	Postdose	Difference	Min	Max
Placebo (n=17)	78 (10.3)	73 (8.3)	-5 (9.8)	-28	10
P02489 (n=12)	77 (5.9)	77 (7.7)	0 (10.2)	-14	16
P02810 (n=53)	79 (10.3)	73 (10.8)	-6 (11.3)	-32	22
P02811 (n=56)	78 (6.0)	75 (7.1)	-3 (7.8)	-15	18
P02812 (n=23)	74 (6.7)	71 (6.1)	-3 (8.1)	-24	12
P02862 (n=35)	73 (9.9)	70 (7.8)	-3 (9.6)	-22	20
Postdose - a single value at least 5 days after POS administration (steady state).					

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付録 2.7.4-115　　体重変動の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Weight (kg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Weight (kg)								
Day 3	MK-5592	71	54.493 (7.985)	[32.900, 71.200]	54.542 (7.958)	[33.100, 71.100]	0.049 (0.952)	[-2.100, 3.100]
	Voriconazole	35	55.134 (12.138)	[34.500, 99.000]	54.294 (11.334)	[34.600, 91.400]	-0.840 (1.348)	[-7.600, 0.300]
Day 8	MK-5592	69	54.232 (8.071)	[33.900, 71.200]	54.502 (7.873)	[34.000, 71.500]	0.270 (1.443)	[-3.200, 4.600]
	Voriconazole	36	54.672 (12.389)	[34.200, 99.000]	53.678 (11.048)	[33.900, 86.000]	-0.994 (2.309)	[-13.000, 1.300]
Day 14	MK-5592	60	54.907 (7.945)	[40.200, 71.200]	55.564 (7.789)	[43.500, 74.000]	0.658 (1.781)	[-4.000, 4.600]
	Voriconazole	36	54.672 (12.389)	[34.200, 99.000]	54.078 (11.122)	[34.500, 82.200]	-0.594 (2.998)	[-16.800, 2.200]
Day 21	MK-5592	50	55.290 (7.310)	[45.600, 69.800]	55.938 (7.167)	[44.800, 70.000]	0.648 (1.775)	[-3.200, 5.600]
	Voriconazole	33	55.242 (12.795)	[34.200, 99.000]	54.900 (11.116)	[34.400, 79.200]	-0.342 (3.732)	[-19.800, 2.800]
Day 28	MK-5592	51	55.249 (7.242)	[45.600, 69.800]	55.387 (7.091)	[44.600, 70.200]	0.138 (1.689)	[-4.000, 3.700]
	Voriconazole	33	55.242 (12.795)	[34.200, 99.000]	54.761 (10.953)	[34.200, 77.600]	-0.482 (4.020)	[-21.400, 3.800]
Day 35	MK-5592	48	55.367 (7.206)	[45.600, 69.800]	55.329 (7.037)	[43.900, 70.300]	-0.037 (1.779)	[-5.000, 4.900]
	Voriconazole	33	55.242 (12.795)	[34.200, 99.000]	54.564 (10.680)	[34.200, 75.500]	-0.679 (4.721)	[-24.900, 5.600]

C Confidential

Mean Change (SD) in Weight (kg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Weight (kg) (Continues)								
Day 42	MK-5592	46	55.726 (7.145)	[45.600, 69.800]	55.470 (6.939)	[44.600, 70.200]	-0.257 (2.226)	[-5.600, 5.300]
	Voriconazole	33	55.242 (12.795)	[34.200, 99.000]	54.594 (10.696)	[34.000, 75.100]	-0.648 (4.874)	[-26.000, 4.700]
Day 56	MK-5592	43	55.784 (7.391)	[45.600, 69.800]	55.493 (7.211)	[44.400, 72.100]	-0.291 (2.443)	[-5.700, 5.600]
	Voriconazole	32	55.469 (12.932)	[34.200, 99.000]	55.044 (10.536)	[34.100, 75.200]	-0.425 (5.345)	[-27.600, 5.700]
Day 70	MK-5592	41	55.641 (7.251)	[45.600, 69.800]	54.895 (6.974)	[44.800, 69.500]	-0.746 (2.304)	[-5.400, 5.000]
	Voriconazole	31	55.419 (13.143)	[34.200, 99.000]	54.923 (10.914)	[33.900, 75.300]	-0.497 (5.529)	[-28.100, 6.200]
Day 84	MK-5592	23	56.722 (8.006)	[45.600, 69.800]	55.426 (7.784)	[43.800, 68.400]	-1.296 (2.709)	[-5.800, 5.800]
	Voriconazole	13	49.700 (10.241)	[34.200, 65.000]	50.008 (10.115)	[34.000, 65.500]	0.308 (1.833)	[-4.000, 2.200]
Post-Treatment	MK-5592	70	52.920 (8.297)	[31.400, 68.500]	51.769 (7.737)	[30.800, 65.100]	-1.151 (2.402)	[-6.200, 6.200]
	Voriconazole	36	54.169 (11.664)	[34.200, 99.000]	53.994 (9.877)	[35.400, 76.500]	-0.175 (5.317)	[-27.500, 9.700]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

Confidential

付録 2.7.4-116　　血圧変動（拡張期血圧）の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Diastolic Blood Pressure (mmHg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Diastolic Blood Pressure (mmHg)								
Day 3	MK-5592	71	70.8 (13.5)	[33.0, 106.0]	69.0 (11.6)	[43.0, 108.0]	-1.8 (10.0)	[-29.0, 20.0]
	Voriconazole	36	69.3 (10.0)	[49.0, 86.0]	70.0 (11.8)	[48.0, 93.0]	0.7 (12.1)	[-19.0, 24.0]
Day 8	MK-5592	69	70.9 (13.3)	[33.0, 106.0]	69.3 (11.0)	[46.0, 98.0]	-1.6 (11.4)	[-29.0, 27.0]
	Voriconazole	36	68.9 (10.3)	[49.0, 86.0]	69.6 (10.7)	[54.0, 102.0]	0.7 (10.7)	[-22.0, 27.0]
Day 14	MK-5592	61	70.6 (13.7)	[33.0, 106.0]	73.9 (12.8)	[49.0, 100.0]	3.3 (15.2)	[-24.0, 50.0]
	Voriconazole	36	68.9 (10.3)	[49.0, 86.0]	72.9 (11.0)	[50.0, 98.0]	4.0 (11.8)	[-22.0, 23.0]
Day 21	MK-5592	50	70.6 (14.6)	[33.0, 106.0]	75.8 (11.6)	[51.0, 99.0]	5.3 (16.4)	[-26.0, 49.0]
	Voriconazole	33	69.6 (10.2)	[49.0, 86.0]	72.7 (9.7)	[53.0, 93.0]	3.2 (10.7)	[-15.0, 26.0]
Day 28	MK-5592	51	70.5 (14.4)	[33.0, 106.0]	75.3 (12.3)	[44.0, 101.0]	4.7 (15.0)	[-26.0, 33.0]
	Voriconazole	33	69.6 (10.2)	[49.0, 86.0]	72.1 (9.4)	[54.0, 91.0]	2.5 (12.5)	[-21.0, 31.0]
Day 35	MK-5592	48	70.9 (14.7)	[33.0, 106.0]	76.9 (12.1)	[48.0, 112.0]	6.0 (13.0)	[-20.0, 30.0]
	Voriconazole	33	69.6 (10.2)	[49.0, 86.0]	73.4 (10.6)	[57.0, 93.0]	3.8 (12.9)	[-23.0, 28.0]

C Confidential

Mean Change (SD) in Diastolic Blood Pressure (mmHg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Diastolic Blood Pressure (mmHg) (Continues)								
Day 42	MK-5592	46	71.3 (14.9)	[33.0, 106.0]	78.4 (11.2)	[51.0, 105.0]	7.2 (13.9)	[-17.0, 32.0]
	Voriconazole	33	69.6 (10.2)	[49.0, 86.0]	70.2 (9.5)	[47.0, 89.0]	0.6 (14.2)	[-39.0, 27.0]
Day 56	MK-5592	43	71.4 (15.3)	[33.0, 106.0]	79.0 (12.2)	[54.0, 108.0]	7.5 (16.0)	[-33.0, 36.0]
	Voriconazole	32	69.7 (10.4)	[49.0, 86.0]	74.8 (8.4)	[60.0, 92.0]	5.1 (12.0)	[-17.0, 23.0]
Day 70	MK-5592	41	72.4 (14.5)	[45.0, 106.0]	77.1 (10.9)	[53.0, 97.0]	4.7 (16.3)	[-35.0, 39.0]
	Voriconazole	31	70.0 (10.4)	[49.0, 86.0]	71.6 (12.6)	[45.0, 91.0]	1.6 (14.3)	[-35.0, 22.0]
Day 84	MK-5592	23	74.0 (14.2)	[47.0, 103.0]	81.9 (9.1)	[66.0, 101.0]	7.9 (14.4)	[-18.0, 35.0]
	Voriconazole	13	67.5 (10.5)	[55.0, 86.0]	75.2 (10.0)	[60.0, 97.0]	7.8 (15.3)	[-13.0, 42.0]
Post-Treatment	MK-5592	75	70.4 (13.2)	[33.0, 106.0]	72.3 (13.5)	[42.0, 113.0]	2.0 (14.7)	[-26.0, 43.0]
	Voriconazole	37	68.6 (10.1)	[49.0, 86.0]	74.5 (10.5)	[54.0, 93.0]	5.9 (12.5)	[-18.0, 31.0]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

C Confidential

付録 2.7.4-117　　血圧変動（収縮期血圧）の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Systolic Blood Pressure (mmHg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Systolic Blood Pressure (mmHg)								
Day 3	MK-5592	71	120.4 (15.1)	[86.0, 160.0]	120.5 (16.6)	[84.0, 163.0]	0.2 (13.9)	[-38.0, 47.0]
	Voriconazole	36	117.8 (19.0)	[82.0, 161.0]	117.5 (21.7)	[78.0, 189.0]	-0.3 (18.4)	[-43.0, 51.0]
Day 8	MK-5592	69	120.6 (13.8)	[87.0, 160.0]	123.6 (14.6)	[93.0, 161.0]	3.1 (14.9)	[-36.0, 56.0]
	Voriconazole	36	116.4 (18.7)	[82.0, 161.0]	115.6 (15.9)	[82.0, 160.0]	-0.8 (18.5)	[-50.0, 46.0]
Day 14	MK-5592	61	119.7 (14.2)	[87.0, 160.0]	127.1 (18.5)	[85.0, 177.0]	7.4 (19.0)	[-41.0, 61.0]
	Voriconazole	36	116.4 (18.7)	[82.0, 161.0]	120.0 (14.6)	[84.0, 143.0]	3.6 (14.6)	[-26.0, 34.0]
Day 21	MK-5592	50	120.4 (15.0)	[87.0, 160.0]	132.4 (18.6)	[98.0, 186.0]	11.9 (21.9)	[-30.0, 72.0]
	Voriconazole	33	117.1 (19.4)	[82.0, 161.0]	118.8 (14.8)	[84.0, 148.0]	1.7 (15.7)	[-24.0, 38.0]
Day 28	MK-5592	51	120.4 (14.9)	[87.0, 160.0]	131.6 (21.5)	[84.0, 172.0]	11.2 (21.6)	[-36.0, 77.0]
	Voriconazole	33	117.1 (19.4)	[82.0, 161.0]	117.1 (13.8)	[88.0, 139.0]	0.0 (18.5)	[-33.0, 38.0]
Day 35	MK-5592	48	120.0 (14.7)	[87.0, 160.0]	135.2 (20.0)	[90.0, 176.0]	15.2 (19.6)	[-30.0, 64.0]
	Voriconazole	33	117.1 (19.4)	[82.0, 161.0]	120.2 (16.9)	[85.0, 162.0]	3.1 (18.5)	[-30.0, 42.0]

C Confidential

Mean Change (SD) in Systolic Blood Pressure (mmHg) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Systolic Blood Pressure (mmHg) (Continues)								
Day 42	MK-5592	46	120.8 (14.4)	[87.0, 160.0]	137.4 (21.5)	[89.0, 188.0]	16.6 (22.0)	[-30.0, 64.0]
	Voriconazole	33	117.1 (19.4)	[82.0, 161.0]	118.5 (14.7)	[92.0, 149.0]	1.4 (19.4)	[-39.0, 57.0]
Day 56	MK-5592	43	120.5 (14.8)	[87.0, 160.0]	135.9 (20.1)	[98.0, 185.0]	15.3 (21.7)	[-28.0, 65.0]
	Voriconazole	32	116.7 (19.6)	[82.0, 161.0]	121.0 (15.1)	[89.0, 158.0]	4.3 (20.8)	[-38.0, 46.0]
Day 70	MK-5592	41	121.7 (14.0)	[94.0, 160.0]	131.5 (18.3)	[87.0, 175.0]	9.9 (21.2)	[-40.0, 55.0]
	Voriconazole	31	116.1 (19.6)	[82.0, 161.0]	116.6 (15.5)	[85.0, 140.0]	0.5 (21.0)	[-42.0, 40.0]
Day 84	MK-5592	23	122.3 (12.6)	[97.0, 141.0]	138.7 (17.5)	[107.0, 164.0]	16.4 (19.4)	[-27.0, 38.0]
	Voriconazole	13	110.2 (19.3)	[82.0, 146.0]	112.8 (12.6)	[89.0, 128.0]	2.6 (17.5)	[-30.0, 25.0]
Post-Treatment	MK-5592	75	120.0 (14.8)	[86.0, 160.0]	126.1 (18.7)	[83.0, 174.0]	6.1 (22.4)	[-52.0, 87.0]
	Voriconazole	37	116.9 (19.0)	[82.0, 161.0]	123.6 (16.6)	[91.0, 152.0]	6.7 (20.9)	[-49.0, 46.0]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

Confidential

付録 2.7.4-118　　心拍数の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Pulse Rate (beats/min) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Pulse Rate (beats/min)								
Day 3	MK-5592	71	79.6 (14.1)	[50.0, 113.0]	78.2 (12.0)	[52.0, 110.0]	-1.4 (12.3)	[-37.0, 28.0]
	Voriconazole	36	82.6 (14.8)	[52.0, 122.0]	81.4 (14.0)	[54.0, 107.0]	-1.2 (15.3)	[-31.0, 53.0]
Day 8	MK-5592	69	79.3 (14.0)	[50.0, 113.0]	74.3 (11.2)	[53.0, 98.0]	-5.0 (11.9)	[-47.0, 25.0]
	Voriconazole	36	82.5 (14.9)	[52.0, 122.0]	81.1 (13.8)	[51.0, 107.0]	-1.4 (11.4)	[-22.0, 26.0]
Day 14	MK-5592	61	80.0 (13.8)	[50.0, 113.0]	75.1 (12.2)	[49.0, 108.0]	-4.8 (12.7)	[-37.0, 39.0]
	Voriconazole	36	82.5 (14.9)	[52.0, 122.0]	83.8 (14.1)	[49.0, 108.0]	1.3 (15.4)	[-26.0, 32.0]
Day 21	MK-5592	50	79.9 (14.6)	[50.0, 113.0]	76.5 (12.5)	[55.0, 111.0]	-3.3 (14.0)	[-34.0, 26.0]
	Voriconazole	33	81.9 (15.2)	[52.0, 122.0]	84.0 (14.3)	[57.0, 112.0]	2.1 (13.3)	[-26.0, 28.0]
Day 28	MK-5592	51	79.8 (14.5)	[50.0, 113.0]	76.6 (13.4)	[54.0, 108.0]	-3.2 (13.1)	[-49.0, 30.0]
	Voriconazole	33	81.9 (15.2)	[52.0, 122.0]	83.1 (13.6)	[51.0, 111.0]	1.2 (12.6)	[-25.0, 32.0]
Day 35	MK-5592	48	79.2 (14.1)	[50.0, 113.0]	77.2 (14.4)	[53.0, 115.0]	-2.0 (13.2)	[-50.0, 35.0]
	Voriconazole	33	81.9 (15.2)	[52.0, 122.0]	83.1 (13.4)	[50.0, 106.0]	1.2 (14.3)	[-36.0, 35.0]

C Confidential

Mean Change (SD) in Pulse Rate (beats/min) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Pulse Rate (beats/min) (Continues)								
Day 42	MK-5592	46	79.7 (14.1)	[50.0, 113.0]	78.8 (16.1)	[54.0, 123.0]	-0.9 (15.0)	[-42.0, 44.0]
	Voriconazole	33	81.9 (15.2)	[52.0, 122.0]	79.5 (15.4)	[50.0, 107.0]	-2.5 (16.7)	[-32.0, 34.0]
Day 56	MK-5592	43	79.9 (14.4)	[50.0, 113.0]	79.0 (15.5)	[56.0, 117.0]	-0.9 (13.6)	[-31.0, 32.0]
	Voriconazole	32	81.9 (15.4)	[52.0, 122.0]	80.0 (13.9)	[51.0, 109.0]	-1.9 (14.6)	[-40.0, 29.0]
Day 70	MK-5592	41	79.8 (14.1)	[50.0, 113.0]	78.5 (13.5)	[59.0, 109.0]	-1.3 (14.5)	[-33.0, 25.0]
	Voriconazole	31	81.6 (15.6)	[52.0, 122.0]	82.6 (14.9)	[51.0, 115.0]	1.0 (15.7)	[-27.0, 32.0]
Day 84	MK-5592	23	78.5 (15.5)	[50.0, 113.0]	77.3 (14.4)	[53.0, 104.0]	-1.2 (13.9)	[-23.0, 25.0]
	Voriconazole	13	80.1 (16.9)	[54.0, 122.0]	82.1 (14.3)	[58.0, 102.0]	2.0 (15.3)	[-27.0, 31.0]
Post-Treatment	MK-5592	75	79.5 (14.3)	[50.0, 113.0]	83.0 (15.4)	[54.0, 123.0]	3.5 (14.6)	[-33.0, 34.0]
	Voriconazole	37	82.3 (14.6)	[52.0, 122.0]	81.8 (14.7)	[51.0, 117.0]	-0.5 (14.0)	[-40.0, 25.0]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

Confidential

付録 2.7.4-119　　体温の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Temperature (C) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Temperature (C)								
Day 3	MK-5592	74	37.04 (0.77)	[35.70, 39.80]	37.12 (0.64)	[35.50, 38.70]	0.09 (0.65)	[-2.00, 1.70]
	Voriconazole	37	36.78 (0.42)	[35.90, 37.80]	36.78 (0.47)	[35.80, 38.40]	-0.01 (0.47)	[-1.10, 1.00]
Day 8	MK-5592	71	37.00 (0.73)	[35.70, 39.80]	37.26 (0.68)	[36.10, 39.30]	0.27 (0.73)	[-1.60, 2.50]
	Voriconazole	36	36.81 (0.40)	[35.90, 37.80]	36.74 (0.48)	[35.90, 38.00]	-0.06 (0.41)	[-1.20, 0.90]
Day 14	MK-5592	62	37.00 (0.74)	[35.70, 39.80]	36.87 (0.68)	[35.10, 38.30]	-0.14 (0.73)	[-2.60, 1.20]
	Voriconazole	36	36.81 (0.40)	[35.90, 37.80]	36.62 (0.41)	[35.70, 37.50]	-0.18 (0.37)	[-1.10, 0.70]
Day 21	MK-5592	52	36.96 (0.73)	[35.70, 39.80]	36.88 (0.64)	[35.90, 39.00]	-0.07 (0.69)	[-1.80, 2.10]
	Voriconazole	33	36.76 (0.37)	[35.90, 37.50]	36.51 (0.46)	[35.70, 37.70]	-0.25 (0.51)	[-1.40, 0.60]
Day 28	MK-5592	51	36.96 (0.74)	[35.70, 39.80]	36.68 (0.59)	[35.70, 39.10]	-0.28 (0.83)	[-3.20, 2.70]
	Voriconazole	33	36.76 (0.37)	[35.90, 37.50]	36.55 (0.34)	[35.70, 37.30]	-0.20 (0.46)	[-1.10, 0.90]
Day 35	MK-5592	48	36.93 (0.74)	[35.70, 39.80]	36.65 (0.53)	[35.70, 38.40]	-0.28 (0.82)	[-2.30, 1.80]
	Voriconazole	33	36.76 (0.37)	[35.90, 37.50]	36.63 (0.36)	[35.90, 37.40]	-0.12 (0.50)	[-1.20, 1.00]

C Confidential

Mean Change (SD) in Temperature (C) from Baseline over Time
Cohort 1 and 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Temperature (C) (Continues)								
Day 42	MK-5592	46	36.87 (0.62)	[35.70, 38.90]	36.59 (0.51)	[35.70, 38.20]	-0.28 (0.73)	[-2.00, 1.50]
	Voriconazole	33	36.76 (0.37)	[35.90, 37.50]	36.56 (0.31)	[36.00, 37.20]	-0.19 (0.42)	[-1.10, 0.60]
Day 56	MK-5592	43	36.87 (0.64)	[35.70, 38.90]	36.60 (0.52)	[35.70, 38.30]	-0.27 (0.70)	[-2.00, 1.40]
	Voriconazole	32	36.76 (0.37)	[35.90, 37.50]	36.50 (0.40)	[35.20, 37.40]	-0.27 (0.44)	[-1.90, 0.40]
Day 70	MK-5592	41	36.82 (0.56)	[35.70, 38.00]	36.59 (0.55)	[35.60, 38.50]	-0.23 (0.62)	[-1.90, 1.00]
	Voriconazole	31	36.77 (0.37)	[35.90, 37.50]	36.45 (0.55)	[35.40, 38.10]	-0.32 (0.52)	[-1.60, 0.90]
Day 84	MK-5592	24	36.75 (0.47)	[36.00, 37.70]	36.58 (0.50)	[35.50, 37.90]	-0.18 (0.47)	[-1.10, 1.00]
	Voriconazole	14	36.82 (0.33)	[36.20, 37.50]	36.56 (0.50)	[35.80, 37.80]	-0.26 (0.55)	[-0.90, 1.20]
Post-Treatment	MK-5592	76	37.05 (0.78)	[35.70, 39.80]	36.80 (0.81)	[35.40, 40.40]	-0.25 (0.80)	[-3.40, 2.40]
	Voriconazole	37	36.79 (0.42)	[35.90, 37.80]	36.58 (0.54)	[35.50, 38.30]	-0.21 (0.56)	[-1.80, 1.20]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

Confidential

付録 2.7.4-120　　血中酸素濃度（SpO_2）の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Mean Change (SD) in Oxygen Saturation (%) from Baseline over Time
Cohort 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Oxygen Saturation (%)								
Day 3	MK-5592	62	96.9 (1.6)	[93.0, 100.0]	97.1 (1.6)	[93.0, 100.0]	0.3 (1.5)	[-4.0, 4.0]
	Voriconazole	30	97.1 (1.4)	[94.0, 100.0]	97.2 (1.4)	[94.0, 100.0]	0.1 (1.4)	[-3.0, 4.0]
Day 8	MK-5592	57	96.8 (1.6)	[93.0, 100.0]	96.9 (1.9)	[91.0, 100.0]	0.0 (1.8)	[-5.0, 5.0]
	Voriconazole	29	97.1 (1.4)	[94.0, 100.0]	97.4 (1.3)	[95.0, 100.0]	0.2 (1.6)	[-3.0, 3.0]
Day 14	MK-5592	52	96.8 (1.6)	[93.0, 100.0]	97.0 (2.0)	[88.0, 100.0]	0.3 (2.0)	[-8.0, 5.0]
	Voriconazole	29	97.1 (1.4)	[94.0, 100.0]	97.4 (1.7)	[91.0, 100.0]	0.3 (1.7)	[-5.0, 4.0]
Day 21	MK-5592	45	96.7 (1.6)	[93.0, 100.0]	96.8 (2.5)	[88.0, 100.0]	0.1 (2.1)	[-8.0, 4.0]
	Voriconazole	26	97.2 (1.5)	[94.0, 100.0]	97.6 (1.2)	[94.0, 99.0]	0.4 (1.9)	[-4.0, 5.0]
Day 28	MK-5592	46	96.8 (1.6)	[93.0, 100.0]	97.2 (1.9)	[91.0, 100.0]	0.4 (2.0)	[-4.0, 4.0]
	Voriconazole	26	97.2 (1.5)	[94.0, 100.0]	97.4 (0.9)	[96.0, 99.0]	0.2 (1.5)	[-2.0, 5.0]
Day 35	MK-5592	43	96.8 (1.7)	[93.0, 100.0]	97.4 (1.8)	[91.0, 100.0]	0.6 (1.9)	[-4.0, 5.0]
	Voriconazole	26	97.2 (1.5)	[94.0, 100.0]	97.5 (1.0)	[96.0, 100.0]	0.3 (1.4)	[-2.0, 4.0]

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Mean Change (SD) in Oxygen Saturation (%) from Baseline over Time
Cohort 2 (ASaT)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
Oxygen Saturation (%) (Continues)								
Day 42	MK-5592	40	96.8 (1.7)	[93.0, 100.0]	97.2 (1.8)	[91.0, 100.0]	0.4 (2.1)	[-6.0, 5.0]
	Voriconazole	26	97.2 (1.5)	[94.0, 100.0]	97.5 (1.3)	[94.0, 100.0]	0.3 (1.6)	[-3.0, 5.0]
Day 56	MK-5592	38	96.8 (1.7)	[93.0, 100.0]	97.3 (1.4)	[93.0, 100.0]	0.5 (1.8)	[-3.0, 5.0]
	Voriconazole	26	97.2 (1.5)	[94.0, 100.0]	97.7 (1.0)	[96.0, 100.0]	0.5 (1.8)	[-3.0, 5.0]
Day 70	MK-5592	36	96.9 (1.7)	[93.0, 100.0]	97.4 (1.5)	[92.0, 99.0]	0.5 (1.6)	[-3.0, 5.0]
	Voriconazole	25	97.2 (1.5)	[94.0, 100.0]	97.4 (1.1)	[95.0, 100.0]	0.2 (1.4)	[-2.0, 4.0]
Day 84	MK-5592	20	97.1 (1.8)	[93.0, 100.0]	97.5 (1.5)	[94.0, 99.0]	0.4 (1.8)	[-4.0, 3.0]
	Voriconazole	8	97.4 (1.2)	[96.0, 99.0]	97.1 (1.1)	[96.0, 99.0]	-0.3 (1.3)	[-2.0, 2.0]
Post-Treatment	MK-5592	60	96.8 (1.6)	[93.0, 100.0]	96.9 (2.5)	[87.0, 100.0]	0.0 (2.1)	[-6.0, 4.0]
	Voriconazole	30	97.1 (1.4)	[94.0, 100.0]	97.4 (1.2)	[94.0, 99.0]	0.3 (1.6)	[-2.0, 4.0]

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A baseline and treatment value are required for a subject to be counted at a time point.

SD=Standard deviation, Min=Minimum, Max=Maximum

Source:　[P101MK5592: adam-advs]

Confidential

付録 2.7.4-121　　事前に規定したバイタルサインの変動基準に合致した被験者の要約

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Vital Sign Findings That Met Predetermined Criteria
Cohort 1 and 2 (ASaT)

Test Name (Unit)	Criterion	MK-5592		Voriconazole	
		n/m	(%)	n/m	(%)
Subjects in population		77		38	
Weight (kg)	WEIGHT decrease ≥ 7 %	12/76	(15.8)	2/38	(5.3)
	WEIGHT increase ≥ 7 %	12/76	(15.8)	3/38	(7.9)
Diastolic Blood Pressure (mmHg)	DBP ≤ 50 mmHg and decrease ≥ 15 mmHg	7/77	(9.1)	4/38	(10.5)
	DBP ≥ 105 mmHg and increase ≥ 15 mmHg	3/77	(3.9)	0/38	(0.0)
Systolic Blood Pressure (mmHg)	SBP ≤ 90 mmHg and decrease ≥ 20 mmHg	5/77	(6.5)	2/38	(5.3)
	SBP ≥ 180 mmHg and increase ≥ 20 mmHg	4/77	(5.2)	1/38	(2.6)
Pulse Rate (beats/min)	PULSE ≤ 50 bpm and decrease ≥ 15 bpm	0/77	(0.0)	0/38	(0.0)
	PULSE ≥ 120 bpm and increase ≥ 15 bpm	1/77	(1.3)	0/38	(0.0)
Temperature (C)	TEMP ≥ 38.3 C and increase ≥ 1 C	36/77	(46.8)	4/38	(10.5)

n / m = Number of subjects in the population with valid predose and postdose values of the given parameter meeting the predefined limit criteria / Number of subjects in the population with valid predose and postdose values of the given parameter.

Source:　[MK5592PN101: adam-advs]

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付録 2.7.4-122　　QTcF 間隔のベースラインからの平均変化量の被験者分布
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02810 試験）（QTcF 間隔のベースライン値が正常†であった被験者）

		QTc (F) Change from Baseline							
		≤0 msec		0 to 30 msec		>30 to 60 msec		>60 msec	
Strata	Treatment	n	%	n	%	n	%	n	%
Young Males	POS	9	64.29	4	28.57	0	0.00	0	0.00
	Placebo	1	00.00	3	75.00	0	0.00	0	0.00
Young Females	POS	10	83.33	1	8.33	0	0.00	0	0.00
	Placebo	4	66.67	1	16.67	0	0.00	0	0.00
Elderly Males	POS	10	76.92	2	15.38	0	0.00	0	0.00
	Placebo	4	100.0	0	0.00	0	0.00	0	0.00
Elderly Females	POS	6	50.00	6	50.00	0	0.00	0	0.00
	Placebo	1	25.00	3	75.00	0	0.00	0	0.00

†Normal: Adult Males ≤430 msec, Adult Female ≤450 msec.
POS = posaconazole

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付録 2.7.4-123　　QTcF 間隔の最大変化量の要約統計量（投与後 24 時間）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02810 試験）

	QTc (Fridericia) (msec)							
	Young Males (18-45 yr)		Young Females (18-45 yr)		Elderly Males (≥ 65yr)		Elderly Females (≥ 65yr)	
	POS (n=13)	Placebo (n=3)	POS (n=11)	Placebo (n=5)	POS (n=12)	Placebo (n=4)	POS (n=12)	Placebo (n=4)
Mean	19.38	27.67	5.18	9.80	14.42	5.00	30.17	40.25
Median	16.00	25.00	3.00	9.00	13.50	4.50	33.00	36.50
Max	57.00	33.00	21.00	22.00	41.00	15.00	56.00	83.00
Min	-18.00	25.00	-10.00	2.00	-10.00	-4.00	2.00	5.00
POS = posaconazole								

付録 2.7.4-124　　QT 及び QTc 間隔の平均ベースラインからの最大変化量の被験者分布
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02810 試験）

P02810	Baseline†	Total	Change from Baseline (msec)	QT		QTc (B)		QTc (F)	
				N	%	N	%	N	%
PLACEBO	Normal	16	<-60	0	0.00	0	0.00	0	0.00
			-60 to <-30	0	0.00	0	0.00	0	0.00
			-30 to <0	5	31.25	2	12.50	3	18.75
			0 to <30	9	56.25	8	50.00	11	68.75
			30 to <60	1	6.25	5	31.25	1	6.25
			>=60	1	6.25	1	6.25	1	6.25
POS	Normal	47	<-60	0	0.00	0	0.00	0	0.00
			-60 to <-30	0	0.00	0	0.00	0	0.00
			-30 to <0	14	29.79	16	34.04	14	29.79
			0 to <30	28	59.57	24	51.06	29	61.70
			30 to <60	5	10.64	7	14.89	4	8.51
			>=60	0	0.00	0	0.00	0	0.00
POS	Borderline	1	<-60	0	0.00	0	0.00	0	0.00
			-60 to <-30	0	0.00	0	0.00	0	0.00
			-30 to <0	0	0.00	1	100.00	1	100.00
			0 to <30	1	100.00	0	0.00	0	0.00
			30 to <60	0	0.00	0	0.00	0	0.00
			>=60	0	0.00	0	0.00	0	0.00

†Baseline is the mean QTcF values over the 0-12 hour interval
Normal: Adult Males <=430 msec, Adult Females <=450 msec
Borderline: Adult Males 431-450 msec, Adult Females 451-470 msec
QTc (B) = Bazett , QTc (F) = Fridericia, POS = Posaconazole

付録 2.7.4-125　　QTcF 間隔のベースラインからの平均変化量の要約統計量（投与 8 日後）

健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験

（P02810 試験）（患者背景別）（All Treated Subjects）

Time Points / QTcF (msec)		SCH 56592 Male 18-45 Years Old (n=13)					SCH 56592 Female 18-45 Years Old (n=11)				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
0 Hours	Baseline Value	391.2	24.6	389.0	346	437	409.6	22.6	410.0	354	444
	Post-Baseline Value	384.5	17.1	384.0	358	413	393.7	21.8	394.0	347	423
	Change from Baseline	-6.7	20.5	-8.0	-37	36	-15.9	11.0	-16.0	-37	7
2 Hours	Baseline Value	383.3	20.4	382.0	349	417	407.6	18.5	415.0	364	430
	Post-Baseline Value	377.0	13.5	378.0	345	398	388.5	21.9	386.0	346	430
	Change from Baseline	-6.3	17.2	-5.0	-33	23	-19.2	11.4	-18.0	-37	3
4 Hours	Baseline Value	384.5	17.4	382.0	357	412	406.6	21.2	408.0	355	440
	Post-Baseline Value	375.2	18.2	373.0	347	415	382.5	15.4	382.0	352	405
	Change from Baseline	-9.2	15.0	-3.0	-41	11	-24.1	11.4	-27.0	-35	-3
5 Hours	Baseline Value	387.4	18.3	378.0	359	417	406.8	21.9	409.0	352	439
	Post-Baseline Value	382.9	15.5	386.0	365	411	389.9	20.7	396.0	355	418
	Change from Baseline	-4.5	15.8	-8.0	-35	31	-16.9	17.7	-16.0	-47	6
6 Hours	Baseline Value	378.5	22.5	375.0	341	434	408.1	17.7	409.0	364	435
	Post-Baseline Value	386.2	13.9	393.0	354	405	389.5	13.4	388.0	372	409
	Change from Baseline	7.7	20.4	8.0	-29	57	-18.5	19.6	-15.0	-43	14
12 Hours	Baseline Value	385.2	22.2	384.0	357	430	398.4	25.0	399.0	352	439
	Post-Baseline Value	383.4	12.5	384.0	364	401	390.6	22.0	390.0	356	427
	Change from Baseline	-1.8	15.2	1.0	-32	23	-7.7	15.0	-14.0	-27	21
24 Hours	Baseline Value	382.8	12.8	386.0	361	405	405.9	22.3	411.0	360	436
	Post-Baseline Value	382.5	14.9	379.0	358	405	395.9	17.9	396.0	374	435
	Change from Baseline	-0.4	21.9	7.0	-32	35	-10.0	20.4	-10.0	-43	16

Time Points / QTcF (msec)		SCH 56592 Male >= 65 Years Old (n=12)					SCH 56592 Female >= 65 Years Old (n=12)				
		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
0 Hours	Baseline Value	414.2	24.7	407.5	374	472	407.8	23.3	399.5	377	438
	Post-Baseline Value	403.2	22.1	402.5	374	438	412.6	13.4	415.5	390	436
	Change from Baseline	-11.0	23.3	-19.0	-38	32	4.8	24.6	-4.5	-31	45
2 Hours	Baseline Value	400.7	14.6	403.5	384	435	409.3	25.8	410.0	372	458
	Post-Baseline Value	399.9	20.5	395.0	374	435	410.7	13.7	412.0	390	433
	Change from Baseline	-0.8	16.6	-6.0	-15	41	1.4	21.7	3.5	-45	35
4 Hours	Baseline Value	402.7	20.2	403.5	375	438	415.3	29.9	412.0	376	487
	Post-Baseline Value	402.7	18.1	402.0	363	430	407.3	14.6	405.0	386	433
	Change from Baseline	0.0	18.4	0.0	-29	26	-8.0	27.4	-8.5	-80	29
5 Hours	Baseline Value	410.3	17.4	410.0	381	433	403.7	25.8	400.0	375	455
	Post-Baseline Value	399.5	22.2	398.0	365	435	420.3	16.2	417.0	396	450
	Change from Baseline	-10.8	16.3	-16.5	-34	16	16.6	25.7	21.5	-49	50
6 Hours	Baseline Value	414.1	15.6	418.0	379	432	409.0	24.2	411.0	372	446
	Post-Baseline Value	399.4	12.9	398.0	380	429	420.6	23.4	416.5	388	472
	Change from Baseline	-14.7	16.5	-19.5	-43	13	11.6	25.2	12.0	-28	56
12 Hours	Baseline Value	411.9	14.3	415.0	385	434	406.6	17.9	405.0	380	436
	Post-Baseline Value	393.4	25.9	390.0	348	439	389.1	36.0	387.5	300	442
	Change from Baseline	-18.5	26.0	-15.5	-82	29	-17.5	36.4	-12.0	-120	35
24 Hours	Baseline Value	404.3	20.8	406.5	368	434	415.4	26.2	417.0	373	459
	Post-Baseline Value	402.3	25.8	405.5	363	446	403.9	25.8	404.5	359	437
	Change from Baseline	-1.9	23.3	2.5	-46	33	-11.5	20.1	-5.5	-50	13

		Placebo Male 18-45 Years Old (n=3)					Placebo Female 18-45 Years Old (n=5)				
Time Points / QTcF (msec)		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
0 Hours	Baseline Value	376.7	15.3	385.0	359	386	414.8	14.0	420.0	400	430
	Post-Baseline Value	383.7	25.0	383.0	359	409	391.2	24.0	402.0	358	413
	Change from Baseline	7.0	14.8	0.0	-3	24	-23.6	11.7	-22.0	-42	-11
2 Hours	Baseline Value	357.0	3.0	357.0	354	360	402.2	16.2	403.0	381	425
	Post-Baseline Value	362.0	14.8	355.0	352	379	398.6	28.0	396.0	365	442
	Change from Baseline	5.0	17.6	-2.0	-8	25	-3.6	13.5	-5.0	-16	17
4 Hours	Baseline Value	363.0	10.8	360.0	354	375	401.2	11.2	398.0	386	415
	Post-Baseline Value	352.0	8.2	354.0	343	359	381.0	21.7	374.0	363	414
	Change from Baseline	-11.0	10.0	-11.0	-21	-1	-20.2	12.4	-23.0	-35	-1
5 Hours	Baseline Value	378.0	14.4	382.0	362	390	408.2	23.2	424.0	379	427
	Post-Baseline Value	370.3	14.5	363.0	361	387	392.4	10.2	392.0	384	409
	Change from Baseline	-7.7	18.6	1.0	-29	5	-15.8	30.9	-31.0	-43	22
6 Hours	Baseline Value	355.7	6.4	352.0	352	363	402.2	14.2	409.0	382	416
	Post-Baseline Value	378.7	8.6	377.0	371	388	394.4	16.2	400.0	373	415
	Change from Baseline	23.0	3.5	25.0	19	25	-7.8	3.9	-9.0	-11	-1
12 Hours	Baseline Value	367.7	25.7	361.0	346	396	396.6	16.3	399.0	372	411
	Post-Baseline Value	378.3	18.0	379.0	360	396	390.8	23.2	404.0	365	411
	Change from Baseline	10.7	19.3	0.0	-1	33	-5.8	12.1	-7.0	-24	9
24 Hours	Baseline Value	372.3	9.3	375.0	362	380	386.0	12.0	388.0	368	400
	Post-Baseline Value	368.7	13.7	371.0	354	381	383.4	19.1	384.0	359	407
	Change from Baseline	-3.7	4.5	-4.0	-8	1	-2.6	22.1	3.0	-41	15

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		Placebo Male >= 65 Years Old (n=4)					Placebo Female >= 65 Years Old (n=4)				
Time Points / QTcF (msec)		Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
0 Hours	Baseline Value	404.8	10.3	401.0	397	420	408.5	10.8	408.5	396	421
	Post-Baseline Value	388.0	17.3	389.0	369	405	435.0	35.6	423.0	407	487
	Change from Baseline	-16.8	14.2	-21.5	-28	4	26.5	41.2	14.5	-6	83
2 Hours	Baseline Value	402.5	18.1	409.5	376	415	387.3	5.7	386.0	382	395
	Post-Baseline Value	386.3	27.8	389.0	357	410	413.0	11.3	414.5	400	423
	Change from Baseline	-16.3	21.4	-12.0	-45	4	25.8	14.9	30.0	5	38
4 Hours	Baseline Value	402.3	13.6	408.5	382	410	416.0	14.2	411.5	405	436
	Post-Baseline Value	395.0	19.6	389.5	378	423	417.8	4.8	419.0	411	422
	Change from Baseline	-7.3	15.3	-10.5	-21	13	1.8	13.6	3.0	-14	15
5 Hours	Baseline Value	405.3	28.0	394.5	386	446	415.5	23.5	410.0	396	446
	Post-Baseline Value	399.0	24.8	396.0	372	432	420.3	17.2	421.0	401	438
	Change from Baseline	-6.3	12.8	-10.5	-16	12	4.8	24.6	2.5	-21	35
6 Hours	Baseline Value	410.3	12.8	410.5	395	425	410.0	8.5	408.0	402	422
	Post-Baseline Value	398.3	24.2	396.0	374	427	414.3	14.3	413.0	400	431
	Change from Baseline	-12.0	12.0	-13.5	-23	2	4.3	11.8	-1.5	-2	22
12 Hours	Baseline Value	400.3	19.6	393.0	386	429	404.0	10.5	401.5	395	418
	Post-Baseline Value	390.3	21.0	384.5	372	420	408.5	4.7	408.5	404	413
	Change from Baseline	-10.0	11.0	-9.5	-24	3	4.5	10.5	3.0	-6	18
24 Hours	Baseline Value	395.5	20.0	387.5	382	425	414.5	12.4	409.0	407	433
	Post-Baseline Value	394.3	21.4	393.5	372	418	408.8	17.6	411.5	385	427
	Change from Baseline	-1.3	11.2	-5.0	-10	15	-5.8	11.7	-3.0	-22	5
For each ECG test, only subjects with a baseline value and at least one post-baseline value are included in this summary table.											

付録 2.7.4-126　　心電図パラメータのベースラインからの平均変化量の要約統計量†

健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験

（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

Parameter		N	Mean	Median	STD	Min	Max	Lower 95% CI	Upper 95% CI
QT Interval (msec)	Baseline	173	377.39	376.67	20.98	322.00	434.33	374.24	380.54
	Post-txt	173	369.72	369.50	21.95	315.67	431.67	366.43	373.02
	Change	173	-7.67	-6.67	15.35	-64.83	36.83	-9.97	-5.37
QTc (Bazett)	Baseline	173	397.41	397.33	21.54	334.50	462.83	394.17	400.64
	Post-txt	173	392.94	392.17	20.91	331.17	448.50	389.80	396.08
	Change	173	-4.47	-3.67	11.78	-42.83	33.33	-6.23	-2.70
QTc (Fridericia)	Baseline	173	390.43	389.00	18.37	330.17	438.67	387.67	393.19
	Post-txt	173	384.84	383.83	18.17	329.33	436.50	382.11	387.57
	Change	173	-5.59	-4.67	10.86	-50.50	25.33	-7.22	-3.96
Vent. Rate (bpm)	Baseline	173	67.24	66.17	8.02	48.33	90.17	66.03	68.44
	Post-txt	173	68.54	68.17	8.55	50.50	91.83	67.25	69.82
	Change	173	1.30	1.00	5.87	-16.67	22.83	0.42	2.18

† Each subject contributes one value - where the value is the mean of all the subject's values in the 0-12 hour interval
txt = treatment

付録 2.7.4-127　　QT 及び QTc 間隔のベースラインからの平均変化量†（投与 0～12 時間後）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）

		QT Interval (msec)			QTc Interval (Fridericia)		
Protocol	N	Median	Mean	STD	Median	Mean	STD
ALL-POS	173	-6.67	-7.67	15.35	-4.67	-5.59	10.86
P02810-Plb	16	-5.00	-6.56	21.48	-2.75	-3.20	14.70
P02489	12	-7.58	-11.65	16.64	-2.33	-5.32	13.66
P02810	48	-7.50	-5.90	13.86	-8.08	-6.80	12.66
P02811	56	-9.17	-9.59	16.97	-4.58	-4.12	10.43
P02812	22	-3.33	-3.48	15.39	-3.50	-3.89	9.79
P02862	35	-4.67	-8.28	14.05	-5.33	-7.46	8.25

†Each subject contributes one QT or QTc change - where the change is the mean of all the time matched changes in the 0-12 hour interval
All data are up to 12 hours
POS = posaconazole, Plb = Placebo

付録 2.7.4-128　　QT 及び QTc 間隔の平均ベースラインからの変化量†の被験者分布
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

			QT		QTc (B)		QTc (F)	
Baseline‡	Total	Change from Baseline	N	%	N	%	N	%
Normal	171	<-60	1	0.58	0	0.00	0	0.00
		-60 to <-30	10	5.85	3	1.75	2	1.17
		-30 to <0	110	64.33	106	61.99	120	70.18
		0 to <30	49	28.65	61	35.67	49	28.65
		30 to <60	1	0.58	1	0.58	0	0.00
		>=60	0	0.00	0	0.00	0	0.00
Borderline	2	<-60	0	0.00	0	0.00	0	0.00
		-60 to <-30	0	0.00	0	0.00	0	0.00
		-30 to <0	2	100.00	1	50.00	1	50.00
		0 to <30	0	0.00	1	50.00	1	50.00
		30 to <60	0	0.00	0	0.00	0	0.00
		>=60	0	0.00	0	0.00	0	0.00

† Each subject contributes one QT or QTc change - where the change is the mean of all the time matched changes in the 0-12 hour interval
‡ Baseline is the mean QTcF values over the 0-12 hour interval
Normal: Adult Males <=430, Adult Females <=450
Borderline: Adult Males 431-450, Adult Females 451-470

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付録 2.7.4-129　　T_{max}における QT 及び QTc 間隔のベースラインからの変化量†
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

		QT Interval (msec)			QTc Interval (Fridericia)		
Protocol	N	Median	Mean	STD	Median	Mean	STD
ALL-POS	173	-4.00	-7.42	24.87	-4.00	-4.42	20.95
P02489	12	-11.50	-16.42	24.21	-9.00	-10.25	19.73
P02810	48	-10.00	-7.08	28.58	-11.00	-7.25	28.37
P02811	56	-10.00	-11.57	24.12	-1.50	-2.13	18.09
P02812	22	0.00	-1.82	17.08	-3.00	-3.36	15.16
P02862	35	4.00	-1.69	24.03	-4.00	-2.86	16.60

All data are up to 12 hours
†Each subject contributes one QT interval change - where the change corresponds to the time of the maximum posaconazole concentration level
POS = posaconazole

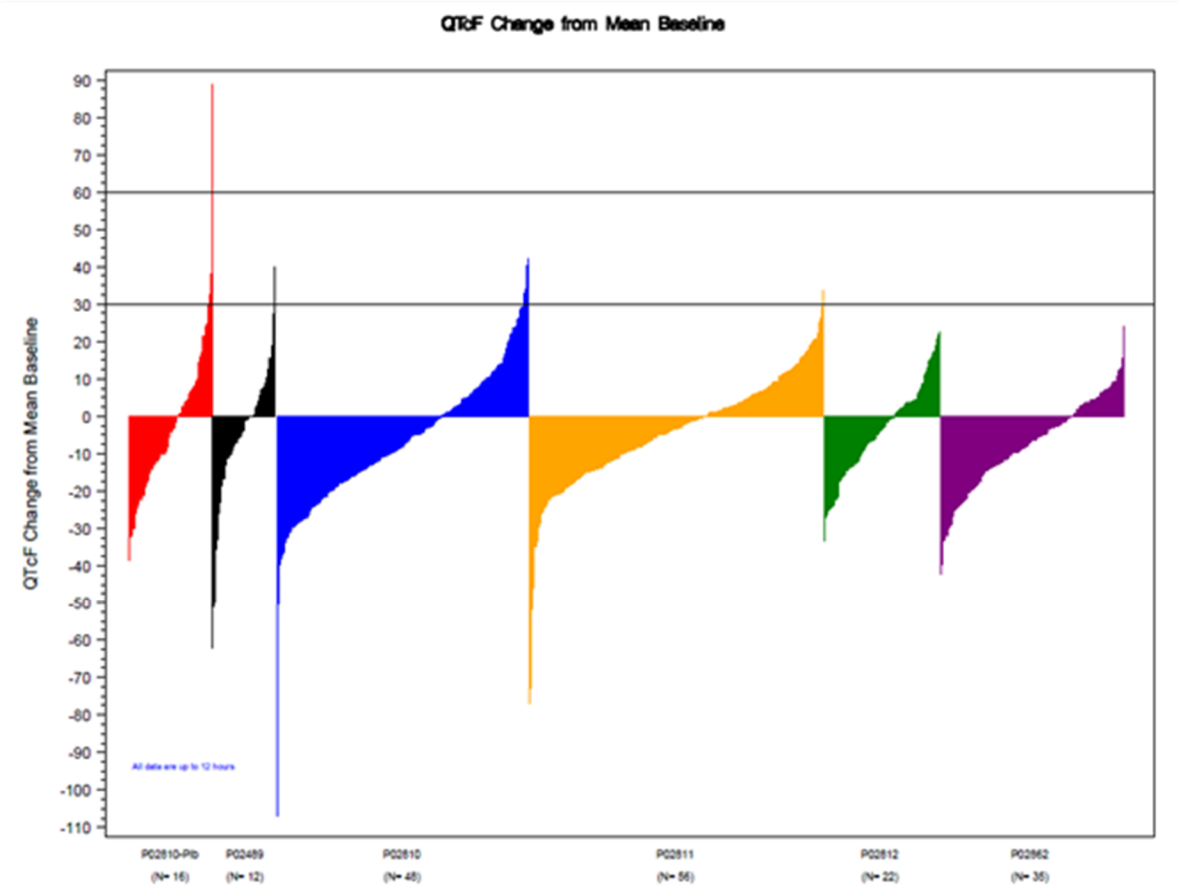
付録 2.7.4-130　　QT 及び QTc 間隔の平均ベースラインからの最大変化量の被験者分布
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）

Baseline†	Total	Change from Baseline	QT		QTc (B)		QTc (F)	
			N	%	N	%	N	%
Normal	171	<-60	0	0.00	0	0.00	0	0.00
		-60 to <-30	4	2.34	0	0.00	0	0.00
		-30 to <0	37	21.64	35	20.47	38	22.22
		0 to <30	115	67.25	118	69.01	127	74.27
		30 to <60	14	8.19	18	10.53	6	3.51
		>=60	1	0.58	0	0.00	0	0.00
Borderline	2	<-60	0	0.00	0	0.00	0	0.00
		-60 to <-30	0	0.00	0	0.00	0	0.00
		-30 to <0	1	50.00	1	50.00	1	50.00
		0 to <30	1	50.00	1	50.00	1	50.00
		30 to <60	0	0.00	0	0.00	0	0.00
		>=60	0	0.00	0	0.00	0	0.00

† Baseline is the mean QTcF values over the 0-12 hour interval
Normal: Adult Males <=430, Adult Females <=450
Borderline: Adult Males 431-450, Adult Females 451-470

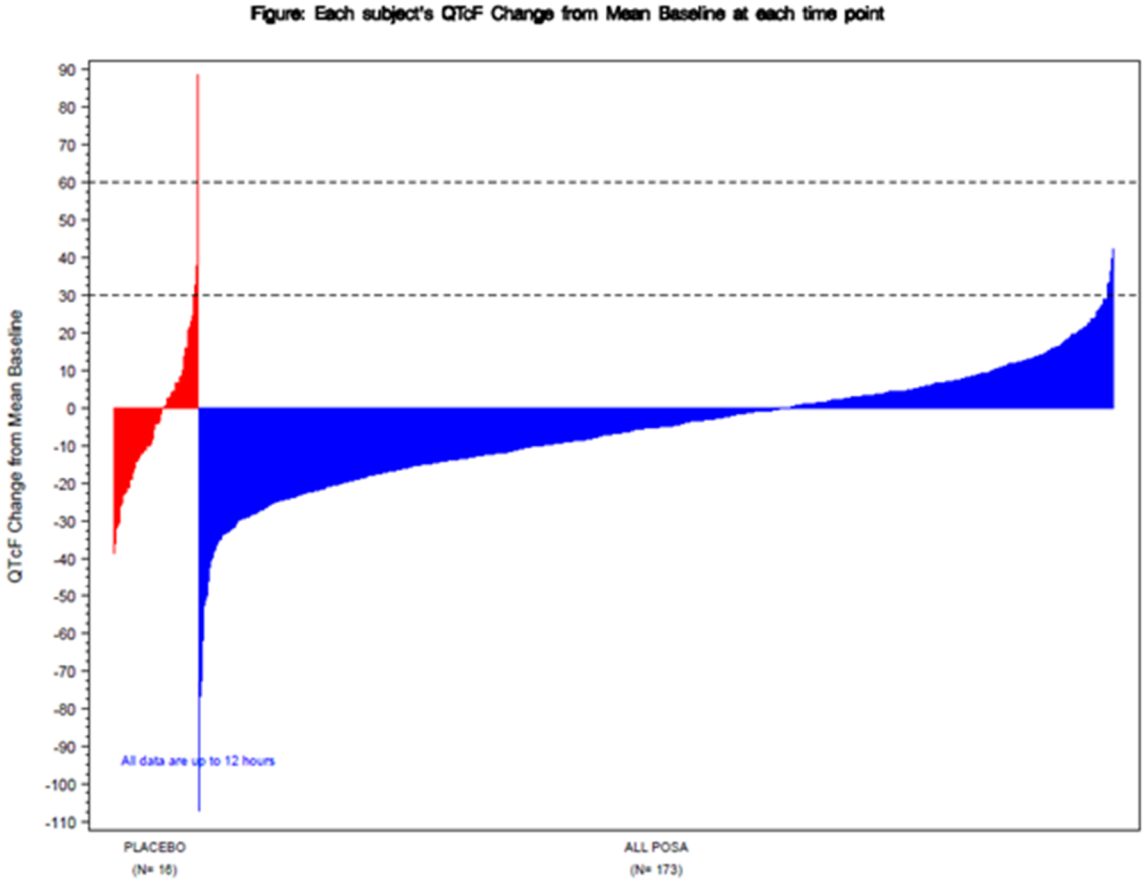
Confidential

付録 2.7.4-131　　QTcF 間隔の平均ベースラインからの変化図（試験別）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）

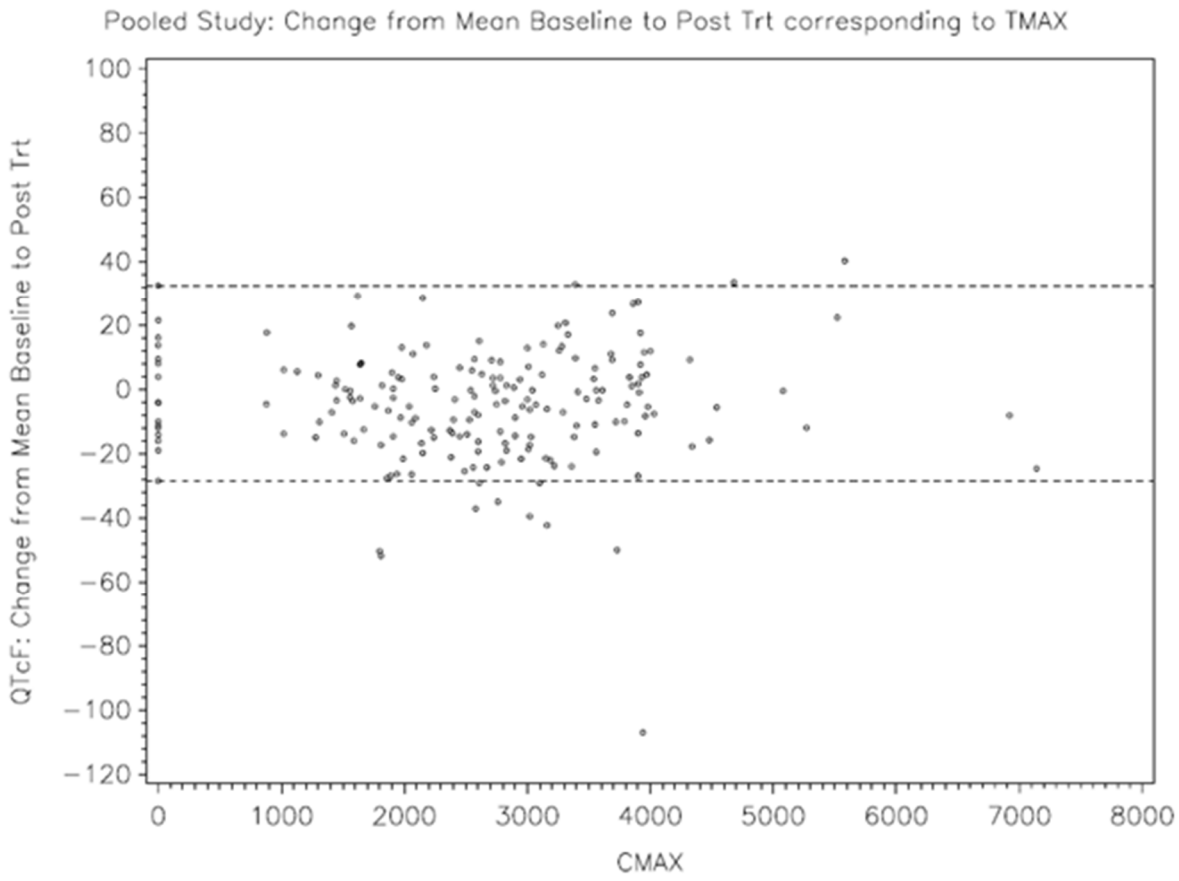


Plb = Placebo

付録 2.7.4-132　　QTcF 間隔の平均ベースラインからの変化図（投与集団別）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）



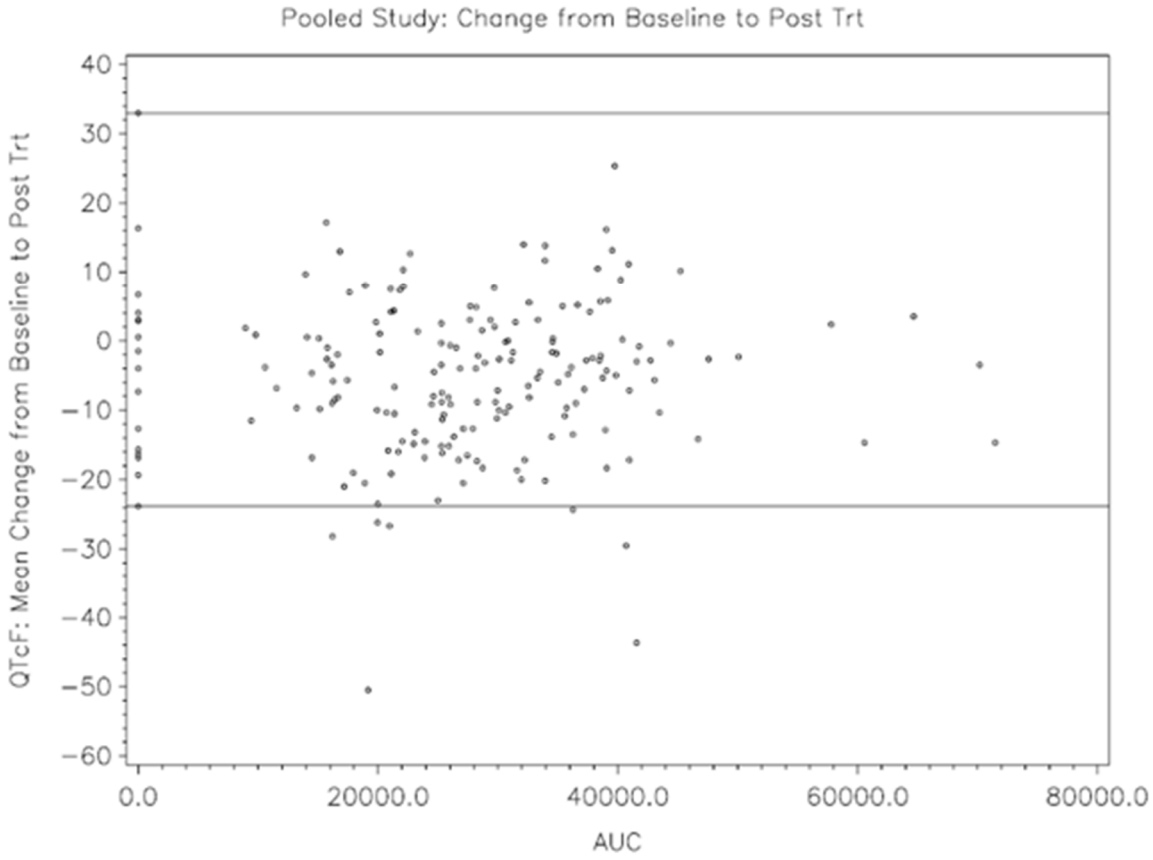
付録 2.7.4-133　　T_{max}における QTcF 間隔の平均ベースラインからの変化図
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）



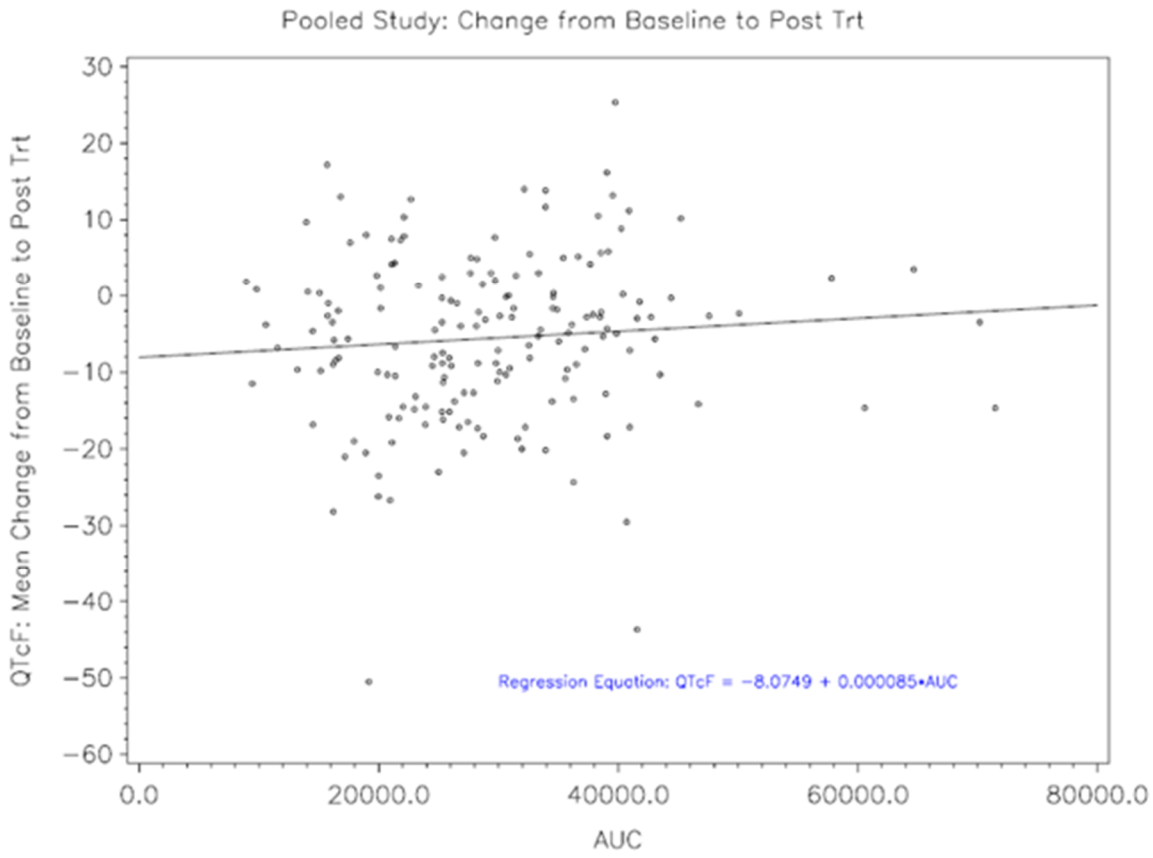
付録 2.7.4-134　　T_{max}における QTcF 間隔のベースラインからの変化図
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）



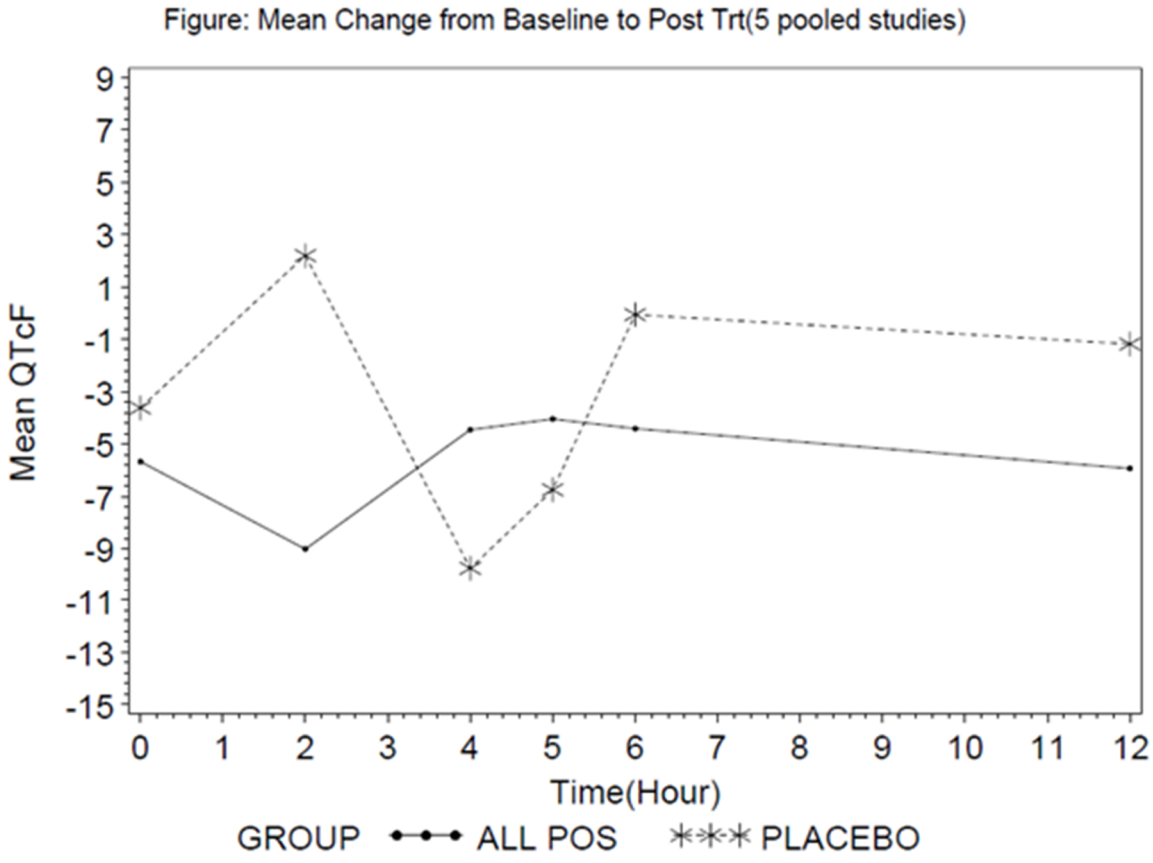
付録 2.7.4-135　　AUC に対する QTcF 間隔のベースラインからの変化図
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）



付録 2.7.4-136　　AUC に対する QTcF 間隔のベースラインからの変化図
健康被験者へのポサコナゾール経口懸濁液 400 mg を 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験の実薬群）



付録 2.7.4-137　　QTcF 間隔のベースラインからの平均変化量の図（投与後 0～12 時間）
健康被験者へのポサコナゾール経口懸濁液 400 mg 又はプラセボを 1 日 2 回投与した試験
（P02489、P02810、P02811、P02812 及び P02862 試験）



付録 2.7.4-138　　QTc 間隔の異常値及びベースラインからの変化量（60 msec 以下区分含む）の要約

健康被験者へのポサコナゾール新錠剤の反復投与試験（P05637 及び P07783 試験パート 2）

n/全被験者数

200 mg MD P05637 (n=10)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec†	9 / 10 (90)	9 / 10 (90)	9 / 10 (90)
Change from Baseline 0-30 msec†	7 / 10 (70)	6 / 10 (60)	6 / 10 (60)
Change from Baseline 31-60 msec†	0 / 10	0 / 10	0 / 10
Change from Baseline >60 msec†	0 / 10	0 / 10	0 / 10
Treatment Phase Value >500 msec‡	0 / 10	0 / 10	0 / 10
Males - Treatment Phase Value >=450 msec‡	0 / 5	0 / 5	0 / 5
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec†	0 / 5	0 / 5	0 / 5
Females - Treatment Phase Value >=470 msec‡	0 / 5	0 / 5	0 / 5
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec†	0 / 5	0 / 5	0 / 5
Any Condition Met‡	10 / 10 (100)	10 / 10 (100)	10 / 10 (100)
300 mg MD P07783 (n=12)	**Any QTc**	**Bazett QTc**	**Fridericia QTc**
Change from Baseline <0 msec†	10 / 12 (83)	9 / 12 (75)	9 / 12 (75)
Change from Baseline 0-30 msec†	6 / 12 (50)	5 / 12 (42)	5 / 12 (42)
Change from Baseline 31-60 msec†	0 / 12	0 / 12	0 / 12
Change from Baseline >60 msec†	0 / 12	0 / 12	0 / 12
Treatment Phase Value >500 msec‡	0 / 12	0 / 12	0 / 12
Males - Treatment Phase Value >=450 msec‡	0 / 6	0 / 6	0 / 6
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec†	0 / 6	0 / 6	0 / 6
Females - Treatment Phase Value >=470 msec‡	0 / 6	0 / 6	0 / 6
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec†	0 / 6	0 / 6	0 / 6
Any Condition Met‡	12 / 12 (100)	12 / 12 (100)	12 / 12 (100)
400 mg MD P05637 (n=9)	**Any QTc**	**Bazett QTc**	**Fridericia QTc**
Change from Baseline <0 msec†	9 / 9 (100)	9 / 9 (100)	8 / 9 (89)
Change from Baseline 0-30 msec†	6 / 9 (67)	5 / 9 (56)	6 / 9 (67)
Change from Baseline 31-60 msec†	1 / 9 (11)	1 / 9 (11)	0 / 9
Change from Baseline >60 msec†	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec‡	0 / 6	0 / 6	0 / 6
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec†	0 / 6	0 / 6	0 / 6
Females - Treatment Phase Value >=470 msec‡	0 / 3	0 / 3	0 / 3
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec†	0 / 3	0 / 3	0 / 3
Any Condition Met‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)

† : Denominator based on subjects with a Baseline value and at least one Treatment Phase value
‡ : Denominator based on subjects with at least one Treatment Phase value
Only in-treatment ECG readings have been included.
MD = Multiple Dose, Chg = change, Base = baseline, Tx phase = treatment phase

付録 2.7.4-139　　QTc 間隔の異常値及びベースラインからの変化量（60 msec 以下区分含む）の要約

健康被験者へのポサコナゾール静注用溶液の投与試験（P06356 試験）

（単回投与の実薬群のみ）　n/全被験者数

POS IV 50 mg SD (n=9)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec †	7 / 9 (78)	7 / 9 (78)	7 / 9 (78)
Change from Baseline 0-30 msec †	4 / 9 (44)	4 / 9 (44)	3 / 9 (33)
Change from Baseline 31-60 msec †	1 / 9 (11)	1 / 9 (11)	1 / 9 (11)
Change from Baseline >60 msec †	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec ‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec ‡	0 / 4	0 / 4	0 / 4
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec †	0 / 4	0 / 4	0 / 4
Females - Treatment Phase Value >=470 msec ‡	0 / 5	0 / 5	0 / 5
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec †	0 / 5	0 / 5	0 / 5
Any Condition Met ‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)
POS IV 100 mg SD (n=9)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec †	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)
Change from Baseline 0-30 msec †	8 / 9 (89)	7 / 9 (78)	6 / 9 (67)
Change from Baseline 31-60 msec †	0 / 9	0 / 9	0 / 9
Change from Baseline >60 msec †	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec ‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec ‡	0 / 6	0 / 6	0 / 6
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec †	0 / 6	0 / 6	0 / 6
Females - Treatment Phase Value >=470 msec ‡	0 / 3	0 / 3	0 / 3
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec †	0 / 3	0 / 3	0 / 3
Any Condition Met ‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)
POS IV 200 mg SD (n=9)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec †	9 / 9 (100)	8 / 9 (89)	9 / 9 (100)
Change from Baseline 0-30 msec †	5 / 9 (56)	4 / 9 (44)	4 / 9 (44)
Change from Baseline 31-60 msec †	1 / 9 (11)	1 / 9 (11)	0 / 9
Change from Baseline >60 msec †	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec ‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec ‡	0 / 4	0 / 4	0 / 4
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec †	0 / 4	0 / 4	0 / 4
Females - Treatment Phase Value >=470 msec ‡	0 / 5	0 / 5	0 / 5
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec †	0 / 5	0 / 5	0 / 5
Any Condition Met ‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)
POS IV 250 mg SD (n=9)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec †	9 / 9 (100)	9 / 9 (100)	8 / 9 (89)
Change from Baseline 0-30 msec †	8 / 9 (89)	8 / 9 (89)	6 / 9 (67)
Change from Baseline 31-60 msec †	0 / 9	0 / 9	0 / 9
Change from Baseline >60 msec †	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec ‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec ‡	0 / 4	0 / 4	0 / 4
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec †	0 / 4	0 / 4	0 / 4
Females - Treatment Phase Value >=470 msec ‡	0 / 5	0 / 5	0 / 5
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec †	0 / 5	0 / 5	0 / 5
Any Condition Met ‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)
POS IV 300 mg SD (n=9)	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline <0 msec †	9 / 9 (100)	8 / 9 (89)	9 / 9 (100)

Change from Baseline 0-30 msec †	6 / 9 (67)	6 / 9 (67)	5 / 9 (56)
Change from Baseline 31-60 msec †	0 / 9	0 / 9	0 / 9
Change from Baseline >60 msec †	0 / 9	0 / 9	0 / 9
Treatment Phase Value >500 msec ‡	0 / 9	0 / 9	0 / 9
Males - Treatment Phase Value >=450 msec ‡	0 / 6	0 / 6	0 / 6
Males - Chg from Base >=60 msec and Tx phase Value >=450 msec †	0 / 6	0 / 6	0 / 6
Females - Treatment Phase Value >=470 msec ‡	0 / 3	0 / 3	0 / 3
Females - Chg from Base >=60 msec and Tx phase Value >=470 msec †	0 / 3	0 / 3	0 / 3
Any Condition Met ‡	9 / 9 (100)	9 / 9 (100)	9 / 9 (100)

†: Denominator based on subjects with a Baseline value and at least one Treatment Phase value
‡: Denominator based on subjects with at least one Treatment Phase value
Only in-treatment ECG readings have been included.
SD = Single Dose, Chg = change, Base = baseline, Tx phase = treatment phase

付録 2.7.4-140　　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）n/全被験者数（%）

Treatment: Posaconazole			
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >=60 msec†	26 / 500 (5)	22 / 500 (4)	15 / 500 (3)
Treatment Phase Value >=500 msec‡	8 / 515 (2)	7 / 515 (1)	3 / 515 (1)
Males - Treatment Phase Value >=450 msec‡	80 / 304 (26)	76 / 304 (25)	37 / 304 (12)
Males - Chg from Base >=60 msec to >=450 msec†	11 / 296 (4)	9 / 296 (3)	3 / 296 (1)
Females - Treatment Phase Value >=470 msec‡	13 / 211 (6)	12 / 211 (6)	6 / 211 (3)
Females - Chg from Base >=60 msec to >=470 msec†	5 / 204 (2)	5 / 204 (2)	4 / 204 (2)
Any Condition Met‡	101 / 515 (20)	96 / 515 (19)	51 / 515 (10)
Treatment: Fluconazole			
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >=60 msec†	25 / 430 (6)	24 / 430 (6)	17 / 430 (4)
Treatment Phase Value >=500 msec‡	5 / 440 (1)	4 / 440 (1)	2 / 440
Males - Treatment Phase Value >=450 msec‡	73 / 260 (28)	73 / 260 (28)	27 / 260 (10)
Males - Chg from Base >=60 msec to >=450 msec†	10 / 251 (4)	10 / 251 (4)	4 / 251 (2)
Females - Treatment Phase Value >=470 msec‡	11 / 180 (6)	10 / 180 (6)	3 / 180 (2)
Females - Chg from Base >=60 msec to >=470 msec†	3 / 179 (2)	3 / 179 (2)	0 / 179
Any Condition Met‡	96 / 440 (22)	94 / 440 (21)	43 / 440 (10)
Treatment: Itraconazole			
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >=60 msec†	6 / 54 (11)	1 / 54 (2)	6 / 54 (11)
Treatment Phase Value >=500 msec‡	1 / 54 (2)	0 / 54	1 / 54 (2)
Males - Treatment Phase Value >=450 msec‡	18 / 29 (62)	17 / 29 (59)	10 / 29 (34)
Males - Chg from Base >=60 msec to >=450 msec†	3 / 29 (10)	1 / 29 (3)	3 / 29 (10)
Females - Treatment Phase Value >=470 msec‡	4 / 25 (16)	4 / 25 (16)	2 / 25 (8)
Females - Chg from Base >=60 msec to >=470 msec†	2 / 25 (8)	0 / 25	2 / 25 (8)
Any Condition Met‡	22 / 54 (41)	21 / 54 (39)	13 / 54 (24)

† : Denominator based on subjects with a Baseline value and at least one Treatment Phase value
‡ : Denominator based on subjects with at least one Treatment Phase value
Chg = change, Base = baseline

付録 2.7.4-141　　QTc 間隔の異常値及びベースラインからの変化量の要約
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）
（All Randomized Subjects）n/全被験者数（%）

Group: Bone Marrow Transplant				
	Any QTc	Bazett QTc	Fridericia QTc	Machine-read QTc
Change from Baseline >=60 msec †	3 / 76 (4)	1 / 74 (1)	2 / 74 (3)	2 / 50 (4)
Treatment Phase Value >=500 msec ‡	2 / 79 (3)	1 / 76 (1)	0 / 76	2 / 53 (4)
Males - Treatment Phase Value >=450 msec ‡	8 / 50 (16)	7 / 49 (14)	0 / 49	3 / 33 (9)
Males - Chg from Base >=60 msec to >=450 msec †	2 / 49 (4)	1 / 48 (2)	0 / 48	2 / 32 (6)
Females - Treatment Phase Value >=470 msec ‡	2 / 29 (7)	2 / 27 (7)	1 / 27 (4)	2 / 20 (10)
Females - Chg from Base >=60 msec to >=470 msec †	0 / 27	0 / 26	0 / 26	0 / 18
Any Condition Met ‡	11 / 79 (14)	9 / 76 (12)	3 / 76 (4)	5 / 53 (9)
Group: Non-BMT				
	Any QTc	Bazett QTc	Fridericia QTc	Machine-read QTc
Change from Baseline >=60 msec †	16 / 198 (8)	12 / 191 (6)	15 / 191 (8)	7 / 140 (5)
Treatment Phase Value >=500 msec ‡	6 / 217 (3)	5 / 212 (2)	2 / 212 (1)	4 / 157 (3)
Males - Treatment Phase Value >=450 msec ‡	36 / 152 (24)	33 / 149 (22)	11 / 149 (7)	19 / 114 (17)
Males - Chg from Base >=60 msec to >=450 msec †	7 / 137 (5)	6 / 132 (5)	3 / 132 (2)	5 / 100 (5)
Females - Treatment Phase Value >=470 msec ‡	6 / 65 (9)	6 / 63 (10)	2 / 63 (3)	2 / 43 (5)
Females - Chg from Base >=60 msec to >=470 msec †	1 / 61 (2)	1 / 59 (2)	1 / 59 (2)	0 / 40
Any Condition Met ‡	49 / 217 (23)	44 / 212 (21)	24 / 212 (11)	23 / 157 (15)
Group: Overall rIFI Pool				
	Any QTc	Bazett QTc	Fridericia QTc	Machine-read QTc
Change from Baseline >=60 msec †	19 / 274 (7)	13 / 265 (5)	17 / 265 (6)	9 / 190 (5)
Treatment Phase Value >=500 msec ‡	8 / 296 (3)	6 / 288 (2)	2 / 288 (1)	6 / 210 (3)
Males - Treatment Phase Value >=450 msec ‡	44 / 202 (22)	40 / 198 (20)	11 / 198 (6)	22 / 147 (15)
Males - Chg from Base >=60 msec to >=450 msec †	9 / 186 (5)	7 / 180 (4)	3 / 180 (2)	7 / 132 (5)
Females - Treatment Phase Value >=470 msec ‡	8 / 94 (9)	8 / 90 (9)	3 / 90 (3)	4 / 63 (6)
Females - Chg from Base >=60 msec to >=470 msec †	1 / 88 (1)	1 / 85 (1)	1 / 85 (1)	0 / 58
Any Condition Met ‡	60 / 296 (20)	53 / 288 (18)	27 / 288 (9)	28 / 210 (13)

† : Denominator based on subjects with a Baseline value and at least one Treatment Phase value
‡ : Denominator based on subjects with at least one Treatment Phase value
Chg = change, Base = baseline

付録 2.7.4-142　　投与開始 1 ヵ月間に発現した有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**562**	**(95.6)**
Blood And Lymphatic System Disorders	**309**	**(52.6)**
Anaemia	115	(19.6)
Bone Marrow Failure	2	(0.3)
Coagulation Factor Deficiency	1	(0.2)
Coagulopathy	9	(1.5)
Eosinophilia	1	(0.2)
Febrile Neutropenia	97	(16.5)
Granulocytopenia	1	(0.2)
Haemolysis	3	(0.5)
Haemolytic Uraemic Syndrome	3	(0.5)
Haemorrhagic Diathesis	1	(0.2)
Haemorrhagic Disorder	1	(0.2)
Hypercoagulation	1	(0.2)
Hypofibrinogenaemia	1	(0.2)
Hypoprothrombinaemia	1	(0.2)
Leukopenia	26	(4.4)
Lymph Node Pain	1	(0.2)
Lymphadenopathy	4	(0.7)
Neutropenia	100	(17.0)
Pancytopenia	9	(1.5)
Protein Deficiency Anaemia	1	(0.2)
Red Cell Fragmentation Syndrome	1	(0.2)
Retroperitoneal Lymphadenopathy	1	(0.2)
Splenomegaly	3	(0.5)
Thrombocytopenia	157	(26.7)
Thrombotic Thrombocytopenic Purpura	5	(0.9)
Cardiac Disorders	**83**	**(14.1)**
Acute Myocardial Infarction	1	(0.2)
Arrhythmia	2	(0.3)
Atrial Fibrillation	8	(1.4)
Atrial Flutter	1	(0.2)
Atrial Hypertrophy	1	(0.2)
Atrial Tachycardia	1	(0.2)
Atrioventricular Block Complete	1	(0.2)
Atrioventricular Block Second Degree	1	(0.2)
Bradycardia	5	(0.9)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Bundle Branch Block Left	1	(0.2)
Bundle Branch Block Right	1	(0.2)
Cardiac Arrest	3	(0.5)
Cardiac Disorder	1	(0.2)
Cardiac Failure	4	(0.7)
Cardiac Failure Congestive	1	(0.2)
Cardio-Respiratory Arrest	1	(0.2)
Cardiomegaly	4	(0.7)
Cardiomyopathy	1	(0.2)
Cardiopulmonary Failure	1	(0.2)
Cardiovascular Insufficiency	1	(0.2)
Congestive Cardiomyopathy	1	(0.2)
Coronary Artery Stenosis	1	(0.2)
Extrasystoles	1	(0.2)
Left Atrial Dilatation	1	(0.2)
Left Ventricular Dysfunction	1	(0.2)
Left Ventricular Hypertrophy	1	(0.2)
Mitral Valve Incompetence	2	(0.3)
Myocardial Infarction	2	(0.3)
Myocardial Ischaemia	2	(0.3)
Myocarditis	1	(0.2)
Palpitations	4	(0.7)
Pericardial Effusion	3	(0.5)
Pericarditis	2	(0.3)
Sinus Arrhythmia	1	(0.2)
Sinus Tachycardia	6	(1.0)
Supraventricular Extrasystoles	3	(0.5)
Supraventricular Tachycardia	2	(0.3)
Tachycardia	35	(6.0)
Torsade De Pointes	1	(0.2)
Tricuspid Valve Incompetence	1	(0.2)
Ventricular Extrasystoles	7	(1.2)
Congenital, Familial And Genetic Disorders	**2**	**(0.3)**
Chimerism	1	(0.2)
Factor II Deficiency	1	(0.2)
Ear And Labyrinth Disorders	**26**	**(4.4)**
Ear Discomfort	2	(0.3)
Ear Disorder	2	(0.3)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
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	Posaconazole n = 588	
Ear Pain	8	(1.4)
Ear Swelling	1	(0.2)
Excessive Cerumen Production	1	(0.2)
Hypoacusis	3	(0.5)
Tinnitus	3	(0.5)
Vertigo	8	(1.4)
Endocrine Disorders	**14**	**(2.4)**
Adrenal Mass	1	(0.2)
Androgen Deficiency	1	(0.2)
Cushing's Syndrome	1	(0.2)
Cushingoid	10	(1.7)
Thyroid Cyst	1	(0.2)
Eye Disorders	**69**	**(11.7)**
Abnormal Sensation In Eye	1	(0.2)
Cataract	3	(0.5)
Conjunctival Haemorrhage	6	(1.0)
Conjunctival Hyperaemia	1	(0.2)
Dry Eye	9	(1.5)
Erythema Of Eyelid	2	(0.3)
Eye Discharge	1	(0.2)
Eye Irritation	8	(1.4)
Eye Pain	4	(0.7)
Eye Swelling	3	(0.5)
Eyelid Oedema	2	(0.3)
Foreign Body Sensation In Eyes	1	(0.2)
Glaucoma	1	(0.2)
Halo Vision	2	(0.3)
Keratitis	1	(0.2)
Lacrimation Increased	2	(0.3)
Myopia	1	(0.2)
Ocular Hyperaemia	2	(0.3)
Periorbital Oedema	1	(0.2)
Photophobia	1	(0.2)
Pupils Unequal	1	(0.2)
Retinal Exudates	1	(0.2)
Retinal Haemorrhage	5	(0.9)
Scleral Discolouration	1	(0.2)
Scleral Haemorrhage	1	(0.2)

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	Posaconazole n = 588	
Vision Blurred	14	(2.4)
Visual Acuity Reduced	2	(0.3)
Visual Impairment	7	(1.2)
Vitreous Floaters	1	(0.2)
Gastrointestinal Disorders	**394**	**(67.0)**
Abdominal Discomfort	15	(2.6)
Abdominal Distension	28	(4.8)
Abdominal Hernia	1	(0.2)
Abdominal Pain	81	(13.8)
Abdominal Pain Lower	6	(1.0)
Abdominal Pain Upper	28	(4.8)
Abdominal Tenderness	6	(1.0)
Acute Abdomen	1	(0.2)
Anal Fissure	5	(0.9)
Anal Haemorrhage	1	(0.2)
Anal Incontinence	1	(0.2)
Anal Pruritus	1	(0.2)
Anal Ulcer	1	(0.2)
Anorectal Discomfort	2	(0.3)
Aphthous Ulcer	2	(0.3)
Aptyalism	1	(0.2)
Ascites	17	(2.9)
Breath Odour	1	(0.2)
Chapped Lips	1	(0.2)
Colitis	10	(1.7)
Colitis Ulcerative	1	(0.2)
Constipation	71	(12.1)
Diarrhoea	162	(27.6)
Diarrhoea Haemorrhagic	2	(0.3)
Diverticulum Intestinal	1	(0.2)
Dry Mouth	11	(1.9)
Duodenitis	2	(0.3)
Dyspepsia	33	(5.6)
Dysphagia	4	(0.7)
Enteritis	3	(0.5)
Enterocolitis	1	(0.2)
Epigastric Discomfort	2	(0.3)
Eructation	2	(0.3)
Faecal Volume Increased	1	(0.2)

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	Posaconazole n = 588	
Flatulence	11	(1.9)
Frequent Bowel Movements	1	(0.2)
Gastric Ulcer Haemorrhage	2	(0.3)
Gastritis	8	(1.4)
Gastritis Erosive	1	(0.2)
Gastritis Haemorrhagic	1	(0.2)
Gastrointestinal Disorder	1	(0.2)
Gastrointestinal Haemorrhage	15	(2.6)
Gastrointestinal Hypomotility	1	(0.2)
Gastrointestinal Pain	1	(0.2)
Gastrointestinal Sounds Abnormal	2	(0.3)
Gastrooesophageal Reflux Disease	10	(1.7)
Gingival Bleeding	17	(2.9)
Gingival Hypertrophy	1	(0.2)
Gingival Pain	2	(0.3)
Glossodynia	3	(0.5)
Haematemesis	5	(0.9)
Haematochezia	12	(2.0)
Haemorrhoidal Haemorrhage	6	(1.0)
Haemorrhoids	26	(4.4)
Haemorrhoids Thrombosed	1	(0.2)
Hiatus Hernia	1	(0.2)
Hyperchlorhydria	1	(0.2)
Hypoaesthesia Oral	3	(0.5)
Ileus	1	(0.2)
Impaired Gastric Emptying	2	(0.3)
Intestinal Haemorrhage	1	(0.2)
Irritable Bowel Syndrome	1	(0.2)
Leukoplakia Oral	1	(0.2)
Lip Blister	2	(0.3)
Lip Dry	2	(0.3)
Lip Exfoliation	1	(0.2)
Lip Pain	1	(0.2)
Lip Ulceration	4	(0.7)
Malabsorption	1	(0.2)
Melaena	7	(1.2)
Mouth Haemorrhage	12	(2.0)
Mouth Ulceration	14	(2.4)
Nausea	145	(24.7)
Neutropenic Colitis	4	(0.7)

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	Posaconazole n = 588	
Odynophagia	4	(0.7)
Oesophageal Ulcer	1	(0.2)
Oesophagitis	7	(1.2)
Oesophagitis Ulcerative	1	(0.2)
Oral Disorder	5	(0.9)
Oral Mucosal Blistering	3	(0.5)
Oral Mucosal Erythema	5	(0.9)
Oral Mucosal Exfoliation	1	(0.2)
Oral Pain	17	(2.9)
Palatal Swelling	1	(0.2)
Pancreatitis	1	(0.2)
Paraesthesia Oral	1	(0.2)
Perianal Erythema	1	(0.2)
Proctalgia	4	(0.7)
Rectal Fissure	1	(0.2)
Rectal Haemorrhage	9	(1.5)
Retching	3	(0.5)
Retroperitoneal Haemorrhage	1	(0.2)
Saliva Altered	1	(0.2)
Salivary Gland Mass	1	(0.2)
Small Intestinal Obstruction	1	(0.2)
Stomatitis	10	(1.7)
Tongue Blistering	1	(0.2)
Tongue Coated	6	(1.0)
Tongue Discolouration	1	(0.2)
Tongue Discomfort	1	(0.2)
Tongue Disorder	1	(0.2)
Tongue Erythema	1	(0.2)
Tongue Haematoma	2	(0.3)
Tongue Ulceration	4	(0.7)
Toothache	6	(1.0)
Trichoglossia	2	(0.3)
Umbilical Hernia	1	(0.2)
Upper Gastrointestinal Haemorrhage	2	(0.3)
Uvulitis	1	(0.2)
Vomiting	98	(16.7)
General Disorders And Administration Site Conditions	**365**	**(62.1)**
Adverse Drug Reaction	1	(0.2)
Application Site Discomfort	1	(0.2)

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	Posaconazole n = 588	
Asthenia	27	(4.6)
Catheter Site Bruise	1	(0.2)
Catheter Site Discharge	2	(0.3)
Catheter Site Erythema	29	(4.9)
Catheter Site Haematoma	2	(0.3)
Catheter Site Haemorrhage	12	(2.0)
Catheter Site Inflammation	8	(1.4)
Catheter Site Pain	20	(3.4)
Catheter Site Phlebitis	2	(0.3)
Catheter Site Pruritus	2	(0.3)
Catheter Site Rash	1	(0.2)
Catheter Site Related Reaction	3	(0.5)
Catheter Site Swelling	1	(0.2)
Chest Discomfort	6	(1.0)
Chest Pain	29	(4.9)
Chills	79	(13.4)
Complication Associated With Device	3	(0.5)
Crepitations	3	(0.5)
Device Related Thrombosis	2	(0.3)
Disease Progression	2	(0.3)
Drug Interaction	2	(0.3)
Drug Intolerance	1	(0.2)
Exercise Tolerance Decreased	1	(0.2)
Face Oedema	6	(1.0)
Facial Pain	1	(0.2)
Fatigue	54	(9.2)
Feeling Cold	1	(0.2)
Feeling Hot	1	(0.2)
Feeling Jittery	4	(0.7)
Gait Disturbance	5	(0.9)
General Physical Health Deterioration	2	(0.3)
Generalised Oedema	10	(1.7)
Granuloma	2	(0.3)
Hyperthermia	4	(0.7)
Hypothermia	1	(0.2)
Induration	1	(0.2)
Inflammation	2	(0.3)
Influenza Like Illness	1	(0.2)
Infusion Site Haemorrhage	1	(0.2)
Infusion Site Inflammation	1	(0.2)

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	Posaconazole n = 588	
Infusion Site Pain	4	(0.7)
Infusion Site Vesicles	1	(0.2)
Localised Oedema	2	(0.3)
Malaise	8	(1.4)
Mass	1	(0.2)
Mucosal Haemorrhage	1	(0.2)
Mucosal Inflammation	76	(12.9)
Mucous Membrane Disorder	1	(0.2)
Multi-Organ Disorder	1	(0.2)
Multiple Organ Dysfunction Syndrome	7	(1.2)
Necrosis	1	(0.2)
Nodule	1	(0.2)
Obstruction	1	(0.2)
Oedema	25	(4.3)
Oedema Peripheral	62	(10.5)
Pain	21	(3.6)
Performance Status Decreased	1	(0.2)
Peripheral Swelling	14	(2.4)
Puncture Site Pain	2	(0.3)
Puncture Site Reaction	3	(0.5)
Pyrexia	181	(30.8)
Swelling	1	(0.2)
Tenderness	2	(0.3)
Therapy Non-Responder	3	(0.5)
Thirst	4	(0.7)
Ulcer	1	(0.2)
Vessel Puncture Site Pain	2	(0.3)
Hepatobiliary Disorders	**60**	**(10.2)**
Cholecystitis	1	(0.2)
Cholelithiasis	6	(1.0)
Cholestasis	2	(0.3)
Gallbladder Polyp	1	(0.2)
Hepatic Cyst	1	(0.2)
Hepatic Failure	4	(0.7)
Hepatic Function Abnormal	3	(0.5)
Hepatic Lesion	1	(0.2)
Hepatitis	1	(0.2)
Hepatitis Acute	1	(0.2)
Hepatocellular Injury	2	(0.3)

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	Posaconazole n = 588	
Hepatomegaly	6	(1.0)
Hepatosplenomegaly	1	(0.2)
Hepatotoxicity	2	(0.3)
Hyperbilirubinaemia	17	(2.9)
Jaundice	15	(2.6)
Jaundice Cholestatic	1	(0.2)
Liver Injury	1	(0.2)
Ocular Icterus	9	(1.5)
Portal Hypertension	1	(0.2)
Immune System Disorders	**55**	**(9.4)**
Drug Hypersensitivity	11	(1.9)
Graft Versus Host Disease	29	(4.9)
Graft Versus Host Disease In Gastrointestinal Tract	13	(2.2)
Graft Versus Host Disease In Liver	8	(1.4)
Graft Versus Host Disease In Skin	7	(1.2)
Hypersensitivity	1	(0.2)
Hypogammaglobulinaemia	1	(0.2)
Transplant Rejection	2	(0.3)
Infections And Infestations	**307**	**(52.2)**
Abscess Neck	1	(0.2)
Acid Fast Bacilli Infection	1	(0.2)
Acute Sinusitis	1	(0.2)
Anal Abscess	1	(0.2)
Anorectal Infection	1	(0.2)
Aspergillus Infection	4	(0.7)
Atypical Pneumonia	1	(0.2)
Bacteraemia	42	(7.1)
Bacterial Disease Carrier	1	(0.2)
Bacterial Infection	8	(1.4)
Bacterial Sepsis	2	(0.3)
Bartholin's Abscess	1	(0.2)
Bartholinitis	1	(0.2)
Bk Virus Infection	1	(0.2)
Bronchitis	6	(1.0)
Bronchopulmonary Aspergillosis	1	(0.2)
Candida Infection	2	(0.3)
Candida Sepsis	1	(0.2)
Catheter Site Cellulitis	2	(0.3)

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	Posaconazole n = 588	
Catheter Site Infection	4	(0.7)
Cellulitis	11	(1.9)
Cerebral Toxoplasmosis	1	(0.2)
Chronic Sinusitis	1	(0.2)
Citrobacter Infection	1	(0.2)
Clostridial Infection	2	(0.3)
Clostridium Difficile Colitis	4	(0.7)
Clostridium Difficile Infection	5	(0.9)
Conjunctivitis	8	(1.4)
Corynebacterium Bacteraemia	1	(0.2)
Corynebacterium Sepsis	1	(0.2)
Cystitis	7	(1.2)
Cytomegalovirus Colitis	3	(0.5)
Cytomegalovirus Gastritis	1	(0.2)
Cytomegalovirus Infection	27	(4.6)
Cytomegalovirus Viraemia	7	(1.2)
Device Related Infection	14	(2.4)
Device Related Sepsis	1	(0.2)
Ear Infection	2	(0.3)
Encephalitis	1	(0.2)
Enterobacter Bacteraemia	2	(0.3)
Enterobacter Infection	2	(0.3)
Enterococcal Bacteraemia	6	(1.0)
Enterococcal Infection	1	(0.2)
Enterovirus Infection	1	(0.2)
Epiglottitis	1	(0.2)
Epstein-Barr Virus Infection	1	(0.2)
Escherichia Bacteraemia	6	(1.0)
Escherichia Sepsis	1	(0.2)
Escherichia Urinary Tract Infection	2	(0.3)
Eye Infection	2	(0.3)
Folliculitis	5	(0.9)
Fungal Infection	6	(1.0)
Fungal Skin Infection	1	(0.2)
Fusobacterium Infection	1	(0.2)
Gastroenteritis Pseudomonas	1	(0.2)
Gastroenteritis Rotavirus	1	(0.2)
Gastrointestinal Infection	1	(0.2)
Genital Herpes	3	(0.5)
Genital Infection Bacterial	1	(0.2)

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	Posaconazole n = 588	
Giardiasis	1	(0.2)
Gingivitis	2	(0.3)
Haemophilus Infection	1	(0.2)
Herpes Dermatitis	1	(0.2)
Herpes Simplex	9	(1.5)
Herpes Virus Infection	10	(1.7)
Herpes Zoster	7	(1.2)
Infected Skin Ulcer	1	(0.2)
Infection	5	(0.9)
Klebsiella Bacteraemia	3	(0.5)
Klebsiella Infection	1	(0.2)
Laryngitis	3	(0.5)
Localised Infection	1	(0.2)
Lower Respiratory Tract Infection	6	(1.0)
Lung Abscess	1	(0.2)
Lymphangitis	1	(0.2)
Mastoiditis	3	(0.5)
Micrococcus Infection	1	(0.2)
Nasopharyngitis	3	(0.5)
Neutropenic Sepsis	4	(0.7)
Onychomycosis	1	(0.2)
Oral Candidiasis	8	(1.4)
Oral Herpes	32	(5.4)
Otitis Media	1	(0.2)
Paronychia	1	(0.2)
Pericoronitis	1	(0.2)
Perineal Abscess	1	(0.2)
Periodontitis	1	(0.2)
Perirectal Abscess	2	(0.3)
Pharyngitis	5	(0.9)
Pharyngitis Bacterial	1	(0.2)
Pilonidal Cyst	1	(0.2)
Pneumococcal Bacteraemia	1	(0.2)
Pneumocystis Jirovecii Infection	1	(0.2)
Pneumocystis Jirovecii Pneumonia	1	(0.2)
Pneumonia	21	(3.6)
Pneumonia Bacterial	5	(0.9)
Pneumonia Cytomegaloviral	2	(0.3)
Pneumonia Fungal	2	(0.3)
Pneumonia Klebsiella	3	(0.5)

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	Posaconazole n = 588	
Pneumonia Staphylococcal	1	(0.2)
Pseudomonal Bacteraemia	1	(0.2)
Pseudomonal Sepsis	2	(0.3)
Pseudomonas Infection	7	(1.2)
Pulmonary Mycosis	2	(0.3)
Pyoderma	1	(0.2)
Rash Pustular	2	(0.3)
Respiratory Syncytial Virus Infection	1	(0.2)
Rhinitis	5	(0.9)
Rotavirus Infection	2	(0.3)
Salmonellosis	1	(0.2)
Sepsis	8	(1.4)
Sepsis Syndrome	1	(0.2)
Septic Rash	1	(0.2)
Septic Shock	11	(1.9)
Serratia Infection	3	(0.5)
Sialoadenitis	1	(0.2)
Sinusitis	8	(1.4)
Staphylococcal Bacteraemia	16	(2.7)
Staphylococcal Infection	16	(2.7)
Staphylococcal Sepsis	3	(0.5)
Staphylococcal Skin Infection	1	(0.2)
Stenotrophomonas Infection	1	(0.2)
Streptococcal Bacteraemia	2	(0.3)
Streptococcal Infection	1	(0.2)
Streptococcal Sepsis	3	(0.5)
Subcutaneous Abscess	1	(0.2)
Systemic Candida	4	(0.7)
Systemic Mycosis	1	(0.2)
Tooth Abscess	3	(0.5)
Tooth Infection	1	(0.2)
Tracheobronchitis	1	(0.2)
Trichomoniasis	1	(0.2)
Upper Respiratory Tract Infection	13	(2.2)
Urinary Tract Infection	13	(2.2)
Urinary Tract Infection Fungal	1	(0.2)
Urinary Tract Infection Staphylococcal	1	(0.2)
Varicella Zoster Virus Infection	1	(0.2)
Viral Haemorrhagic Cystitis	1	(0.2)
Viral Infection	1	(0.2)

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	Posaconazole n = 588	
Vulvitis	1	(0.2)
Vulvovaginal Mycotic Infection	1	(0.2)
Vulvovaginitis	1	(0.2)
Injury, Poisoning And Procedural Complications	**88**	**(15.0)**
Allergic Transfusion Reaction	3	(0.5)
Anal Injury	1	(0.2)
Arthropod Bite	1	(0.2)
Complications Of Transplant Surgery	1	(0.2)
Compression Fracture	1	(0.2)
Contusion	8	(1.4)
Excoriation	2	(0.3)
Eye Burns	1	(0.2)
Fall	14	(2.4)
Incision Site Pain	1	(0.2)
Inflammation Of Wound	1	(0.2)
Infusion Related Reaction	4	(0.7)
Laceration	5	(0.9)
Lip Injury	1	(0.2)
Lumbar Vertebral Fracture	1	(0.2)
Mouth Injury	1	(0.2)
Muscle Strain	1	(0.2)
Post Lumbar Puncture Syndrome	1	(0.2)
Post Procedural Complication	1	(0.2)
Post Procedural Haematoma	1	(0.2)
Post Procedural Haemorrhage	2	(0.3)
Postoperative Fever	1	(0.2)
Procedural Pain	11	(1.9)
Rib Fracture	1	(0.2)
Sedation Complication	1	(0.2)
Skin Abrasion	3	(0.5)
Skin Injury	1	(0.2)
Subarachnoid Haemorrhage	1	(0.2)
Subdural Haematoma	2	(0.3)
Tooth Fracture	1	(0.2)
Toxicity To Various Agents	4	(0.7)
Transfusion Reaction	24	(4.1)
Wound	1	(0.2)
Wound Complication	1	(0.2)

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	Posaconazole n = 588	
Investigations	**234**	**(39.8)**
Alanine Aminotransferase Increased	21	(3.6)
Ammonia Increased	1	(0.2)
Aspartate Aminotransferase Abnormal	1	(0.2)
Aspartate Aminotransferase Increased	8	(1.4)
Aspiration Bronchial	1	(0.2)
Bacterial Test Positive	7	(1.2)
Bilirubin Conjugated Increased	1	(0.2)
Blast Cells Present	1	(0.2)
Bleeding Time Prolonged	2	(0.3)
Blood Albumin Decreased	4	(0.7)
Blood Alkaline Phosphatase Increased	10	(1.7)
Blood Bicarbonate Decreased	1	(0.2)
Blood Bilirubin Abnormal	1	(0.2)
Blood Bilirubin Increased	21	(3.6)
Blood Calcium Decreased	2	(0.3)
Blood Chloride Increased	1	(0.2)
Blood Cholesterol Increased	3	(0.5)
Blood Creatine Increased	1	(0.2)
Blood Creatine Phosphokinase Increased	1	(0.2)
Blood Creatinine Increased	19	(3.2)
Blood Culture Positive	10	(1.7)
Blood Glucose Increased	5	(0.9)
Blood Immunoglobulin G Decreased	1	(0.2)
Blood Lactate Dehydrogenase Increased	7	(1.2)
Blood Magnesium Decreased	11	(1.9)
Blood Magnesium Increased	1	(0.2)
Blood Phosphorus Decreased	2	(0.3)
Blood Potassium	1	(0.2)
Blood Potassium Decreased	5	(0.9)
Blood Pressure Increased	3	(0.5)
Blood Pressure Orthostatic	2	(0.3)
Blood Testosterone Decreased	1	(0.2)
Blood Thyroid Stimulating Hormone Decreased	1	(0.2)
Blood Urea Increased	5	(0.9)
Blood Uric Acid Increased	2	(0.3)
Blood Urine Present	1	(0.2)
Body Temperature	1	(0.2)
Body Temperature Increased	2	(0.3)

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	Posaconazole n = 588	
Breath Sounds Abnormal	13	(2.2)
C-Reactive Protein Abnormal	1	(0.2)
C-Reactive Protein Increased	3	(0.5)
Cardiac Murmur	8	(1.4)
Central Venous Pressure Decreased	1	(0.2)
Chest X-Ray Abnormal	2	(0.3)
Clostridium Test Positive	3	(0.5)
Coagulation Test Abnormal	1	(0.2)
Coagulation Time Prolonged	1	(0.2)
Coagulation Time Shortened	1	(0.2)
Computerised Tomogram Abnormal	1	(0.2)
Creatinine Renal Clearance Decreased	1	(0.2)
Culture Stool Positive	1	(0.2)
Cytomegalovirus Test	3	(0.5)
Cytomegalovirus Test Positive	16	(2.7)
Drug Level Increased	5	(0.9)
Echocardiogram Abnormal	1	(0.2)
Ejection Fraction Decreased	2	(0.3)
Electrocardiogram Abnormal	2	(0.3)
Electrocardiogram Qt Prolonged	18	(3.1)
Electrocardiogram Repolarisation Abnormality	1	(0.2)
Electrocardiogram St Segment Abnormal	1	(0.2)
Electrocardiogram St-T Change	1	(0.2)
Electrocardiogram St-T Segment Abnormal	1	(0.2)
Electrocardiogram T Wave Abnormal	4	(0.7)
Electrocardiogram T Wave Inversion	1	(0.2)
Electroencephalogram Abnormal	1	(0.2)
Fungal Test Positive	3	(0.5)
Gamma-Glutamyltransferase Increased	28	(4.8)
Haemoglobin Decreased	5	(0.9)
Heart Rate Irregular	3	(0.5)
Heart Sounds Abnormal	1	(0.2)
Hepatic Enzyme Abnormal	1	(0.2)
Hepatic Enzyme Increased	7	(1.2)
High Density Lipoprotein Increased	1	(0.2)
Immunoglobulins Decreased	1	(0.2)
International Normalised Ratio Abnormal	2	(0.3)
International Normalised Ratio Increased	1	(0.2)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	10	(1.7)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Microbiology Test Normal	1	(0.2)
Neutrophil Count Decreased	1	(0.2)
Nuclear Magnetic Resonance Imaging Brain Abnormal	1	(0.2)
Occult Blood Positive	3	(0.5)
Oxygen Saturation Decreased	5	(0.9)
Platelet Count Decreased	8	(1.4)
Po2 Decreased	1	(0.2)
Prothrombin Time Prolonged	5	(0.9)
Prothrombin Time Shortened	2	(0.3)
Red Blood Cell Count Decreased	1	(0.2)
Scan Bone Marrow Abnormal	1	(0.2)
Serum Ferritin Increased	1	(0.2)
Sputum Abnormal	1	(0.2)
Thrombin Time Prolonged	1	(0.2)
Total Lung Capacity Decreased	1	(0.2)
Transaminases Increased	9	(1.5)
Troponin Increased	1	(0.2)
Urine Output Decreased	2	(0.3)
Urine Output Increased	1	(0.2)
Viral Test Positive	1	(0.2)
Weight Decreased	21	(3.6)
Weight Increased	7	(1.2)
White Blood Cell Count Decreased	1	(0.2)
X-Ray Abnormal	1	(0.2)
Metabolism And Nutrition Disorders	**270**	**(45.9)**
Acidosis	4	(0.7)
Decreased Appetite	42	(7.1)
Dehydration	14	(2.4)
Diabetes Mellitus	13	(2.2)
Electrolyte Imbalance	4	(0.7)
Failure To Thrive	1	(0.2)
Fluid Overload	18	(3.1)
Fluid Retention	10	(1.7)
Food Aversion	1	(0.2)
Food Craving	1	(0.2)
Gout	3	(0.5)
Hypercalcaemia	1	(0.2)
Hypercholesterolaemia	3	(0.5)
Hypercreatininaemia	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Hyperglycaemia	46	(7.8)
Hyperinsulinaemic Hypoglycaemia	1	(0.2)
Hyperkalaemia	10	(1.7)
Hypermagnesaemia	5	(0.9)
Hypernatraemia	2	(0.3)
Hyperphosphataemia	6	(1.0)
Hyperuricaemia	1	(0.2)
Hypervolaemia	1	(0.2)
Hypoalbuminaemia	18	(3.1)
Hypocalcaemia	46	(7.8)
Hypoglycaemia	5	(0.9)
Hypokalaemia	118	(20.1)
Hypomagnesaemia	75	(12.8)
Hyponatraemia	20	(3.4)
Hypophagia	6	(1.0)
Hypophosphataemia	36	(6.1)
Hypoproteinaemia	2	(0.3)
Hypovolaemia	2	(0.3)
Malnutrition	2	(0.3)
Metabolic Acidosis	7	(1.2)
Phosphorus Metabolism Disorder	1	(0.2)
Polydipsia	2	(0.3)
Vitamin K Deficiency	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**159**	**(27.0)**
Arthralgia	29	(4.9)
Arthritis	3	(0.5)
Back Pain	36	(6.1)
Bone Pain	13	(2.2)
Bursitis	1	(0.2)
Chondritis	1	(0.2)
Flank Pain	4	(0.7)
Haemarthrosis	1	(0.2)
Intervertebral Disc Protrusion	1	(0.2)
Joint Swelling	6	(1.0)
Limb Discomfort	1	(0.2)
Mobility Decreased	1	(0.2)
Muscle Atrophy	2	(0.3)
Muscle Contracture	1	(0.2)
Muscle Fatigue	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Muscle Spasms	17	(2.9)
Muscle Twitching	3	(0.5)
Muscular Weakness	19	(3.2)
Musculoskeletal Chest Pain	5	(0.9)
Musculoskeletal Discomfort	1	(0.2)
Musculoskeletal Pain	11	(1.9)
Musculoskeletal Stiffness	2	(0.3)
Myalgia	13	(2.2)
Myopathy	11	(1.9)
Myositis	1	(0.2)
Neck Pain	6	(1.0)
Osteopenia	1	(0.2)
Pain In Extremity	32	(5.4)
Pain In Jaw	3	(0.5)
Sjogren's Syndrome	1	(0.2)
Spinal Osteoarthritis	2	(0.3)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**27**	**(4.6)**
Acute Myeloid Leukaemia	6	(1.0)
Acute Myeloid Leukaemia Recurrent	5	(0.9)
Breast Neoplasm	1	(0.2)
Colon Adenoma	1	(0.2)
Haemangioma Of Liver	1	(0.2)
Leukaemia	2	(0.3)
Leukaemia Recurrent	2	(0.3)
Lymphoma	1	(0.2)
Meningioma	1	(0.2)
Myelodysplastic Syndrome	1	(0.2)
Nasal Neoplasm	1	(0.2)
Neoplasm Malignant	1	(0.2)
Renal Cancer	1	(0.2)
Renal Neoplasm	1	(0.2)
Thyroid Adenoma	1	(0.2)
Tumour Pain	1	(0.2)
Uterine Leiomyoma	2	(0.3)
Vaginal Neoplasm	1	(0.2)
Nervous System Disorders	**180**	**(30.6)**
Ageusia	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Amnesia	1	(0.2)
Aphasia	1	(0.2)
Ataxia	2	(0.3)
Balance Disorder	1	(0.2)
Brain Oedema	2	(0.3)
Burning Sensation	3	(0.5)
Cerebellar Haemorrhage	2	(0.3)
Cerebral Haemorrhage	5	(0.9)
Cerebral Infarction	1	(0.2)
Clonus	1	(0.2)
Cluster Headache	1	(0.2)
Cognitive Disorder	1	(0.2)
Coma	1	(0.2)
Demyelination	1	(0.2)
Depressed Level Of Consciousness	1	(0.2)
Dizziness	30	(5.1)
Dizziness Postural	1	(0.2)
Dysaesthesia	1	(0.2)
Dysarthria	1	(0.2)
Dysgeusia	6	(1.0)
Encephalopathy	4	(0.7)
Extrapyramidal Disorder	1	(0.2)
Facial Paralysis	1	(0.2)
Haemorrhagic Stroke	1	(0.2)
Headache	83	(14.1)
Hemiplegia	1	(0.2)
Hypoaesthesia	3	(0.5)
Hypogeusia	1	(0.2)
Hyporeflexia	2	(0.3)
Hypotonia	1	(0.2)
Lethargy	7	(1.2)
Leukoencephalopathy	2	(0.3)
Loss Of Consciousness	2	(0.3)
Memory Impairment	2	(0.3)
Meningism	1	(0.2)
Metabolic Encephalopathy	1	(0.2)
Migraine	1	(0.2)
Nervous System Disorder	1	(0.2)
Neurological Symptom	1	(0.2)
Neuropathy Peripheral	5	(0.9)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Paraesthesia	8	(1.4)
Paralysis	1	(0.2)
Parosmia	1	(0.2)
Peroneal Nerve Palsy	1	(0.2)
Poor Quality Sleep	1	(0.2)
Presyncope	2	(0.3)
Psychomotor Hyperactivity	2	(0.3)
Sciatica	1	(0.2)
Seizure	5	(0.9)
Sensory Loss	2	(0.3)
Sinus Headache	1	(0.2)
Somnolence	11	(1.9)
Stupor	2	(0.3)
Syncope	9	(1.5)
Toxic Neuropathy	1	(0.2)
Tremor	30	(5.1)
Visual Field Defect	1	(0.2)
Product Issues	**11**	**(1.9)**
Device Leakage	2	(0.3)
Device Occlusion	6	(1.0)
Thrombosis In Device	3	(0.5)
Psychiatric Disorders	**145**	**(24.7)**
Affective Disorder	1	(0.2)
Agitation	7	(1.2)
Anger	1	(0.2)
Anxiety	24	(4.1)
Confusional State	22	(3.7)
Delirium	4	(0.7)
Depressed Mood	4	(0.7)
Depression	33	(5.6)
Disorientation	1	(0.2)
Emotional Distress	1	(0.2)
Euphoric Mood	1	(0.2)
Flat Affect	2	(0.3)
Hallucination	3	(0.5)
Hallucination, Visual	1	(0.2)
Hypomania	1	(0.2)
Insomnia	66	(11.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Irritability	1	(0.2)
Mental Status Changes	8	(1.4)
Mood Altered	4	(0.7)
Nervousness	1	(0.2)
Nightmare	2	(0.3)
Obsessive-Compulsive Disorder	1	(0.2)
Psychotic Disorder	1	(0.2)
Restlessness	2	(0.3)
Sleep Disorder	3	(0.5)
Suicidal Ideation	1	(0.2)
Renal And Urinary Disorders	**119**	**(20.2)**
Acute Kidney Injury	11	(1.9)
Anuria	1	(0.2)
Bladder Pain	1	(0.2)
Bladder Spasm	3	(0.5)
Choluria	1	(0.2)
Chromaturia	1	(0.2)
Chronic Kidney Disease	1	(0.2)
Costovertebral Angle Tenderness	1	(0.2)
Cystitis Haemorrhagic	7	(1.2)
Dysuria	22	(3.7)
Haematuria	27	(4.6)
Hydronephrosis	2	(0.3)
Incontinence	1	(0.2)
Micturition Urgency	4	(0.7)
Nephrolithiasis	3	(0.5)
Nocturia	3	(0.5)
Oliguria	8	(1.4)
Pollakiuria	13	(2.2)
Polyuria	6	(1.0)
Renal Failure	25	(4.3)
Renal Haematoma	1	(0.2)
Renal Impairment	7	(1.2)
Renal Vein Thrombosis	1	(0.2)
Stress Urinary Incontinence	1	(0.2)
Urethral Haemorrhage	1	(0.2)
Urinary Incontinence	8	(1.4)
Urinary Retention	7	(1.2)
Urine Abnormality	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Urine Odour Abnormal	1	(0.2)
Reproductive System And Breast Disorders	**41**	**(7.0)**
Adnexa Uteri Cyst	1	(0.2)
Balanoposthitis	1	(0.2)
Benign Prostatic Hyperplasia	1	(0.2)
Dysfunctional Uterine Bleeding	1	(0.2)
Dysmenorrhoea	2	(0.3)
Epididymal Disorder	1	(0.2)
Menopausal Symptoms	1	(0.2)
Menorrhagia	2	(0.3)
Menstrual Disorder	1	(0.2)
Metrorrhagia	5	(0.9)
Pelvic Haematoma	1	(0.2)
Pelvic Pain	2	(0.3)
Penile Haemorrhage	1	(0.2)
Penile Oedema	1	(0.2)
Perineal Pain	1	(0.2)
Prostatism	1	(0.2)
Prostatitis	1	(0.2)
Pruritus Genital	1	(0.2)
Scrotal Oedema	2	(0.3)
Scrotal Swelling	1	(0.2)
Vaginal Haemorrhage	16	(2.7)
Vulval Oedema	1	(0.2)
Vulvovaginal Burning Sensation	2	(0.3)
Vulvovaginal Discomfort	1	(0.2)
Vulvovaginal Dryness	1	(0.2)
Vulvovaginal Pain	1	(0.2)
Vulvovaginal Pruritus	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**248**	**(42.2)**
Acute Promyelocytic Leukaemia Differentiation Syndrome	1	(0.2)
Acute Pulmonary Oedema	1	(0.2)
Acute Respiratory Distress Syndrome	3	(0.5)
Acute Respiratory Failure	3	(0.5)
Apnoea	1	(0.2)
Asthma	3	(0.5)
Atelectasis	14	(2.4)
Bronchial Wall Thickening	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Bronchospasm	6	(1.0)
Chronic Obstructive Pulmonary Disease	1	(0.2)
Cough	76	(12.9)
Diaphragmalgia	1	(0.2)
Dysphonia	2	(0.3)
Dyspnoea	52	(8.8)
Dyspnoea Exertional	12	(2.0)
Emphysema	1	(0.2)
Epistaxis	53	(9.0)
Haemoptysis	10	(1.7)
Hiccups	7	(1.2)
Hyperventilation	2	(0.3)
Hypocapnia	1	(0.2)
Hypoxia	13	(2.2)
Increased Bronchial Secretion	4	(0.7)
Increased Upper Airway Secretion	1	(0.2)
Increased Viscosity Of Bronchial Secretion	2	(0.3)
Interstitial Lung Disease	2	(0.3)
Lung Consolidation	2	(0.3)
Lung Disorder	2	(0.3)
Lung Infiltration	12	(2.0)
Nasal Congestion	11	(1.9)
Nasal Discomfort	2	(0.3)
Nasal Dryness	1	(0.2)
Nasal Obstruction	1	(0.2)
Nasal Septum Disorder	1	(0.2)
Nocturnal Dyspnoea	1	(0.2)
Oropharyngeal Pain	32	(5.4)
Oropharyngeal Swelling	1	(0.2)
Orthopnoea	1	(0.2)
Painful Respiration	1	(0.2)
Paranasal Sinus Discomfort	2	(0.3)
Paranasal Sinus Hypersecretion	1	(0.2)
Pharyngeal Erythema	1	(0.2)
Pharyngeal Lesion	1	(0.2)
Pleural Effusion	22	(3.7)
Pleuritic Pain	4	(0.7)
Pneumonia Aspiration	2	(0.3)
Pneumonitis	3	(0.5)
Pneumothorax	2	(0.3)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Productive Cough	15	(2.6)
Prolonged Expiration	1	(0.2)
Pulmonary Alveolar Haemorrhage	3	(0.5)
Pulmonary Congestion	2	(0.3)
Pulmonary Embolism	3	(0.5)
Pulmonary Haemorrhage	4	(0.7)
Pulmonary Hypertension	1	(0.2)
Pulmonary Mass	3	(0.5)
Pulmonary Oedema	11	(1.9)
Rales	24	(4.1)
Respiratory Acidosis	1	(0.2)
Respiratory Disorder	2	(0.3)
Respiratory Distress	6	(1.0)
Respiratory Failure	16	(2.7)
Respiratory Tract Congestion	1	(0.2)
Rhinalgia	1	(0.2)
Rhinorrhoea	9	(1.5)
Rhonchi	2	(0.3)
Sinus Congestion	6	(1.0)
Sinus Disorder	1	(0.2)
Sinus Pain	1	(0.2)
Sinus Polyp	2	(0.3)
Sneezing	1	(0.2)
Sputum Discoloured	1	(0.2)
Sputum Increased	1	(0.2)
Tachypnoea	10	(1.7)
Throat Lesion	1	(0.2)
Throat Tightness	1	(0.2)
Tonsillar Disorder	1	(0.2)
Tonsillar Ulcer	1	(0.2)
Upper-Airway Cough Syndrome	5	(0.9)
Wheezing	9	(1.5)
Skin And Subcutaneous Tissue Disorders	**217**	**(36.9)**
Acne	1	(0.2)
Alopecia	28	(4.8)
Alopecia Totalis	1	(0.2)
Angioedema	1	(0.2)
Blister	7	(1.2)
Blood Blister	3	(0.5)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Cold Sweat	2	(0.3)
Decubitus Ulcer	1	(0.2)
Dermatitis	4	(0.7)
Dermatitis Acneiform	1	(0.2)
Dermatitis Allergic	6	(1.0)
Dermatitis Contact	2	(0.3)
Drug Eruption	4	(0.7)
Dry Skin	7	(1.2)
Ecchymosis	6	(1.0)
Eczema	2	(0.3)
Erythema	24	(4.1)
Erythrosis	1	(0.2)
Hirsutism	1	(0.2)
Hyperhidrosis	14	(2.4)
Ingrowing Nail	1	(0.2)
Leukoplakia	1	(0.2)
Lichenification	2	(0.3)
Neurodermatitis	1	(0.2)
Night Sweats	7	(1.2)
Pain Of Skin	3	(0.5)
Palmar Erythema	2	(0.3)
Palmar-Plantar Erythrodysaesthesia Syndrome	4	(0.7)
Papule	2	(0.3)
Petechiae	48	(8.2)
Photosensitivity Reaction	1	(0.2)
Pigmentation Disorder	1	(0.2)
Pruritus	39	(6.6)
Pruritus Generalised	3	(0.5)
Purpura	5	(0.9)
Purpura Senile	1	(0.2)
Rash	73	(12.4)
Rash Erythematous	7	(1.2)
Rash Follicular	1	(0.2)
Rash Generalised	3	(0.5)
Rash Macular	2	(0.3)
Rash Maculo-Papular	10	(1.7)
Rash Papular	2	(0.3)
Rash Pruritic	7	(1.2)
Rash Vesicular	1	(0.2)
Red Man Syndrome	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Scab	1	(0.2)
Skin Burning Sensation	1	(0.2)
Skin Discolouration	1	(0.2)
Skin Disorder	5	(0.9)
Skin Exfoliation	3	(0.5)
Skin Haemorrhage	1	(0.2)
Skin Hyperpigmentation	5	(0.9)
Skin Hypopigmentation	1	(0.2)
Skin Lesion	13	(2.2)
Skin Mass	4	(0.7)
Skin Striae	1	(0.2)
Skin Ulcer	5	(0.9)
Swelling Face	5	(0.9)
Transient Acantholytic Dermatosis	1	(0.2)
Urticaria	6	(1.0)
Surgical And Medical Procedures	**5**	**(0.9)**
Astringent Therapy	1	(0.2)
Sinus Operation	1	(0.2)
Therapeutic Procedure	1	(0.2)
Tooth Extraction	1	(0.2)
Wisdom Teeth Removal	1	(0.2)
Vascular Disorders	**153**	**(26.0)**
Air Embolism	1	(0.2)
Arteriovenous Fistula	1	(0.2)
Capillary Leak Syndrome	1	(0.2)
Deep Vein Thrombosis	5	(0.9)
Flushing	3	(0.5)
Haematoma	11	(1.9)
Haemodynamic Instability	1	(0.2)
Haemorrhage	4	(0.7)
Hypertension	69	(11.7)
Hypertensive Crisis	1	(0.2)
Hypotension	47	(8.0)
Hypovolaemic Shock	2	(0.3)
Ischaemia	1	(0.2)
Microangiopathy	1	(0.2)
Orthostatic Hypotension	10	(1.7)
Pallor	3	(0.5)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Peripheral Circulatory Failure	1	(0.2)
Peripheral Vascular Disorder	1	(0.2)
Peripheral Venous Disease	1	(0.2)
Phlebitis	3	(0.5)
Postpartum Venous Thrombosis	1	(0.2)
Subclavian Vein Thrombosis	1	(0.2)
Thrombophlebitis	4	(0.7)
Venous Thrombosis	2	(0.3)
Venous Thrombosis Limb	1	(0.2)
Every subject is counted a single time for each applicable row and column. MedDRA Version 20.1		

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付録 2.7.4-143　　投与開始 1 ヵ月間に発現した副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**160**	**(27.2)**
Blood And Lymphatic System Disorders	**10**	**(1.7)**
Anaemia	4	(0.7)
Bone Marrow Failure	1	(0.2)
Eosinophilia	1	(0.2)
Leukopenia	1	(0.2)
Neutropenia	1	(0.2)
Splenomegaly	1	(0.2)
Thrombocytopenia	3	(0.5)
Cardiac Disorders	**9**	**(1.5)**
Atrial Fibrillation	2	(0.3)
Bradycardia	1	(0.2)
Bundle Branch Block Left	1	(0.2)
Cardiomegaly	1	(0.2)
Extrasystoles	1	(0.2)
Sinus Arrhythmia	1	(0.2)
Supraventricular Extrasystoles	1	(0.2)
Tachycardia	1	(0.2)
Torsade De Pointes	1	(0.2)
Ventricular Extrasystoles	2	(0.3)
Ear And Labyrinth Disorders	**1**	**(0.2)**
Ear Pain	1	(0.2)
Eye Disorders	**4**	**(0.7)**
Photophobia	1	(0.2)
Vision Blurred	3	(0.5)
Gastrointestinal Disorders	**76**	**(12.9)**
Abdominal Discomfort	1	(0.2)
Abdominal Distension	4	(0.7)
Abdominal Pain	5	(0.9)
Abdominal Pain Upper	6	(1.0)
Aptyalism	1	(0.2)
Constipation	4	(0.7)
Diarrhoea	18	(3.1)
Diarrhoea Haemorrhagic	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Dry Mouth	1	(0.2)
Dyspepsia	5	(0.9)
Dysphagia	2	(0.3)
Epigastric Discomfort	1	(0.2)
Flatulence	2	(0.3)
Gastritis	2	(0.3)
Gastritis Haemorrhagic	1	(0.2)
Gastrointestinal Hypomotility	1	(0.2)
Gastrooesophageal Reflux Disease	1	(0.2)
Hypoaesthesia Oral	1	(0.2)
Melaena	1	(0.2)
Mouth Ulceration	1	(0.2)
Nausea	34	(5.8)
Oesophageal Ulcer	1	(0.2)
Oesophagitis	1	(0.2)
Tongue Coated	1	(0.2)
Tongue Discomfort	1	(0.2)
Vomiting	21	(3.6)
General Disorders And Administration Site Conditions	**19**	**(3.2)**
Asthenia	3	(0.5)
Drug Interaction	2	(0.3)
Fatigue	7	(1.2)
Generalised Oedema	1	(0.2)
Mucosal Inflammation	5	(0.9)
Pyrexia	2	(0.3)
Thirst	1	(0.2)
Hepatobiliary Disorders	**13**	**(2.2)**
Cholelithiasis	1	(0.2)
Cholestasis	1	(0.2)
Hepatitis	1	(0.2)
Hepatitis Acute	1	(0.2)
Hepatocellular Injury	2	(0.3)
Hepatotoxicity	1	(0.2)
Hyperbilirubinaemia	5	(0.9)
Jaundice	4	(0.7)
Immune System Disorders	**4**	**(0.7)**
Drug Hypersensitivity	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Graft Versus Host Disease	2	(0.3)
Hypersensitivity	1	(0.2)
Infections And Infestations	**2**	**(0.3)**
Encephalitis	1	(0.2)
Gingivitis	1	(0.2)
Injury, Poisoning And Procedural Complications	**3**	**(0.5)**
Fall	1	(0.2)
Toxicity To Various Agents	2	(0.3)
Investigations	**48**	**(8.2)**
Alanine Aminotransferase Increased	9	(1.5)
Aspartate Aminotransferase Abnormal	1	(0.2)
Aspartate Aminotransferase Increased	5	(0.9)
Bilirubin Conjugated Increased	1	(0.2)
Blood Alkaline Phosphatase Increased	2	(0.3)
Blood Bilirubin Increased	5	(0.9)
Blood Creatinine Increased	4	(0.7)
Blood Glucose Increased	1	(0.2)
Blood Lactate Dehydrogenase Increased	3	(0.5)
Blood Magnesium Decreased	1	(0.2)
Blood Potassium	1	(0.2)
Drug Level Increased	4	(0.7)
Ejection Fraction Decreased	1	(0.2)
Electrocardiogram Abnormal	1	(0.2)
Electrocardiogram Qt Prolonged	10	(1.7)
Electrocardiogram T Wave Abnormal	1	(0.2)
Electroencephalogram Abnormal	1	(0.2)
Gamma-Glutamyltransferase Increased	8	(1.4)
Hepatic Enzyme Increased	3	(0.5)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	2	(0.3)
Platelet Count Decreased	1	(0.2)
Transaminases Increased	3	(0.5)
Weight Decreased	1	(0.2)
Metabolism And Nutrition Disorders	**17**	**(2.9)**
Decreased Appetite	2	(0.3)
Electrolyte Imbalance	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Fluid Retention	1	(0.2)
Hypercholesterolaemia	1	(0.2)
Hyperglycaemia	1	(0.2)
Hyperkalaemia	2	(0.3)
Hypokalaemia	8	(1.4)
Hypomagnesaemia	1	(0.2)
Hypophagia	1	(0.2)
Hypophosphataemia	2	(0.3)
Metabolic Acidosis	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**4**	**(0.7)**
Muscle Spasms	2	(0.3)
Muscular Weakness	1	(0.2)
Myalgia	2	(0.3)
Nervous System Disorders	**24**	**(4.1)**
Ataxia	1	(0.2)
Burning Sensation	2	(0.3)
Dizziness	2	(0.3)
Dysaesthesia	1	(0.2)
Dysgeusia	3	(0.5)
Encephalopathy	2	(0.3)
Headache	5	(0.9)
Hyporeflexia	2	(0.3)
Lethargy	1	(0.2)
Meningism	1	(0.2)
Migraine	1	(0.2)
Neuropathy Peripheral	1	(0.2)
Paraesthesia	2	(0.3)
Seizure	1	(0.2)
Sensory Loss	1	(0.2)
Somnolence	2	(0.3)
Stupor	1	(0.2)
Syncope	2	(0.3)
Tremor	3	(0.5)
Visual Field Defect	1	(0.2)
Psychiatric Disorders	**5**	**(0.9)**
Confusional State	2	(0.3)
Disorientation	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Insomnia	1	(0.2)
Mental Status Changes	2	(0.3)
Psychotic Disorder	1	(0.2)
Renal And Urinary Disorders	**6**	**(1.0)**
Acute Kidney Injury	1	(0.2)
Dysuria	2	(0.3)
Haematuria	1	(0.2)
Nephrolithiasis	1	(0.2)
Pollakiuria	1	(0.2)
Renal Failure	1	(0.2)
Renal Impairment	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**4**	**(0.7)**
Cough	3	(0.5)
Interstitial Lung Disease	1	(0.2)
Rales	1	(0.2)
Upper-Airway Cough Syndrome	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**21**	**(3.6)**
Dermatitis Acneiform	1	(0.2)
Hyperhidrosis	1	(0.2)
Papule	1	(0.2)
Pruritus	4	(0.7)
Rash	7	(1.2)
Rash Follicular	1	(0.2)
Rash Generalised	2	(0.3)
Rash Macular	1	(0.2)
Rash Maculo-Papular	3	(0.5)
Rash Papular	1	(0.2)
Rash Pruritic	2	(0.3)
Skin Exfoliation	1	(0.2)
Urticaria	1	(0.2)
Vascular Disorders	**1**	**(0.2)**
Hypertension	1	(0.2)

Every subject is counted a single time for each applicable row and column.
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付録 2.7.4-144　　投与開始 1 ヵ月間に発現した重篤な有害事象の発現例数（%）
（発現割合 0%超）ポサコナゾール経口懸濁液の予防投与試験
（C/I98-316 及び P01899 試験）（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**242**	**(41.2)**
Blood And Lymphatic System Disorders	**97**	**(16.5)**
Anaemia	29	(4.9)
Bone Marrow Failure	1	(0.2)
Febrile Neutropenia	14	(2.4)
Haemolytic Uraemic Syndrome	2	(0.3)
Hypercoagulation	1	(0.2)
Leukopenia	3	(0.5)
Neutropenia	22	(3.7)
Pancytopenia	4	(0.7)
Thrombocytopenia	53	(9.0)
Thrombotic Thrombocytopenic Purpura	4	(0.7)
Cardiac Disorders	**23**	**(3.9)**
Arrhythmia	1	(0.2)
Atrial Fibrillation	3	(0.5)
Atrial Flutter	1	(0.2)
Bradycardia	1	(0.2)
Bundle Branch Block Left	1	(0.2)
Cardiac Arrest	3	(0.5)
Cardiac Failure	3	(0.5)
Cardiac Failure Congestive	1	(0.2)
Cardio-Respiratory Arrest	1	(0.2)
Cardiomegaly	1	(0.2)
Cardiopulmonary Failure	1	(0.2)
Cardiovascular Insufficiency	1	(0.2)
Left Atrial Dilatation	1	(0.2)
Left Ventricular Hypertrophy	1	(0.2)
Mitral Valve Incompetence	1	(0.2)
Myocardial Infarction	2	(0.3)
Myocarditis	1	(0.2)
Palpitations	1	(0.2)
Pericardial Effusion	1	(0.2)
Pericarditis	1	(0.2)
Sinus Tachycardia	1	(0.2)
Supraventricular Tachycardia	1	(0.2)
Tachycardia	2	(0.3)
Torsade De Pointes	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Ventricular Extrasystoles	1	(0.2)
Ear And Labyrinth Disorders	**1**	**(0.2)**
Vertigo	1	(0.2)
Eye Disorders	**3**	**(0.5)**
Glaucoma	1	(0.2)
Pupils Unequal	1	(0.2)
Vision Blurred	1	(0.2)
Visual Impairment	1	(0.2)
Gastrointestinal Disorders	**41**	**(7.0)**
Abdominal Pain	4	(0.7)
Abdominal Pain Upper	1	(0.2)
Acute Abdomen	1	(0.2)
Ascites	2	(0.3)
Colitis	1	(0.2)
Diarrhoea	9	(1.5)
Diarrhoea Haemorrhagic	1	(0.2)
Dysphagia	1	(0.2)
Enterocolitis	1	(0.2)
Gastric Ulcer Haemorrhage	2	(0.3)
Gastritis Erosive	1	(0.2)
Gastritis Haemorrhagic	1	(0.2)
Gastrointestinal Haemorrhage	8	(1.4)
Gingival Bleeding	1	(0.2)
Haematemesis	3	(0.5)
Haematochezia	1	(0.2)
Haemorrhoids	2	(0.3)
Intestinal Haemorrhage	1	(0.2)
Malabsorption	1	(0.2)
Melaena	1	(0.2)
Nausea	4	(0.7)
Neutropenic Colitis	3	(0.5)
Pancreatitis	1	(0.2)
Rectal Haemorrhage	2	(0.3)
Small Intestinal Obstruction	1	(0.2)
Tongue Discomfort	1	(0.2)
Upper Gastrointestinal Haemorrhage	1	(0.2)
Vomiting	5	(0.9)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
General Disorders And Administration Site Conditions	**52**	**(8.8)**
Asthenia	3	(0.5)
Catheter Site Haemorrhage	1	(0.2)
Chest Discomfort	1	(0.2)
Chest Pain	3	(0.5)
Chills	5	(0.9)
Disease Progression	1	(0.2)
Drug Interaction	2	(0.3)
Fatigue	2	(0.3)
General Physical Health Deterioration	1	(0.2)
Generalised Oedema	1	(0.2)
Hypothermia	1	(0.2)
Mucosal Inflammation	4	(0.7)
Multi-Organ Disorder	1	(0.2)
Multiple Organ Dysfunction Syndrome	7	(1.2)
Oedema Peripheral	2	(0.3)
Pyrexia	23	(3.9)
Therapy Non-Responder	3	(0.5)
Hepatobiliary Disorders	**19**	**(3.2)**
Cholestasis	1	(0.2)
Hepatic Failure	4	(0.7)
Hepatic Function Abnormal	1	(0.2)
Hepatitis	1	(0.2)
Hepatitis Acute	1	(0.2)
Hepatocellular Injury	1	(0.2)
Hepatotoxicity	1	(0.2)
Hyperbilirubinaemia	7	(1.2)
Jaundice	2	(0.3)
Liver Injury	1	(0.2)
Immune System Disorders	**28**	**(4.8)**
Drug Hypersensitivity	2	(0.3)
Graft Versus Host Disease	19	(3.2)
Graft Versus Host Disease In Gastrointestinal Tract	8	(1.4)
Graft Versus Host Disease In Liver	4	(0.7)
Graft Versus Host Disease In Skin	3	(0.5)
Transplant Rejection	2	(0.3)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Infections And Infestations	**88**	**(15.0)**
Acute Sinusitis	1	(0.2)
Anal Abscess	1	(0.2)
Anorectal Infection	1	(0.2)
Aspergillus Infection	1	(0.2)
Bacteraemia	14	(2.4)
Bacterial Infection	2	(0.3)
Bacterial Sepsis	2	(0.3)
Bk Virus Infection	1	(0.2)
Bronchitis	1	(0.2)
Bronchopulmonary Aspergillosis	1	(0.2)
Catheter Site Infection	1	(0.2)
Cellulitis	1	(0.2)
Cerebral Toxoplasmosis	1	(0.2)
Chronic Sinusitis	1	(0.2)
Citrobacter Infection	1	(0.2)
Corynebacterium Sepsis	1	(0.2)
Cystitis	2	(0.3)
Cytomegalovirus Colitis	3	(0.5)
Cytomegalovirus Gastritis	1	(0.2)
Cytomegalovirus Infection	13	(2.2)
Cytomegalovirus Viraemia	2	(0.3)
Device Related Infection	2	(0.3)
Device Related Sepsis	1	(0.2)
Encephalitis	1	(0.2)
Enterobacter Infection	1	(0.2)
Enterococcal Bacteraemia	1	(0.2)
Enterococcal Sepsis	1	(0.2)
Fungal Infection	1	(0.2)
Herpes Simplex	2	(0.3)
Infection	2	(0.3)
Lower Respiratory Tract Infection	2	(0.3)
Lung Abscess	1	(0.2)
Mastoiditis	1	(0.2)
Micrococcus Infection	1	(0.2)
Neutropenic Sepsis	1	(0.2)
Perirectal Abscess	1	(0.2)
Pneumocystis Jirovecii Pneumonia	1	(0.2)
Pneumonia	7	(1.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Pneumonia Bacterial	3	(0.5)
Pneumonia Cytomegaloviral	2	(0.3)
Pneumonia Fungal	2	(0.3)
Pneumonia Staphylococcal	1	(0.2)
Pseudomonal Sepsis	2	(0.3)
Pseudomonas Infection	1	(0.2)
Pulmonary Mycosis	2	(0.3)
Sepsis	8	(1.4)
Sepsis Syndrome	1	(0.2)
Septic Shock	11	(1.9)
Sinusitis	1	(0.2)
Staphylococcal Bacteraemia	3	(0.5)
Staphylococcal Infection	1	(0.2)
Streptococcal Bacteraemia	1	(0.2)
Tooth Abscess	1	(0.2)
Upper Respiratory Tract Infection	2	(0.3)
Injury, Poisoning And Procedural Complications	**9**	**(1.5)**
Complications Of Transplant Surgery	1	(0.2)
Compression Fracture	1	(0.2)
Fall	3	(0.5)
Lumbar Vertebral Fracture	1	(0.2)
Post Procedural Haemorrhage	1	(0.2)
Subarachnoid Haemorrhage	1	(0.2)
Subdural Haematoma	1	(0.2)
Toxicity To Various Agents	2	(0.3)
Investigations	**45**	**(7.7)**
Alanine Aminotransferase Increased	6	(1.0)
Aspartate Aminotransferase Increased	2	(0.3)
Bacterial Test Positive	2	(0.3)
Bilirubin Conjugated Increased	1	(0.2)
Blood Alkaline Phosphatase Increased	3	(0.5)
Blood Bicarbonate Decreased	1	(0.2)
Blood Bilirubin Increased	4	(0.7)
Blood Creatinine Increased	1	(0.2)
Blood Culture Positive	2	(0.3)
Blood Lactate Dehydrogenase Increased	1	(0.2)
Blood Pressure Increased	1	(0.2)
Blood Pressure Orthostatic	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Body Temperature	1	(0.2)
Body Temperature Increased	1	(0.2)
C-Reactive Protein Increased	1	(0.2)
Cytomegalovirus Test Positive	1	(0.2)
Drug Level Increased	2	(0.3)
Ejection Fraction Decreased	1	(0.2)
Electrocardiogram Abnormal	1	(0.2)
Electrocardiogram Qt Prolonged	1	(0.2)
Electrocardiogram T Wave Abnormal	1	(0.2)
Fungal Test Positive	1	(0.2)
Gamma-Glutamyltransferase Increased	6	(1.0)
Haemoglobin Decreased	2	(0.3)
Hepatic Enzyme Abnormal	1	(0.2)
Hepatic Enzyme Increased	4	(0.7)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	1	(0.2)
Occult Blood Positive	1	(0.2)
Platelet Count Decreased	1	(0.2)
Red Blood Cell Count Decreased	1	(0.2)
Transaminases Increased	2	(0.3)
Weight Decreased	1	(0.2)
Metabolism And Nutrition Disorders	**28**	**(4.8)**
Acidosis	2	(0.3)
Decreased Appetite	1	(0.2)
Dehydration	3	(0.5)
Diabetes Mellitus	3	(0.5)
Electrolyte Imbalance	1	(0.2)
Failure To Thrive	1	(0.2)
Gout	1	(0.2)
Hyperglycaemia	4	(0.7)
Hyperkalaemia	3	(0.5)
Hypoalbuminaemia	1	(0.2)
Hypocalcaemia	1	(0.2)
Hypokalaemia	3	(0.5)
Hypomagnesaemia	2	(0.3)
Hyponatraemia	1	(0.2)
Hypovolaemia	1	(0.2)
Malnutrition	1	(0.2)
Metabolic Acidosis	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Polydipsia	1	(0.2)
Tumour Lysis Syndrome	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**10**	**(1.7)**
Bone Pain	1	(0.2)
Muscle Contracture	1	(0.2)
Muscular Weakness	4	(0.7)
Musculoskeletal Pain	1	(0.2)
Myalgia	1	(0.2)
Myopathy	2	(0.3)
Pain In Extremity	1	(0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**15**	**(2.6)**
Acute Myeloid Leukaemia	3	(0.5)
Acute Myeloid Leukaemia Recurrent	5	(0.9)
Leukaemia	1	(0.2)
Leukaemia Recurrent	2	(0.3)
Myelodysplastic Syndrome	1	(0.2)
Neoplasm Malignant	1	(0.2)
Renal Cancer	1	(0.2)
Uterine Leiomyoma	1	(0.2)
Nervous System Disorders	**24**	**(4.1)**
Ataxia	1	(0.2)
Balance Disorder	1	(0.2)
Brain Oedema	2	(0.3)
Cerebellar Haemorrhage	2	(0.3)
Cerebral Haemorrhage	5	(0.9)
Cerebral Infarction	1	(0.2)
Coma	1	(0.2)
Depressed Level Of Consciousness	1	(0.2)
Dizziness	2	(0.3)
Encephalopathy	4	(0.7)
Haemorrhagic Stroke	1	(0.2)
Headache	3	(0.5)
Hyporeflexia	1	(0.2)
Leukoencephalopathy	1	(0.2)
Loss Of Consciousness	2	(0.3)
Meningism	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Metabolic Encephalopathy	1	(0.2)
Migraine	1	(0.2)
Nervous System Disorder	1	(0.2)
Neuropathy Peripheral	1	(0.2)
Seizure	5	(0.9)
Sensory Loss	1	(0.2)
Stupor	2	(0.3)
Syncope	2	(0.3)
Psychiatric Disorders	**8**	**(1.4)**
Confusional State	4	(0.7)
Depression	2	(0.3)
Mental Status Changes	1	(0.2)
Obsessive-Compulsive Disorder	1	(0.2)
Psychotic Disorder	1	(0.2)
Suicidal Ideation	1	(0.2)
Renal And Urinary Disorders	**24**	**(4.1)**
Acute Kidney Injury	6	(1.0)
Cystitis Haemorrhagic	2	(0.3)
Dysuria	1	(0.2)
Haematuria	6	(1.0)
Nephrolithiasis	1	(0.2)
Polyuria	1	(0.2)
Renal Failure	10	(1.7)
Renal Haematoma	1	(0.2)
Renal Impairment	1	(0.2)
Reproductive System And Breast Disorders	**4**	**(0.7)**
Prostatitis	1	(0.2)
Vaginal Haemorrhage	3	(0.5)
Respiratory, Thoracic And Mediastinal Disorders	**53**	**(9.0)**
Acute Pulmonary Oedema	1	(0.2)
Acute Respiratory Distress Syndrome	2	(0.3)
Acute Respiratory Failure	3	(0.5)
Apnoea	1	(0.2)
Atelectasis	1	(0.2)
Cough	6	(1.0)
Dyspnoea	9	(1.5)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Dyspnoea Exertional	1	(0.2)
Haemoptysis	3	(0.5)
Hypoxia	5	(0.9)
Interstitial Lung Disease	2	(0.3)
Lung Infiltration	1	(0.2)
Nocturnal Dyspnoea	1	(0.2)
Oropharyngeal Pain	1	(0.2)
Pleural Effusion	3	(0.5)
Pleuritic Pain	1	(0.2)
Pneumonia Aspiration	2	(0.3)
Pneumonitis	1	(0.2)
Pneumothorax	1	(0.2)
Productive Cough	2	(0.3)
Pulmonary Alveolar Haemorrhage	3	(0.5)
Pulmonary Embolism	3	(0.5)
Pulmonary Haemorrhage	4	(0.7)
Pulmonary Mass	1	(0.2)
Pulmonary Oedema	6	(1.0)
Rales	1	(0.2)
Respiratory Disorder	1	(0.2)
Respiratory Distress	3	(0.5)
Respiratory Failure	14	(2.4)
Rhinorrhoea	2	(0.3)
Sinus Disorder	1	(0.2)
Sputum Discoloured	1	(0.2)
Tonsillar Disorder	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**3**	**(0.5)**
Pruritus	1	(0.2)
Rash Maculo-Papular	1	(0.2)
Rash Pruritic	1	(0.2)
Rash Vesicular	1	(0.2)
Vascular Disorders	**22**	**(3.7)**
Haemodynamic Instability	1	(0.2)
Hypertension	3	(0.5)
Hypotension	15	(2.6)
Hypovolaemic Shock	2	(0.3)
Microangiopathy	1	(0.2)
Orthostatic Hypotension	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Peripheral Circulatory Failure	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-145　　投与開始 1 ヵ月間に発現した重篤な副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**43**	**(7.3)**
Blood And Lymphatic System Disorders	**3**	**(0.5)**
Anaemia	1	(0.2)
Bone Marrow Failure	1	(0.2)
Thrombocytopenia	1	(0.2)
Cardiac Disorders	**4**	**(0.7)**
Atrial Fibrillation	2	(0.3)
Bundle Branch Block Left	1	(0.2)
Torsade De Pointes	1	(0.2)
Eye Disorders	**1**	**(0.2)**
Vision Blurred	1	(0.2)
Gastrointestinal Disorders	**6**	**(1.0)**
Abdominal Pain Upper	1	(0.2)
Diarrhoea	2	(0.3)
Dysphagia	1	(0.2)
Gastritis Haemorrhagic	1	(0.2)
Melaena	1	(0.2)
Nausea	2	(0.3)
Tongue Discomfort	1	(0.2)
Vomiting	2	(0.3)
General Disorders And Administration Site Conditions	**3**	**(0.5)**
Drug Interaction	2	(0.3)
Mucosal Inflammation	1	(0.2)
Hepatobiliary Disorders	**8**	**(1.4)**
Cholestasis	1	(0.2)
Hepatitis	1	(0.2)
Hepatitis Acute	1	(0.2)
Hepatocellular Injury	1	(0.2)
Hepatotoxicity	1	(0.2)
Hyperbilirubinaemia	3	(0.5)
Jaundice	1	(0.2)
Immune System Disorders	**3**	**(0.5)**

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Drug Hypersensitivity	1	(0.2)
Graft Versus Host Disease	2	(0.3)
Infections And Infestations	**1**	**(0.2)**
Encephalitis	1	(0.2)
Injury, Poisoning And Procedural Complications	**3**	**(0.5)**
Fall	1	(0.2)
Toxicity To Various Agents	2	(0.3)
Investigations	**17**	**(2.9)**
Alanine Aminotransferase Increased	3	(0.5)
Aspartate Aminotransferase Increased	2	(0.3)
Bilirubin Conjugated Increased	1	(0.2)
Blood Alkaline Phosphatase Increased	1	(0.2)
Blood Bilirubin Increased	2	(0.3)
Blood Creatinine Increased	1	(0.2)
Drug Level Increased	2	(0.3)
Ejection Fraction Decreased	1	(0.2)
Electrocardiogram Qt Prolonged	1	(0.2)
Electrocardiogram T Wave Abnormal	1	(0.2)
Gamma-Glutamyltransferase Increased	2	(0.3)
Hepatic Enzyme Increased	2	(0.3)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	1	(0.2)
Transaminases Increased	1	(0.2)
Metabolism And Nutrition Disorders	**1**	**(0.2)**
Hyperkalaemia	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**1**	**(0.2)**
Muscular Weakness	1	(0.2)
Nervous System Disorders	**6**	**(1.0)**
Ataxia	1	(0.2)
Dizziness	1	(0.2)
Encephalopathy	2	(0.3)
Hyporeflexia	1	(0.2)
Meningism	1	(0.2)
Migraine	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 588	
Neuropathy Peripheral	1	(0.2)
Seizure	1	(0.2)
Sensory Loss	1	(0.2)
Stupor	1	(0.2)
Syncope	2	(0.3)
Psychiatric Disorders	**1**	**(0.2)**
Mental Status Changes	1	(0.2)
Psychotic Disorder	1	(0.2)
Renal And Urinary Disorders	**4**	**(0.7)**
Acute Kidney Injury	1	(0.2)
Haematuria	1	(0.2)
Nephrolithiasis	1	(0.2)
Renal Failure	1	(0.2)
Renal Impairment	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**2**	**(0.3)**
Cough	1	(0.2)
Interstitial Lung Disease	1	(0.2)
Rales	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**1**	**(0.2)**
Pruritus	1	(0.2)
Rash Maculo-Papular	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-146　　投与開始 1 ヵ月間に発現した投与中止に至った有害事象の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**138**	**(23.5)**
Blood And Lymphatic System Disorders	**10**	**(1.7)**
Febrile Neutropenia	8	(1.4)
Thrombocytopenia	2	(0.3)
Cardiac Disorders	**8**	**(1.4)**
Atrial Fibrillation	1	(0.2)
Bradycardia	1	(0.2)
Cardiac Arrest	2	(0.3)
Cardiac Failure	2	(0.3)
Cardiopulmonary Failure	1	(0.2)
Torsade De Pointes	1	(0.2)
Ventricular Extrasystoles	1	(0.2)
Eye Disorders	**2**	**(0.3)**
Photophobia	1	(0.2)
Vision Blurred	1	(0.2)
Gastrointestinal Disorders	**34**	**(5.8)**
Abdominal Pain	2	(0.3)
Abdominal Pain Upper	1	(0.2)
Acute Abdomen	1	(0.2)
Aptyalism	1	(0.2)
Ascites	1	(0.2)
Diarrhoea	4	(0.7)
Dyspepsia	2	(0.3)
Dysphagia	2	(0.3)
Gastrointestinal Haemorrhage	2	(0.3)
Nausea	14	(2.4)
Neutropenic Colitis	1	(0.2)
Tongue Discomfort	1	(0.2)
Trichoglossia	1	(0.2)
Upper Gastrointestinal Haemorrhage	1	(0.2)
Vomiting	12	(2.0)
General Disorders And Administration Site Conditions	**16**	**(2.7)**
Asthenia	1	(0.2)

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Chills	1	(0.2)
Fatigue	1	(0.2)
Feeling Jittery	1	(0.2)
Hyperthermia	1	(0.2)
Mucosal Inflammation	3	(0.5)
Multi-Organ Disorder	1	(0.2)
Multiple Organ Dysfunction Syndrome	1	(0.2)
Pyrexia	6	(1.0)
Therapy Non-Responder	1	(0.2)
Hepatobiliary Disorders	**5**	**(0.9)**
Hepatitis Acute	1	(0.2)
Hepatotoxicity	1	(0.2)
Hyperbilirubinaemia	2	(0.3)
Jaundice	2	(0.3)
Ocular Icterus	1	(0.2)
Immune System Disorders	**9**	**(1.5)**
Drug Hypersensitivity	2	(0.3)
Graft Versus Host Disease	4	(0.7)
Graft Versus Host Disease In Gastrointestinal Tract	2	(0.3)
Graft Versus Host Disease In Liver	1	(0.2)
Infections And Infestations	**23**	**(3.9)**
Acid Fast Bacilli Infection	1	(0.2)
Aspergillus Infection	1	(0.2)
Bacteraemia	1	(0.2)
Candida Infection	1	(0.2)
Candida Sepsis	1	(0.2)
Fungal Infection	3	(0.5)
Neutropenic Sepsis	1	(0.2)
Pneumonia	4	(0.7)
Pneumonia Bacterial	2	(0.3)
Pneumonia Fungal	2	(0.3)
Pulmonary Mycosis	1	(0.2)
Sepsis	1	(0.2)
Septic Shock	2	(0.3)
Staphylococcal Infection	1	(0.2)
Systemic Candida	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Systemic Mycosis	1	(0.2)
Injury, Poisoning And Procedural Complications	**1**	**(0.2)**
Subdural Haematoma	1	(0.2)
Investigations	**20**	**(3.4)**
Blood Bilirubin Increased	3	(0.5)
Blood Creatinine Increased	1	(0.2)
Drug Level Increased	1	(0.2)
Electrocardiogram Qt Prolonged	7	(1.2)
Hepatic Enzyme Increased	2	(0.3)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	3	(0.5)
Transaminases Increased	2	(0.3)
Metabolism And Nutrition Disorders	**1**	**(0.2)**
Metabolic Acidosis	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**1**	**(0.2)**
Arthritis	1	(0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**7**	**(1.2)**
Acute Myeloid Leukaemia	3	(0.5)
Acute Myeloid Leukaemia Recurrent	1	(0.2)
Leukaemia	1	(0.2)
Myelodysplastic Syndrome	1	(0.2)
Renal Cancer	1	(0.2)
Nervous System Disorders	**14**	**(2.4)**
Brain Oedema	1	(0.2)
Cerebral Haemorrhage	3	(0.5)
Coma	1	(0.2)
Depressed Level Of Consciousness	1	(0.2)
Dysgeusia	1	(0.2)
Encephalopathy	2	(0.3)
Haemorrhagic Stroke	1	(0.2)
Headache	3	(0.5)
Meningism	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Migraine	1	(0.2)
Neuropathy Peripheral	1	(0.2)
Seizure	2	(0.3)
Stupor	2	(0.3)
Tremor	2	(0.3)
Psychiatric Disorders	**5**	**(0.9)**
Confusional State	1	(0.2)
Depression	1	(0.2)
Hallucination, Visual	1	(0.2)
Mental Status Changes	2	(0.3)
Renal And Urinary Disorders	**5**	**(0.9)**
Acute Kidney Injury	2	(0.3)
Renal Failure	2	(0.3)
Renal Impairment	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**15**	**(2.6)**
Acute Respiratory Failure	1	(0.2)
Bronchospasm	1	(0.2)
Cough	2	(0.3)
Dyspnoea	1	(0.2)
Haemoptysis	1	(0.2)
Hypoxia	1	(0.2)
Interstitial Lung Disease	1	(0.2)
Lung Disorder	1	(0.2)
Lung Infiltration	2	(0.3)
Nasal Congestion	1	(0.2)
Pulmonary Haemorrhage	1	(0.2)
Pulmonary Mass	1	(0.2)
Pulmonary Oedema	1	(0.2)
Respiratory Failure	2	(0.3)
Skin And Subcutaneous Tissue Disorders	**2**	**(0.3)**
Pruritus	1	(0.2)
Rash	2	(0.3)
Vascular Disorders	**2**	**(0.3)**
Hypotension	1	(0.2)

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Hypovolaemic Shock	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

C Confidential

付録 2.7.4-147　　投与開始 1 ヵ月間に発現した投与中止に至った副作用の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Treated Subjects）

Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Subjects Reporting Any Adverse Event	**43**	**(7.3)**
Cardiac Disorders	**3**	**(0.5)**
Atrial Fibrillation	1	(0.2)
Bradycardia	1	(0.2)
Torsade De Pointes	1	(0.2)
Eye Disorders	**2**	**(0.3)**
Photophobia	1	(0.2)
Vision Blurred	1	(0.2)
Gastrointestinal Disorders	**19**	**(3.2)**
Abdominal Pain	1	(0.2)
Abdominal Pain Upper	1	(0.2)
Aptyalism	1	(0.2)
Diarrhoea	3	(0.5)
Dyspepsia	2	(0.3)
Dysphagia	1	(0.2)
Nausea	10	(1.7)
Tongue Discomfort	1	(0.2)
Vomiting	8	(1.4)
General Disorders And Administration Site Conditions	**3**	**(0.5)**
Asthenia	1	(0.2)
Fatigue	1	(0.2)
Mucosal Inflammation	1	(0.2)
Hepatobiliary Disorders	**5**	**(0.9)**
Hepatitis Acute	1	(0.2)
Hepatotoxicity	1	(0.2)
Hyperbilirubinaemia	2	(0.3)
Jaundice	1	(0.2)
Immune System Disorders	**2**	**(0.3)**
Drug Hypersensitivity	1	(0.2)
Graft Versus Host Disease	1	(0.2)
Investigations	**14**	**(2.4)**

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Pooled Prophylaxis Safety Analysis: C/I98316, P01899
All Treated Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 588	
Blood Bilirubin Increased	2	(0.3)
Blood Creatinine Increased	1	(0.2)
Drug Level Increased	1	(0.2)
Electrocardiogram Qt Prolonged	5	(0.9)
Hepatic Enzyme Increased	2	(0.3)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	1	(0.2)
Transaminases Increased	1	(0.2)
Nervous System Disorders	**4**	**(0.7)**
Dysgeusia	1	(0.2)
Encephalopathy	1	(0.2)
Headache	1	(0.2)
Meningism	1	(0.2)
Migraine	1	(0.2)
Neuropathy Peripheral	1	(0.2)
Seizure	1	(0.2)
Stupor	1	(0.2)
Tremor	2	(0.3)
Psychiatric Disorders	**1**	**(0.2)**
Mental Status Changes	1	(0.2)
Renal And Urinary Disorders	**1**	**(0.2)**
Renal Impairment	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**2**	**(0.3)**
Cough	1	(0.2)
Interstitial Lung Disease	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**2**	**(0.3)**
Pruritus	1	(0.2)
Rash	2	(0.3)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-148　　投与開始 1 ヵ月間に発現した有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**381**	**(89.0)**
Blood And Lymphatic System Disorders	**87**	**(20.3)**
Anaemia	38	(8.9)
Aplastic Anaemia	2	(0.5)
Coagulopathy	4	(0.9)
Disseminated Intravascular Coagulation	3	(0.7)
Eosinophilia	1	(0.2)
Febrile Neutropenia	8	(1.9)
Haemolysis	1	(0.2)
Haemolytic Anaemia	1	(0.2)
Haemolytic Uraemic Syndrome	1	(0.2)
Leukopenia	2	(0.5)
Neutropenia	16	(3.7)
Pancytopenia	7	(1.6)
Retroperitoneal Lymphadenopathy	1	(0.2)
Splenic Infarction	1	(0.2)
Splenomegaly	1	(0.2)
Thrombocytopenia	34	(7.9)
Thrombotic Thrombocytopenic Purpura	3	(0.7)
Cardiac Disorders	**76**	**(17.8)**
Angina Pectoris	1	(0.2)
Arrhythmia	1	(0.2)
Atrial Fibrillation	7	(1.6)
Atrial Flutter	1	(0.2)
Atrioventricular Block	1	(0.2)
Atrioventricular Block First Degree	2	(0.5)
Bradycardia	6	(1.4)
Bundle Branch Block	1	(0.2)
Cardiac Arrest	4	(0.9)
Cardiac Failure	4	(0.9)
Cardiac Failure Congestive	5	(1.2)
Cardiac Valve Disease	1	(0.2)
Cardio-Respiratory Arrest	5	(1.2)
Cardiogenic Shock	1	(0.2)
Cardiomegaly	2	(0.5)
Cardiomyopathy	1	(0.2)
Cardiopulmonary Failure	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Coronary Artery Occlusion	1	(0.2)
Cyanosis	1	(0.2)
Dilatation Atrial	1	(0.2)
Extrasystoles	1	(0.2)
Left Atrial Enlargement	1	(0.2)
Left Ventricular Hypertrophy	1	(0.2)
Mitral Valve Incompetence	1	(0.2)
Myocardial Infarction	1	(0.2)
Pericardial Effusion	8	(1.9)
Pericardial Rub	1	(0.2)
Pericarditis	1	(0.2)
Sinus Tachycardia	4	(0.9)
Supraventricular Tachycardia	6	(1.4)
Tachycardia	26	(6.1)
Ventricular Extrasystoles	3	(0.7)
Ventricular Fibrillation	1	(0.2)
Ventricular Hypertrophy	1	(0.2)
Ventricular Tachycardia	5	(1.2)
Congenital, Familial And Genetic Disorders	**1**	**(0.2)**
Aplasia	1	(0.2)
Ear And Labyrinth Disorders	**13**	**(3.0)**
Cerumen Impaction	1	(0.2)
Deafness	2	(0.5)
Ear Pain	5	(1.2)
Ear Pruritus	1	(0.2)
Hypoacusis	1	(0.2)
Middle Ear Effusion	1	(0.2)
Vertigo	2	(0.5)
Endocrine Disorders	**8**	**(1.9)**
Adrenal Insufficiency	4	(0.9)
Adrenocortical Insufficiency Acute	1	(0.2)
Cushingoid	2	(0.5)
Hyperthyroidism	1	(0.2)
Hypothyroidism	1	(0.2)
Eye Disorders	**44**	**(10.3)**
Blindness	1	(0.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Cataract	1	(0.2)
Conjunctival Haemorrhage	2	(0.5)
Conjunctival Hyperaemia	1	(0.2)
Conjunctival Irritation	1	(0.2)
Conjunctival Oedema	2	(0.5)
Corneal Epithelium Defect	1	(0.2)
Corneal Perforation	1	(0.2)
Dry Eye	4	(0.9)
Erythema Of Eyelid	2	(0.5)
Exophthalmos	1	(0.2)
Eye Irritation	4	(0.9)
Eye Movement Disorder	1	(0.2)
Eye Oedema	1	(0.2)
Eye Pain	2	(0.5)
Eye Pruritus	2	(0.5)
Eye Swelling	2	(0.5)
Lacrimation Increased	1	(0.2)
Myopia	1	(0.2)
Ocular Hyperaemia	2	(0.5)
Periorbital Oedema	1	(0.2)
Photophobia	1	(0.2)
Pupils Unequal	2	(0.5)
Scleral Discolouration	1	(0.2)
Scleral Haemorrhage	1	(0.2)
Uveitis	1	(0.2)
Vision Blurred	13	(3.0)
Visual Impairment	1	(0.2)
Gastrointestinal Disorders	**230**	**(53.7)**
Abdominal Discomfort	2	(0.5)
Abdominal Distension	16	(3.7)
Abdominal Pain	31	(7.2)
Abdominal Pain Lower	2	(0.5)
Abdominal Pain Upper	20	(4.7)
Abdominal Tenderness	1	(0.2)
Abnormal Faeces	1	(0.2)
Anal Incontinence	1	(0.2)
Ascites	5	(1.2)
Cheilitis	1	(0.2)
Colitis	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Constipation	34	(7.9)
Dental Discomfort	1	(0.2)
Diarrhoea	70	(16.4)
Diarrhoea Haemorrhagic	2	(0.5)
Dry Mouth	3	(0.7)
Duodenal Ulcer	1	(0.2)
Duodenitis	2	(0.5)
Dyspepsia	10	(2.3)
Dysphagia	9	(2.1)
Eructation	1	(0.2)
Faeces Discoloured	1	(0.2)
Faeces Soft	1	(0.2)
Flatulence	12	(2.8)
Gastric Haemorrhage	1	(0.2)
Gastric Perforation	1	(0.2)
Gastric Polyps	1	(0.2)
Gastric Ulcer	1	(0.2)
Gastritis	3	(0.7)
Gastrointestinal Haemorrhage	5	(1.2)
Gastrointestinal Pain	1	(0.2)
Gastrointestinal Sounds Abnormal	1	(0.2)
Gastrooesophageal Reflux Disease	2	(0.5)
Gingival Bleeding	3	(0.7)
Gingival Swelling	1	(0.2)
Glossitis	1	(0.2)
Glossodynia	2	(0.5)
Haematemesis	2	(0.5)
Haematochezia	4	(0.9)
Haemorrhoids	4	(0.9)
Hiatus Hernia	2	(0.5)
Hypoaesthesia Oral	2	(0.5)
Ileus	5	(1.2)
Ileus Paralytic	1	(0.2)
Intestinal Dilatation	1	(0.2)
Intestinal Ischaemia	1	(0.2)
Lip Dry	7	(1.6)
Lip Swelling	2	(0.5)
Mouth Haemorrhage	1	(0.2)
Mouth Ulceration	1	(0.2)
Nausea	80	(18.7)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Obstruction Gastric	1	(0.2)
Odynophagia	3	(0.7)
Oesophageal Pain	1	(0.2)
Oesophageal Perforation	1	(0.2)
Oesophagitis	3	(0.7)
Oral Discomfort	1	(0.2)
Oral Disorder	3	(0.7)
Oral Mucosal Blistering	1	(0.2)
Palatal Swelling	1	(0.2)
Pancreatic Atrophy	1	(0.2)
Pancreatitis	3	(0.7)
Pancreatitis Haemorrhagic	1	(0.2)
Proctalgia	1	(0.2)
Rectal Haemorrhage	1	(0.2)
Retching	2	(0.5)
Stomatitis	1	(0.2)
Submaxillary Gland Enlargement	1	(0.2)
Tongue Coated	2	(0.5)
Tongue Ulceration	1	(0.2)
Toothache	1	(0.2)
Umbilical Hernia	1	(0.2)
Upper Gastrointestinal Haemorrhage	1	(0.2)
Vomiting	68	(15 9)
General Disorders And Administration Site Conditions	**194**	**(45.3)**
Asthenia	31	(7.2)
Brain Death	1	(0.2)
Catheter Site Discharge	1	(0.2)
Catheter Site Erythema	5	(1.2)
Catheter Site Haematoma	1	(0.2)
Catheter Site Haemorrhage	1	(0.2)
Catheter Site Pain	3	(0.7)
Catheter Site Swelling	1	(0.2)
Chest Discomfort	1	(0.2)
Chest Pain	30	(7.0)
Chills	22	(5.1)
Crepitations	2	(0.5)
Cyst	1	(0.2)
Discomfort	1	(0.2)
Disease Progression	17	(4.0)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Drug Interaction	1	(0.2)
Face Oedema	3	(0.7)
Facial Pain	2	(0.5)
Fatigue	17	(4.0)
Gait Disturbance	5	(1.2)
General Physical Health Deterioration	2	(0.5)
Generalised Oedema	10	(2.3)
Hyperthermia	1	(0.2)
Hypothermia	1	(0.2)
Influenza Like Illness	1	(0.2)
Infusion Site Inflammation	1	(0.2)
Localised Oedema	1	(0.2)
Malaise	3	(0.7)
Mucosal Dryness	1	(0.2)
Mucosal Inflammation	14	(3.3)
Multiple Organ Dysfunction Syndrome	9	(2.1)
Nodule	3	(0.7)
Oedema	12	(2.8)
Oedema Peripheral	30	(7.0)
Pain	5	(1.2)
Peripheral Swelling	7	(1.6)
Pseudocyst	1	(0.2)
Puncture Site Pain	1	(0.2)
Pyrexia	74	(17 3)
Secretion Discharge	2	(0.5)
Suprapubic Pain	2	(0.5)
Swelling	2	(0.5)
Vessel Puncture Site Haematoma	1	(0.2)
Vessel Puncture Site Pain	1	(0.2)
Hepatobiliary Disorders	**19**	**(4.4)**
Cholecystitis	2	(0.5)
Cholelithiasis	1	(0.2)
Cholestasis	1	(0.2)
Hepatic Failure	3	(0.7)
Hepatic Function Abnormal	2	(0.5)
Hepatic Necrosis	1	(0.2)
Hepatitis Acute	1	(0.2)
Hepatomegaly	1	(0.2)
Hepatosplenomegaly	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Hyperbilirubinaemia	2	(0.5)
Jaundice	3	(0.7)
Liver Disorder	1	(0.2)
Ocular Icterus	3	(0.7)
Immune System Disorders	**30**	**(7.0)**
Drug Hypersensitivity	3	(0.7)
Graft Versus Host Disease	8	(1.9)
Graft Versus Host Disease In Gastrointestinal Tract	3	(0.7)
Graft Versus Host Disease In Liver	1	(0.2)
Graft Versus Host Disease In Lung	1	(0.2)
Graft Versus Host Disease In Skin	12	(2.8)
Hypersensitivity	2	(0.5)
Hypogammaglobulinaemia	2	(0.5)
Iodine Allergy	1	(0.2)
Transplant Rejection	2	(0.5)
Infections And Infestations	**167**	**(39.0)**
Abdominal Abscess	1	(0.2)
Abdominal Infection	1	(0.2)
Abscess	3	(0.7)
Abscess Neck	1	(0.2)
Acarodermatitis	1	(0.2)
Acid Fast Bacilli Infection	1	(0.2)
Actinomycosis	1	(0.2)
Alpha Haemolytic Streptococcal Infection	2	(0.5)
Aspergilloma	2	(0.5)
Aspergillus Infection	4	(0.9)
Atypical Pneumonia	1	(0.2)
Bacteraemia	8	(1.9)
Bacterial Disease Carrier	1	(0.2)
Bacterial Infection	10	(2.3)
Bronchiolitis	1	(0.2)
Bronchitis	3	(0.7)
Bronchopulmonary Aspergillosis	3	(0.7)
Catheter Site Infection	1	(0.2)
Cellulitis	2	(0.5)
Cellulitis Of Male External Genital Organ	1	(0.2)
Cellulitis Orbital	1	(0.2)
Cerebral Aspergillosis	2	(0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Chronic Sinusitis	1	(0.2)
Clostridium Difficile Colitis	2	(0.5)
Clostridium Difficile Infection	1	(0.2)
Conjunctivitis	6	(1.4)
Corynebacterium Infection	1	(0.2)
Corynebacterium Sepsis	2	(0.5)
Cytomegalovirus Chorioretinitis	2	(0.5)
Cytomegalovirus Infection	6	(1.4)
Dacryocystitis	1	(0.2)
Device Related Infection	4	(0.9)
Endocarditis Bacterial	1	(0.2)
Endophthalmitis	1	(0.2)
Enterococcal Bacteraemia	4	(0.9)
Enterococcal Infection	11	(2.6)
Enterococcal Sepsis	1	(0.2)
Escherichia Bacteraemia	1	(0.2)
Escherichia Sepsis	1	(0.2)
Eye Infection Staphylococcal	1	(0.2)
Fungaemia	1	(0.2)
Fungal Infection	2	(0.5)
Fungal Rhinitis	1	(0.2)
Fungal Sepsis	2	(0.5)
Fungal Skin Infection	1	(0.2)
Fusarium Infection	1	(0.2)
Helicobacter Gastritis	1	(0.2)
Hepatic Candidiasis	1	(0.2)
Herpes Simplex	3	(0.7)
Herpes Simplex Pneumonia	1	(0.2)
Lung Abscess	1	(0.2)
Lung Infection	1	(0.2)
Meningitis	1	(0.2)
Meningitis Cryptococcal	2	(0.5)
Mycobacterial Infection	1	(0.2)
Mycobacterium Avium Complex Infection	1	(0.2)
Nasopharyngitis	1	(0.2)
Neurosyphilis	1	(0.2)
Nocardiosis	1	(0.2)
Oral Candidiasis	4	(0.9)
Oral Fungal Infection	2	(0.5)
Oral Hairy Leukoplakia	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Oral Herpes	4	(0.9)
Osteomyelitis	2	(0.5)
Otitis Media	1	(0.2)
Parainfluenzae Virus Infection	1	(0.2)
Pelvic Abscess	1	(0.2)
Pharyngotonsillitis	1	(0.2)
Pneumocystis Jirovecii Pneumonia	4	(0.9)
Pneumonia	21	(4.9)
Pneumonia Bacterial	2	(0.5)
Pneumonia Fungal	12	(2.8)
Pneumonia Pseudomonal	1	(0.2)
Pneumonia Staphylococcal	1	(0.2)
Postoperative Wound Infection	1	(0.2)
Proctitis Herpes	1	(0.2)
Pseudallescheria Infection	1	(0.2)
Pseudomonas Infection	2	(0.5)
Purulent Discharge	1	(0.2)
Pyelonephritis	1	(0.2)
Respiratory Syncytial Virus Infection	1	(0.2)
Respiratory Tract Infection	1	(0.2)
Retinitis	1	(0.2)
Rhinitis	1	(0.2)
Sepsis	8	(1.9)
Septic Embolus	4	(0.9)
Septic Shock	5	(1.2)
Sinusitis	5	(1.2)
Sinusitis Aspergillus	1	(0.2)
Sinusitis Fungal	2	(0.5)
Staphylococcal Bacteraemia	6	(1.4)
Staphylococcal Infection	5	(1.2)
Staphylococcal Sepsis	3	(0.7)
Staphylococcal Skin Infection	1	(0.2)
Stenotrophomonas Infection	2	(0.5)
Stenotrophomonas Sepsis	1	(0.2)
Syphilis	1	(0.2)
Tooth Abscess	1	(0.2)
Tracheitis	1	(0.2)
Upper Respiratory Tract Infection	7	(1.6)
Urinary Tract Infection	12	(2.8)
Varicella	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Varicella Zoster Virus Infection	1	(0.2)
Viral Infection	2	(0.5)
Wound Infection	1	(0.2)
Injury, Poisoning And Procedural Complications	**47**	**(11.0)**
Contusion	4	(0.9)
Eschar	1	(0.2)
Eye Burns	1	(0.2)
Fall	10	(2.3)
Graft Complication	1	(0.2)
Hyphaema	1	(0.2)
Incision Site Haematoma	1	(0.2)
Infusion Related Reaction	2	(0.5)
Injury	1	(0.2)
Laceration	1	(0.2)
Muscle Strain	1	(0.2)
Overdose	1	(0.2)
Post Lumbar Puncture Syndrome	1	(0.2)
Post Procedural Haemorrhage	3	(0.7)
Procedural Complication	1	(0.2)
Procedural Pain	7	(1.6)
Skin Abrasion	1	(0.2)
Toxicity To Various Agents	3	(0.7)
Transfusion Reaction	6	(1.4)
Wound Complication	1	(0.2)
Wound Decomposition	1	(0.2)
Wound Necrosis	1	(0.2)
Investigations	**142**	**(33.2)**
Activated Partial Thromboplastin Time Prolonged	1	(0.2)
Alanine Aminotransferase Increased	13	(3.0)
Ammonia Increased	1	(0.2)
Amylase	1	(0.2)
Amylase Increased	2	(0.5)
Aspartate Aminotransferase Increased	7	(1.6)
Aspiration Pleural Cavity	1	(0.2)
Bacterial Test Positive	2	(0.5)
Bilirubin Conjugated Increased	2	(0.5)
Blood Alkaline Phosphatase Increased	10	(2.3)
Blood Bilirubin Increased	10	(2.3)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Summary of Treatment-Emergent Adverse Events
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	Posaconazole n = 428	
Blood Creatinine Increased	16	(3.7)
Blood Culture Positive	7	(1.6)
Blood Electrolytes Decreased	1	(0.2)
Blood Glucose Decreased	1	(0.2)
Blood Glucose Increased	1	(0.2)
Blood Lactate Dehydrogenase Increased	2	(0.5)
Blood Lactic Acid Increased	1	(0.2)
Blood Magnesium Decreased	1	(0.2)
Blood Phosphorus Increased	2	(0.5)
Blood Potassium Decreased	2	(0.5)
Blood Potassium Increased	1	(0.2)
Blood Pressure Decreased	1	(0.2)
Blood Pressure Increased	4	(0.9)
Blood Pressure Orthostatic	1	(0.2)
Blood Pressure Systolic Increased	1	(0.2)
Blood Sodium Decreased	1	(0.2)
Blood Sodium Increased	1	(0.2)
Blood Triglycerides Increased	1	(0.2)
Blood Urea Increased	6	(1.4)
Blood Uric Acid	1	(0.2)
Blood Uric Acid Increased	2	(0.5)
Body Temperature Increased	2	(0.5)
Breath Sounds Abnormal	6	(1.4)
Carbon Dioxide Increased	2	(0.5)
Cardiac Murmur	2	(0.5)
Cardioactive Drug Level Increased	2	(0.5)
Chest X-Ray Abnormal	1	(0.2)
Clostridium Test	1	(0.2)
Clostridium Test Positive	6	(1.4)
Computerised Tomogram Abnormal	2	(0.5)
Csf Protein Increased	1	(0.2)
Culture Urine Positive	1	(0.2)
Cytomegalovirus Test	1	(0.2)
Cytomegalovirus Test Positive	1	(0.2)
Drug Level Changed	1	(0.2)
Drug Level Increased	4	(0.9)
Ejection Fraction Decreased	2	(0.5)
Electrocardiogram Abnormal	3	(0.7)
Electrocardiogram Change	1	(0.2)
Electrocardiogram Qt Prolonged	7	(1.6)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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During the First 30 days of Treatment

	Posaconazole n = 428	
Electrocardiogram St Segment Abnormal	1	(0.2)
Electrocardiogram St Segment Elevation	1	(0.2)
Electrocardiogram T Wave Abnormal	1	(0.2)
Eosinophil Count Increased	1	(0.2)
Fungal Test Positive	3	(0.7)
Gamma-Glutamyltransferase Increased	2	(0.5)
General Physical Condition Abnormal	1	(0.2)
Glucocorticoids Decreased	1	(0.2)
Haemoglobin Decreased	4	(0.9)
Heart Rate Irregular	2	(0.5)
Hepatic Enzyme Increased	4	(0.9)
International Normalised Ratio Decreased	1	(0.2)
Lipase	1	(0.2)
Lipase Increased	2	(0.5)
Liver Function Test Abnormal	2	(0.5)
Liver Function Test Increased	10	(2.3)
Medical Observation Normal	1	(0.2)
Myocardial Necrosis Marker Increased	1	(0.2)
Occult Blood Positive	2	(0.5)
Oxygen Saturation Decreased	3	(0.7)
Pancreatic Enzymes Increased	1	(0.2)
Platelet Count Decreased	3	(0.7)
Platelet Count Increased	1	(0.2)
Prothrombin Time Prolonged	3	(0.7)
Prothrombin Time Shortened	3	(0.7)
Pupillary Light Reflex Tests Abnormal	1	(0.2)
Right Ventricular Systolic Pressure Increased	1	(0.2)
Troponin Increased	1	(0.2)
Urine Output Decreased	2	(0.5)
Weight Decreased	9	(2.1)
White Blood Cell Count Decreased	1	(0.2)
White Blood Cell Count Increased	5	(1.2)
X-Ray Abnormal	1	(0.2)
Metabolism And Nutrition Disorders	**146**	**(34.1)**
Acidosis	2	(0.5)
Cachexia	3	(0.7)
Decreased Appetite	28	(6.5)
Dehydration	9	(2.1)
Diabetes Mellitus	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Electrolyte Imbalance	4	(0.9)
Failure To Thrive	2	(0.5)
Fluid Overload	7	(1.6)
Hypercalcaemia	6	(1.4)
Hypercholesterolaemia	1	(0.2)
Hyperglycaemia	19	(4.4)
Hyperkalaemia	15	(3.5)
Hypernatraemia	4	(0.9)
Hyperphosphataemia	1	(0.2)
Hypertriglyceridaemia	1	(0.2)
Hyperuricaemia	2	(0.5)
Hypervolaemia	2	(0.5)
Hypoalbuminaemia	3	(0.7)
Hypocalcaemia	13	(3.0)
Hypoglycaemia	5	(1.2)
Hypokalaemia	34	(7.9)
Hypomagnesaemia	20	(4.7)
Hyponatraemia	9	(2.1)
Hypophosphataemia	3	(0.7)
Hypoproteinaemia	2	(0.5)
Hypovolaemia	4	(0.9)
Iron Overload	1	(0.2)
Lactic Acidosis	1	(0.2)
Malnutrition	5	(1.2)
Metabolic Acidosis	9	(2.1)
Metabolic Alkalosis	2	(0.5)
Metabolic Disorder	1	(0.2)
Polydipsia	1	(0.2)
Vitamin K Deficiency	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**89**	**(20.8)**
Amyotrophy	1	(0.2)
Arthralgia	9	(2.1)
Arthritis	1	(0.2)
Back Pain	18	(4.2)
Bone Pain	8	(1.9)
Compartment Syndrome	1	(0.2)
Fistula	1	(0.2)
Fistula Discharge	1	(0.2)
Flank Pain	7	(1.6)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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	Posaconazole n = 428	
Haemarthrosis	1	(0.2)
Joint Swelling	1	(0.2)
Muscle Atrophy	1	(0.2)
Muscle Rigidity	1	(0.2)
Muscle Spasms	2	(0.5)
Muscle Twitching	2	(0.5)
Muscular Weakness	8	(1.9)
Musculoskeletal Chest Pain	3	(0.7)
Musculoskeletal Discomfort	1	(0.2)
Musculoskeletal Pain	8	(1.9)
Musculoskeletal Stiffness	2	(0.5)
Myalgia	8	(1.9)
Myopathy	3	(0.7)
Myositis	1	(0.2)
Neck Pain	4	(0.9)
Nuchal Rigidity	4	(0.9)
Pain In Extremity	23	(5.4)
Pain In Jaw	2	(0.5)
Pathological Fracture	1	(0.2)
Tendon Pain	1	(0.2)
Vertebral Lesion	1	(0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**35**	**(8.2)**
Acute Lymphocytic Leukaemia Recurrent	1	(0.2)
Acute Myeloid Leukaemia	18	(4.2)
Acute Myeloid Leukaemia Recurrent	2	(0.5)
Anogenital Warts	1	(0.2)
Blast Cell Crisis	1	(0.2)
Chronic Lymphocytic Leukaemia Recurrent	1	(0.2)
Chronic Myeloid Leukaemia	4	(0.9)
Hepatic Neoplasm	1	(0.2)
Leukaemia	2	(0.5)
Leukaemic Retinopathy	1	(0.2)
Lung Neoplasm	1	(0.2)
Neoplasm	1	(0.2)
Non-Hodgkin's Lymphoma	2	(0.5)
Respiratory Tract Neoplasm	2	(0.5)
Nervous System Disorders	**134**	**(31.3)**
Amnesia	2	(0.5)

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Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Arachnoiditis	1	(0.2)
Asterixis	1	(0.2)
Ataxia	1	(0.2)
Brain Oedema	1	(0.2)
Brain Stem Syndrome	1	(0.2)
Cauda Equina Syndrome	1	(0.2)
Central Nervous System Inflammation	1	(0.2)
Central Nervous System Lesion	2	(0.5)
Cerebral Atrophy	1	(0.2)
Cerebral Disorder	1	(0.2)
Cerebral Haematoma	1	(0.2)
Cerebral Haemorrhage	3	(0.7)
Cerebral Infarction	3	(0.7)
Cerebrovascular Accident	1	(0.2)
Choreoathetosis	1	(0.2)
Coma	5	(1.2)
Coordination Abnormal	1	(0.2)
Cranial Nerve Disorder	1	(0.2)
Depressed Level Of Consciousness	5	(1.2)
Dizziness	23	(5.4)
Dizziness Postural	1	(0.2)
Dysarthria	5	(1.2)
Dysgeusia	2	(0.5)
Dyskinesia	1	(0.2)
Dystonia	1	(0.2)
Encephalomalacia	1	(0.2)
Encephalopathy	1	(0.2)
Facial Paralysis	3	(0.7)
Facial Paresis	1	(0.2)
Haemorrhage Intracranial	1	(0.2)
Headache	54	(12.6)
Hemiparesis	3	(0.7)
Hemiplegia	1	(0.2)
Hypoaesthesia	3	(0.7)
Hypokinesia	1	(0.2)
Hyporeflexia	2	(0.5)
Hypotonia	1	(0.2)
Intellectual Disability	1	(0.2)
Intracranial Pressure Increased	1	(0.2)
Ischaemic Stroke	1	(0.2)

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	Posaconazole n = 428	
Lethargy	10	(2.3)
Loss Of Consciousness	4	(0.9)
Memory Impairment	2	(0.5)
Mental Impairment	2	(0.5)
Metabolic Encephalopathy	1	(0.2)
Myoclonus	1	(0.2)
Nervous System Disorder	1	(0.2)
Neurological Decompensation	1	(0.2)
Paraesthesia	4	(0.9)
Presyncope	2	(0.5)
Psychomotor Skills Impaired	1	(0.2)
Restless Legs Syndrome	2	(0.5)
Seizure	4	(0.9)
Sensory Loss	3	(0.7)
Sinus Headache	1	(0.2)
Somnolence	10	(2.3)
Speech Disorder	4	(0.9)
Syncope	1	(0.2)
Toxic Encephalopathy	1	(0.2)
Tremor	13	(3.0)
Unresponsive To Stimuli	8	(1.9)
Visual Field Defect	1	(0.2)
Vocal Cord Paralysis	1	(0.2)
Product Issues	**2**	**(0.5)**
Device Occlusion	1	(0.2)
Thrombosis In Device	1	(0.2)
Psychiatric Disorders	**108**	**(25.2)**
Adjustment Disorder	1	(0.2)
Aggression	1	(0.2)
Agitation	10	(2.3)
Anxiety	28	(6.5)
Belligerence	1	(0.2)
Blunted Affect	1	(0.2)
Confusional State	23	(5.4)
Delirium	3	(0.7)
Delusion	1	(0.2)
Depression	23	(5.4)
Disorientation	5	(1.2)

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Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Echolalia	1	(0.2)
Flat Affect	1	(0.2)
Hallucination	1	(0.2)
Hallucination, Auditory	1	(0.2)
Hallucination, Visual	2	(0.5)
Insomnia	31	(7.2)
Irritability	1	(0.2)
Mental Disorder	1	(0.2)
Mental Status Changes	19	(4.4)
Mood Altered	1	(0.2)
Nervousness	1	(0.2)
Nightmare	1	(0.2)
Organic Brain Syndrome	1	(0.2)
Perseveration	1	(0.2)
Posturing	1	(0.2)
Psychomotor Retardation	1	(0.2)
Restlessness	4	(0.9)
Staring	1	(0.2)
Substance-Induced Psychotic Disorder	1	(0.2)
Renal And Urinary Disorders	**68**	**(15.9)**
Acute Kidney Injury	9	(2.1)
Anuria	2	(0.5)
Azotaemia	2	(0.5)
Bladder Pain	1	(0.2)
Bladder Spasm	2	(0.5)
Cystitis Haemorrhagic	4	(0.9)
Dysuria	6	(1.4)
Haematuria	3	(0.7)
Incontinence	3	(0.7)
Micturition Urgency	2	(0.5)
Nephritis	1	(0.2)
Nephrolithiasis	1	(0.2)
Nephropathy Toxic	1	(0.2)
Oliguria	1	(0.2)
Pollakiuria	2	(0.5)
Polyuria	2	(0.5)
Renal Colic	1	(0.2)
Renal Disorder	2	(0.5)
Renal Failure	31	(7.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Renal Impairment	2	(0.5)
Renal Tubular Acidosis	2	(0.5)
Urinary Hesitation	3	(0.7)
Urinary Incontinence	3	(0.7)
Urinary Retention	2	(0.5)
Reproductive System And Breast Disorders	**13**	**(3.0)**
Breast Tenderness	1	(0.2)
Erectile Dysfunction	1	(0.2)
Hypomenorrhoea	1	(0.2)
Pruritus Genital	1	(0.2)
Scrotal Oedema	1	(0.2)
Scrotal Pain	1	(0.2)
Scrotal Ulcer	1	(0.2)
Vaginal Haemorrhage	5	(1.2)
Vulvovaginal Pain	1	(0.2)
Vulvovaginal Pruritus	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**176**	**(41.1)**
Acute Respiratory Distress Syndrome	3	(0.7)
Acute Respiratory Failure	1	(0.2)
Apnoea	2	(0.5)
Atelectasis	2	(0.5)
Bronchial Obstruction	1	(0.2)
Bronchiectasis	2	(0.5)
Bronchospasm	1	(0.2)
Chronic Obstructive Pulmonary Disease	4	(0.9)
Cough	40	(9.3)
Dysphonia	4	(0.9)
Dyspnoea	45	(10 5)
Dyspnoea Exertional	3	(0.7)
Epistaxis	27	(6.3)
Haemoptysis	20	(4.7)
Haemothorax	2	(0.5)
Hiccups	2	(0.5)
Hypercapnia	1	(0.2)
Hypopnoea	1	(0.2)
Hypoxia	11	(2.6)
Interstitial Lung Disease	1	(0.2)
Lower Respiratory Tract Congestion	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Lung Infiltration	9	(2.1)
Mediastinal Haematoma	1	(0.2)
Nasal Congestion	7	(1.6)
Nasal Dryness	2	(0.5)
Obliterative Bronchiolitis	1	(0.2)
Obstructive Airways Disorder	1	(0.2)
Organising Pneumonia	2	(0.5)
Oropharyngeal Pain	10	(2.3)
Oropharyngeal Plaque	1	(0.2)
Orthopnoea	2	(0.5)
Painful Respiration	1	(0.2)
Paranasal Sinus Hypersecretion	1	(0.2)
Pharyngeal Disorder	1	(0.2)
Pharyngeal Ulceration	1	(0.2)
Pleural Effusion	19	(4.4)
Pleuritic Pain	7	(1.6)
Pneumonitis	1	(0.2)
Pneumothorax	4	(0.9)
Productive Cough	3	(0.7)
Pulmonary Alveolar Haemorrhage	1	(0.2)
Pulmonary Congestion	2	(0.5)
Pulmonary Fibrosis	2	(0.5)
Pulmonary Haemorrhage	1	(0.2)
Pulmonary Hypertension	1	(0.2)
Pulmonary Infarction	1	(0.2)
Pulmonary Mass	1	(0.2)
Pulmonary Oedema	8	(1.9)
Rales	6	(1.4)
Respiratory Acidosis	3	(0.7)
Respiratory Alkalosis	1	(0.2)
Respiratory Arrest	3	(0.7)
Respiratory Disorder	1	(0.2)
Respiratory Distress	14	(3.3)
Respiratory Failure	28	(6.5)
Respiratory Tract Congestion	1	(0.2)
Rhinitis Allergic	2	(0.5)
Rhinorrhoea	6	(1.4)
Rhonchi	3	(0.7)
Sinus Congestion	3	(0.7)
Tachypnoea	11	(2.6)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Upper-Airway Cough Syndrome	3	(0.7)
Vocal Cord Disorder	1	(0.2)
Wheezing	9	(2.1)
Skin And Subcutaneous Tissue Disorders	**120**	**(28.0)**
Alopecia	4	(0.9)
Blister	3	(0.7)
Blood Blister	1	(0.2)
Cold Sweat	1	(0.2)
Cutaneous Lupus Erythematosus	1	(0.2)
Decubitus Ulcer	6	(1.4)
Dermatitis Allergic	2	(0.5)
Drug Eruption	3	(0.7)
Dry Skin	5	(1.2)
Ecchymosis	5	(1.2)
Erythema	6	(1.4)
Hyperhidrosis	6	(1.4)
Livedo Reticularis	1	(0.2)
Macule	1	(0.2)
Neutrophilic Dermatosis	1	(0.2)
Night Sweats	6	(1.4)
Petechiae	9	(2.1)
Pigmentation Disorder	1	(0.2)
Prurigo	1	(0.2)
Pruritus	19	(4.4)
Pruritus Allergic	1	(0.2)
Pruritus Generalised	2	(0.5)
Rash	25	(5.8)
Rash Erythematous	3	(0.7)
Rash Generalised	5	(1.2)
Rash Macular	4	(0.9)
Rash Maculo-Papular	4	(0.9)
Rash Papular	1	(0.2)
Rash Pruritic	5	(1.2)
Scab	1	(0.2)
Skin Disorder	2	(0.5)
Skin Exfoliation	1	(0.2)
Skin Lesion	8	(1.9)
Skin Mass	3	(0.7)
Skin Ulcer	2	(0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Subcutaneous Emphysema	1	(0.2)
Swelling Face	2	(0.5)
Urticaria	3	(0.7)
Urticaria Papular	1	(0.2)
Social Circumstances	**1**	**(0.2)**
Treatment Noncompliance	1	(0.2)
Surgical And Medical Procedures	**27**	**(6.3)**
Abdominal Cavity Drainage	1	(0.2)
Cataract Operation	2	(0.5)
Catheter Removal	1	(0.2)
Chemotherapy	1	(0.2)
Choledocholithotomy	1	(0.2)
Debridement	3	(0.7)
Endotracheal Intubation	1	(0.2)
Haemofiltration	1	(0.2)
Laparotomy	1	(0.2)
Lung Lobectomy	1	(0.2)
Maxillofacial Operation	1	(0.2)
Medical Device Implantation	1	(0.2)
Sinus Operation	6	(1.4)
Skin Graft	1	(0.2)
Splenectomy	1	(0.2)
Stem Cell Transplant	1	(0.2)
Therapeutic Procedure	2	(0.5)
Thoracotomy	1	(0.2)
Tooth Extraction	1	(0.2)
Transplant	1	(0.2)
Wound Drainage	1	(0.2)
Vascular Disorders	**79**	**(18.5)**
Aneurysm	1	(0.2)
Aortic Aneurysm	2	(0.5)
Arterial Insufficiency	1	(0.2)
Arteriosclerosis	2	(0.5)
Circulatory Collapse	1	(0.2)
Deep Vein Thrombosis	2	(0.5)
Flushing	3	(0.7)
Haematoma	5	(1.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Haemorrhage	3	(0.7)
Hypertension	22	(5.1)
Hypoperfusion	1	(0.2)
Hypotension	38	(8.9)
Hypovolaemic Shock	2	(0.5)
Ischaemia	2	(0.5)
Orthostatic Hypotension	3	(0.7)
Peripheral Ischaemia	1	(0.2)
Phlebitis	2	(0.5)
Thrombophlebitis	1	(0.2)
Venous Thrombosis	1	(0.2)
Every subject is counted a single time for each applicable row and column. MedDRA Version 20.1		

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付録 2.7.4-149　　投与開始 1 ヵ月間に発現した副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**123**	**(28.7)**
Blood And Lymphatic System Disorders	**6**	**(1.4)**
Anaemia	2	(0.5)
Eosinophilia	1	(0.2)
Pancytopenia	1	(0.2)
Thrombocytopenia	2	(0.5)
Cardiac Disorders	**9**	**(2.1)**
Atrial Fibrillation	3	(0.7)
Atrial Flutter	1	(0.2)
Left Ventricular Hypertrophy	1	(0.2)
Myocardial Infarction	1	(0.2)
Supraventricular Tachycardia	3	(0.7)
Tachycardia	1	(0.2)
Ventricular Extrasystoles	2	(0.5)
Ventricular Hypertrophy	1	(0.2)
Ventricular Tachycardia	1	(0.2)
Ear And Labyrinth Disorders	**1**	**(0.2)**
Ear Pain	1	(0.2)
Endocrine Disorders	**1**	**(0.2)**
Adrenal Insufficiency	1	(0.2)
Adrenocortical Insufficiency Acute	1	(0.2)
Eye Disorders	**6**	**(1.4)**
Conjunctival Hyperaemia	1	(0.2)
Erythema Of Eyelid	1	(0.2)
Eye Irritation	1	(0.2)
Vision Blurred	3	(0.7)
Gastrointestinal Disorders	**63**	**(14.7)**
Abdominal Distension	2	(0.5)
Abdominal Pain	6	(1.4)
Abdominal Pain Upper	8	(1.9)
Abnormal Faeces	1	(0.2)
Constipation	3	(0.7)
Diarrhoea	13	(3.0)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Dry Mouth	2	(0.5)
Dyspepsia	2	(0.5)
Dysphagia	1	(0.2)
Eructation	1	(0.2)
Faeces Soft	1	(0.2)
Flatulence	2	(0.5)
Ileus	1	(0.2)
Lip Dry	2	(0.5)
Lip Swelling	1	(0.2)
Nausea	31	(7.2)
Oral Disorder	1	(0.2)
Pancreatitis	1	(0.2)
Vomiting	22	(5.1)
General Disorders And Administration Site Conditions	**12**	**(2.8)**
Asthenia	3	(0.7)
Chest Pain	1	(0.2)
Chills	1	(0.2)
Fatigue	4	(0.9)
Malaise	1	(0.2)
Mucosal Inflammation	1	(0.2)
Oedema Peripheral	1	(0.2)
Pyrexia	2	(0.5)
Hepatobiliary Disorders	**2**	**(0.5)**
Hepatic Function Abnormal	1	(0.2)
Hepatosplenomegaly	1	(0.2)
Immune System Disorders	**1**	**(0.2)**
Drug Hypersensitivity	1	(0.2)
Infections And Infestations	**2**	**(0.5)**
Conjunctivitis	2	(0.5)
Injury, Poisoning And Procedural Complications	**3**	**(0.7)**
Overdose	1	(0.2)
Toxicity To Various Agents	1	(0.2)
Transfusion Reaction	1	(0.2)
Investigations	**34**	**(7.9)**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Alanine Aminotransferase Increased	6	(1.4)
Amylase	1	(0.2)
Aspartate Aminotransferase Increased	5	(1.2)
Bilirubin Conjugated Increased	1	(0.2)
Blood Alkaline Phosphatase Increased	3	(0.7)
Blood Bilirubin Increased	1	(0.2)
Blood Creatinine Increased	3	(0.7)
Cardioactive Drug Level Increased	1	(0.2)
Drug Level Changed	1	(0.2)
Drug Level Increased	2	(0.5)
Electrocardiogram Change	1	(0.2)
Electrocardiogram Qt Prolonged	4	(0.9)
Gamma-Glutamyltransferase Increased	1	(0.2)
Glucocorticoids Decreased	1	(0.2)
Hepatic Enzyme Increased	2	(0.5)
Lipase	1	(0.2)
Liver Function Test Abnormal	1	(0.2)
Liver Function Test Increased	3	(0.7)
Pancreatic Enzymes Increased	1	(0.2)
Platelet Count Decreased	1	(0.2)
Metabolism And Nutrition Disorders	**7**	**(1.6)**
Decreased Appetite	3	(0.7)
Electrolyte Imbalance	1	(0.2)
Hyperkalaemia	1	(0.2)
Hyperphosphataemia	1	(0.2)
Hypokalaemia	1	(0.2)
Metabolic Acidosis	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**8**	**(1.9)**
Arthralgia	1	(0.2)
Back Pain	1	(0.2)
Bone Pain	2	(0.5)
Myalgia	1	(0.2)
Nuchal Rigidity	1	(0.2)
Pain In Extremity	2	(0.5)
Pain In Jaw	1	(0.2)
Nervous System Disorders	**26**	**(6.1)**
Dizziness	7	(1.6)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Dysgeusia	1	(0.2)
Headache	14	(3.3)
Hypotonia	1	(0.2)
Memory Impairment	1	(0.2)
Mental Impairment	1	(0.2)
Paraesthesia	1	(0.2)
Seizure	1	(0.2)
Somnolence	3	(0.7)
Speech Disorder	1	(0.2)
Psychiatric Disorders	**4**	**(0.9)**
Confusional State	2	(0.5)
Delirium	1	(0.2)
Mental Status Changes	2	(0.5)
Renal And Urinary Disorders	**3**	**(0.7)**
Acute Kidney Injury	1	(0.2)
Renal Failure	1	(0.2)
Renal Tubular Acidosis	1	(0.2)
Urinary Hesitation	1	(0.2)
Reproductive System And Breast Disorders	**1**	**(0.2)**
Hypomenorrhoea	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**1**	**(0.2)**
Dyspnoea	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**19**	**(4.4)**
Dry Skin	3	(0.7)
Hyperhidrosis	1	(0.2)
Pruritus	4	(0.9)
Rash	5	(1.2)
Rash Macular	1	(0.2)
Rash Maculo-Papular	1	(0.2)
Rash Papular	1	(0.2)
Rash Pruritic	2	(0.5)
Urticaria	1	(0.2)
Urticaria Papular	1	(0.2)
Surgical And Medical Procedures	**1**	**(0.2)**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Therapeutic Procedure	1	(0.2)
Vascular Disorders	**2**	**(0.5)**
Hypertension	1	(0.2)
Hypotension	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-150　　投与開始 1 ヵ月間に発現した
重篤な有害事象の発現例数（%）（発現割合 0%超）
ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**170**	**(39.7)**
Blood And Lymphatic System Disorders	**34**	**(7.9)**
Anaemia	4	(0.9)
Aplastic Anaemia	2	(0.5)
Disseminated Intravascular Coagulation	1	(0.2)
Eosinophilia	1	(0.2)
Febrile Neutropenia	7	(1.6)
Haemolysis	1	(0.2)
Haemolytic Uraemic Syndrome	1	(0.2)
Neutropenia	5	(1.2)
Pancytopenia	2	(0.5)
Splenic Infarction	1	(0.2)
Thrombocytopenia	11	(2.6)
Thrombotic Thrombocytopenic Purpura	3	(0.7)
Cardiac Disorders	**32**	**(7.5)**
Atrial Fibrillation	4	(0.9)
Atrial Flutter	1	(0.2)
Atrioventricular Block First Degree	1	(0.2)
Bradycardia	4	(0.9)
Cardiac Arrest	4	(0.9)
Cardiac Failure	4	(0.9)
Cardiac Failure Congestive	3	(0.7)
Cardiac Valve Disease	1	(0.2)
Cardio-Respiratory Arrest	5	(1.2)
Cardiogenic Shock	1	(0.2)
Cardiopulmonary Failure	1	(0.2)
Coronary Artery Occlusion	1	(0.2)
Myocardial Infarction	1	(0.2)
Pericardial Effusion	1	(0.2)
Sinus Tachycardia	2	(0.5)
Supraventricular Tachycardia	4	(0.9)
Tachycardia	2	(0.5)
Ventricular Extrasystoles	2	(0.5)
Ventricular Fibrillation	1	(0.2)
Ventricular Hypertrophy	1	(0.2)
Ventricular Tachycardia	5	(1.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Congenital, Familial And Genetic Disorders	**1**	**(0.2)**
Aplasia	1	(0.2)
Endocrine Disorders	**1**	**(0.2)**
Adrenal Insufficiency	1	(0.2)
Eye Disorders	**1**	**(0.2)**
Corneal Perforation	1	(0.2)
Gastrointestinal Disorders	**29**	**(6.8)**
Abdominal Distension	1	(0.2)
Abdominal Pain	3	(0.7)
Abdominal Pain Lower	1	(0.2)
Abdominal Pain Upper	1	(0.2)
Colitis	1	(0.2)
Diarrhoea	6	(1.4)
Duodenal Ulcer	1	(0.2)
Duodenitis	2	(0.5)
Dysphagia	1	(0.2)
Gastric Haemorrhage	1	(0.2)
Gastric Perforation	1	(0.2)
Gastritis	1	(0.2)
Gastrointestinal Haemorrhage	2	(0.5)
Gingival Bleeding	1	(0.2)
Haematemesis	1	(0.2)
Haematochezia	2	(0.5)
Ileus	2	(0.5)
Intestinal Ischaemia	1	(0.2)
Nausea	7	(1.6)
Pancreatitis	2	(0.5)
Pancreatitis Haemorrhagic	1	(0.2)
Stomatitis	1	(0.2)
Upper Gastrointestinal Haemorrhage	1	(0.2)
Vomiting	9	(2.1)
General Disorders And Administration Site Conditions	**58**	**(13.6)**
Asthenia	4	(0.9)
Brain Death	1	(0.2)
Chest Pain	2	(0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Chills	2	(0.5)
Disease Progression	17	(4.0)
Drug Interaction	1	(0.2)
Fatigue	2	(0.5)
Gait Disturbance	1	(0.2)
Generalised Oedema	3	(0.7)
Multiple Organ Dysfunction Syndrome	9	(2.1)
Oedema Peripheral	2	(0.5)
Pyrexia	24	(5.6)
Hepatobiliary Disorders	**7**	**(1.6)**
Cholecystitis	1	(0.2)
Cholelithiasis	1	(0.2)
Hepatic Failure	3	(0.7)
Hepatic Function Abnormal	1	(0.2)
Hepatic Necrosis	1	(0.2)
Hepatitis Acute	1	(0.2)
Immune System Disorders	**16**	**(3.7)**
Drug Hypersensitivity	1	(0.2)
Graft Versus Host Disease	7	(1.6)
Graft Versus Host Disease In Gastrointestinal Tract	2	(0.5)
Graft Versus Host Disease In Lung	1	(0.2)
Graft Versus Host Disease In Skin	4	(0.9)
Transplant Rejection	2	(0.5)
Infections And Infestations	**75**	**(17.5)**
Abdominal Infection	1	(0.2)
Abscess	1	(0.2)
Abscess Neck	1	(0.2)
Aspergilloma	1	(0.2)
Aspergillus Infection	3	(0.7)
Atypical Pneumonia	1	(0.2)
Bacteraemia	4	(0.9)
Bacterial Infection	2	(0.5)
Bronchiolitis	1	(0.2)
Bronchopulmonary Aspergillosis	1	(0.2)
Catheter Site Infection	1	(0.2)
Cellulitis Of Male External Genital Organ	1	(0.2)
Cellulitis Orbital	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Cerebral Aspergillosis	1	(0.2)
Cytomegalovirus Chorioretinitis	1	(0.2)
Device Related Infection	1	(0.2)
Enterococcal Bacteraemia	1	(0.2)
Enterococcal Infection	2	(0.5)
Enterococcal Sepsis	1	(0.2)
Escherichia Sepsis	1	(0.2)
Fungaemia	1	(0.2)
Fungal Infection	2	(0.5)
Fungal Sepsis	2	(0.5)
Fusarium Infection	1	(0.2)
Meningitis	1	(0.2)
Meningitis Cryptococcal	2	(0.5)
Mycobacterial Infection	1	(0.2)
Osteomyelitis	1	(0.2)
Pelvic Abscess	1	(0.2)
Pneumocystis Jirovecii Pneumonia	2	(0.5)
Pneumonia	15	(3.5)
Pneumonia Bacterial	1	(0.2)
Pneumonia Fungal	10	(2.3)
Pneumonia Staphylococcal	1	(0.2)
Pseudallescheria Infection	1	(0.2)
Pseudomonas Infection	1	(0.2)
Pyelonephritis	1	(0.2)
Retinitis	1	(0.2)
Sepsis	7	(1.6)
Septic Embolus	3	(0.7)
Septic Shock	5	(1.2)
Sinusitis	1	(0.2)
Staphylococcal Bacteraemia	1	(0.2)
Staphylococcal Infection	2	(0.5)
Staphylococcal Sepsis	3	(0.7)
Stenotrophomonas Sepsis	1	(0.2)
Upper Respiratory Tract Infection	1	(0.2)
Urinary Tract Infection	1	(0.2)
Wound Infection	1	(0.2)
Injury, Poisoning And Procedural Complications	**3**	**(0.7)**
Overdose	1	(0.2)
Procedural Complication	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Toxicity To Various Agents	1	(0.2)
Investigations	**24**	**(5.6)**
Amylase	1	(0.2)
Bacterial Test Positive	1	(0.2)
Blood Creatinine Increased	2	(0.5)
Blood Culture Positive	2	(0.5)
Blood Pressure Decreased	1	(0.2)
Cytomegalovirus Test	1	(0.2)
Drug Level Increased	2	(0.5)
Ejection Fraction Decreased	1	(0.2)
Electrocardiogram Qt Prolonged	2	(0.5)
Electrocardiogram St Segment Abnormal	1	(0.2)
Eosinophil Count Increased	1	(0.2)
Gamma-Glutamyltransferase Increased	1	(0.2)
Hepatic Enzyme Increased	2	(0.5)
Lipase	1	(0.2)
Liver Function Test Increased	4	(0.9)
Oxygen Saturation Decreased	1	(0.2)
Pancreatic Enzymes Increased	1	(0.2)
Platelet Count Decreased	1	(0.2)
Pupillary Light Reflex Tests Abnormal	1	(0.2)
Weight Decreased	1	(0.2)
Metabolism And Nutrition Disorders	**22**	**(5.1)**
Acidosis	1	(0.2)
Cachexia	1	(0.2)
Decreased Appetite	1	(0.2)
Dehydration	3	(0.7)
Electrolyte Imbalance	2	(0.5)
Failure To Thrive	1	(0.2)
Fluid Overload	1	(0.2)
Hyperglycaemia	1	(0.2)
Hyperkalaemia	4	(0.9)
Hypervolaemia	1	(0.2)
Hypocalcaemia	1	(0.2)
Hypokalaemia	2	(0.5)
Hypomagnesaemia	3	(0.7)
Hyponatraemia	1	(0.2)
Lactic Acidosis	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Metabolic Acidosis	3	(0.7)
Musculoskeletal And Connective Tissue Disorders	**6**	**(1.4)**
Arthralgia	1	(0.2)
Back Pain	1	(0.2)
Compartment Syndrome	1	(0.2)
Flank Pain	2	(0.5)
Myopathy	1	(0.2)
Pathological Fracture	1	(0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**28**	**(6.5)**
Acute Lymphocytic Leukaemia Recurrent	1	(0.2)
Acute Myeloid Leukaemia	17	(4.0)
Acute Myeloid Leukaemia Recurrent	1	(0.2)
Blast Cell Crisis	1	(0.2)
Chronic Lymphocytic Leukaemia Recurrent	1	(0.2)
Chronic Myeloid Leukaemia	4	(0.9)
Leukaemia	1	(0.2)
Non-Hodgkin's Lymphoma	2	(0.5)
Respiratory Tract Neoplasm	1	(0.2)
Nervous System Disorders	**32**	**(7.5)**
Amnesia	1	(0.2)
Arachnoiditis	1	(0.2)
Brain Oedema	1	(0.2)
Cauda Equina Syndrome	1	(0.2)
Cerebral Atrophy	1	(0.2)
Cerebral Haemorrhage	2	(0.5)
Cerebral Infarction	2	(0.5)
Coma	4	(0.9)
Depressed Level Of Consciousness	2	(0.5)
Dizziness	2	(0.5)
Dystonia	1	(0.2)
Encephalomalacia	1	(0.2)
Encephalopathy	1	(0.2)
Facial Paralysis	1	(0.2)
Haemorrhage Intracranial	1	(0.2)
Headache	3	(0.7)
Hemiparesis	2	(0.5)
Hemiplegia	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Intracranial Pressure Increased	1	(0.2)
Loss Of Consciousness	1	(0.2)
Mental Impairment	1	(0.2)
Metabolic Encephalopathy	1	(0.2)
Nervous System Disorder	1	(0.2)
Presyncope	1	(0.2)
Seizure	3	(0.7)
Somnolence	2	(0.5)
Speech Disorder	1	(0.2)
Tremor	1	(0.2)
Unresponsive To Stimuli	7	(1.6)
Psychiatric Disorders	**15**	**(3.5)**
Anxiety	1	(0.2)
Confusional State	6	(1.4)
Delirium	2	(0.5)
Delusion	1	(0.2)
Disorientation	2	(0.5)
Echolalia	1	(0.2)
Mental Status Changes	8	(1.9)
Perseveration	1	(0.2)
Restlessness	1	(0.2)
Renal And Urinary Disorders	**27**	**(6.3)**
Acute Kidney Injury	4	(0.9)
Anuria	2	(0.5)
Bladder Spasm	1	(0.2)
Cystitis Haemorrhagic	4	(0.9)
Dysuria	2	(0.5)
Nephrolithiasis	1	(0.2)
Renal Colic	1	(0.2)
Renal Failure	16	(3.7)
Renal Tubular Acidosis	2	(0.5)
Urinary Retention	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**62**	**(14.5)**
Acute Respiratory Distress Syndrome	3	(0.7)
Acute Respiratory Failure	1	(0.2)
Apnoea	1	(0.2)
Bronchiectasis	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Chronic Obstructive Pulmonary Disease	2	(0.5)
Dyspnoea	12	(2.8)
Epistaxis	1	(0.2)
Haemoptysis	4	(0.9)
Haemothorax	2	(0.5)
Hypoxia	6	(1.4)
Interstitial Lung Disease	1	(0.2)
Lung Infiltration	4	(0.9)
Obliterative Bronchiolitis	1	(0.2)
Pleural Effusion	6	(1.4)
Pleuritic Pain	2	(0.5)
Pneumonitis	1	(0.2)
Pneumothorax	3	(0.7)
Pulmonary Alveolar Haemorrhage	1	(0.2)
Pulmonary Haemorrhage	1	(0.2)
Pulmonary Hypertension	1	(0.2)
Pulmonary Infarction	1	(0.2)
Pulmonary Oedema	5	(1.2)
Respiratory Acidosis	1	(0.2)
Respiratory Arrest	3	(0.7)
Respiratory Disorder	1	(0.2)
Respiratory Distress	10	(2.3)
Respiratory Failure	27	(6.3)
Tachypnoea	3	(0.7)
Skin And Subcutaneous Tissue Disorders	**5**	**(1.2)**
Decubitus Ulcer	1	(0.2)
Hyperhidrosis	1	(0.2)
Rash	2	(0.5)
Rash Maculo-Papular	1	(0.2)
Rash Pruritic	1	(0.2)
Surgical And Medical Procedures	**10**	**(2.3)**
Cataract Operation	1	(0.2)
Catheter Removal	1	(0.2)
Debridement	1	(0.2)
Endotracheal Intubation	1	(0.2)
Laparotomy	1	(0.2)
Lung Lobectomy	1	(0.2)
Maxillofacial Operation	1	(0.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Skin Graft	1	(0.2)
Splenectomy	1	(0.2)
Therapeutic Procedure	1	(0.2)
Thoracotomy	1	(0.2)
Vascular Disorders	**24**	**(5.6)**
Aneurysm	1	(0.2)
Aortic Aneurysm	2	(0.5)
Circulatory Collapse	1	(0.2)
Deep Vein Thrombosis	1	(0.2)
Haematoma	1	(0.2)
Haemorrhage	3	(0.7)
Hypertension	2	(0.5)
Hypoperfusion	1	(0.2)
Hypotension	14	(3.3)
Hypovolaemic Shock	1	(0.2)
Ischaemia	1	(0.2)
Phlebitis	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-151　　投与開始 1 ヵ月間に発現した重篤な副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**20**	**(4.7)**
Blood And Lymphatic System Disorders	**2**	**(0.5)**
Eosinophilia	1	(0.2)
Pancytopenia	1	(0.2)
Cardiac Disorders	**5**	**(1.2)**
Atrial Fibrillation	2	(0.5)
Myocardial Infarction	1	(0.2)
Supraventricular Tachycardia	2	(0.5)
Ventricular Extrasystoles	2	(0.5)
Ventricular Hypertrophy	1	(0.2)
Ventricular Tachycardia	1	(0.2)
Endocrine Disorders	**1**	**(0.2)**
Adrenal Insufficiency	1	(0.2)
Gastrointestinal Disorders	**2**	**(0.5)**
Abdominal Pain	1	(0.2)
Diarrhoea	2	(0.5)
Ileus	1	(0.2)
Nausea	2	(0.5)
Pancreatitis	1	(0.2)
Vomiting	2	(0.5)
Hepatobiliary Disorders	**1**	**(0.2)**
Hepatic Function Abnormal	1	(0.2)
Immune System Disorders	**1**	**(0.2)**
Drug Hypersensitivity	1	(0.2)
Injury, Poisoning And Procedural Complications	**2**	**(0.5)**
Overdose	1	(0.2)
Toxicity To Various Agents	1	(0.2)
Investigations	**6**	**(1.4)**
Amylase	1	(0.2)
Drug Level Increased	1	(0.2)
Gamma-Glutamyltransferase Increased	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Serious Adverse Events
During the First 30 days of Treatment

	Posaconazole n = 428	
Hepatic Enzyme Increased	2	(0.5)
Lipase	1	(0.2)
Liver Function Test Increased	1	(0.2)
Pancreatic Enzymes Increased	1	(0.2)
Metabolism And Nutrition Disorders	**1**	**(0.2)**
Electrolyte Imbalance	1	(0.2)
Nervous System Disorders	**4**	**(0.9)**
Dizziness	2	(0.5)
Mental Impairment	1	(0.2)
Seizure	1	(0.2)
Psychiatric Disorders	**2**	**(0.5)**
Delirium	1	(0.2)
Mental Status Changes	2	(0.5)
Renal And Urinary Disorders	**1**	**(0.2)**
Acute Kidney Injury	1	(0.2)
Renal Tubular Acidosis	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**1**	**(0.2)**
Dyspnoea	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**4**	**(0.9)**
Rash	2	(0.5)
Rash Maculo-Papular	1	(0.2)
Rash Pruritic	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-152　　投与開始 1 ヵ月間に発現した投与中止に至った有害事象の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）（All Randomized Subjects）
Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**66**	**(15.4)**
Blood And Lymphatic System Disorders	**2**	**(0.5)**
Thrombocytopenia	1	(0.2)
Thrombotic Thrombocytopenic Purpura	1	(0.2)
Cardiac Disorders	**6**	**(1.4)**
Bradycardia	1	(0.2)
Cardiac Arrest	2	(0.5)
Cardio-Respiratory Arrest	1	(0.2)
Ventricular Tachycardia	2	(0.5)
Gastrointestinal Disorders	**10**	**(2.3)**
Abdominal Pain	2	(0.5)
Diarrhoea	1	(0.2)
Dysphagia	1	(0.2)
Haematemesis	1	(0.2)
Intestinal Ischaemia	1	(0.2)
Nausea	5	(1.2)
Pancreatitis	1	(0.2)
Upper Gastrointestinal Haemorrhage	1	(0.2)
Vomiting	4	(0.9)
General Disorders And Administration Site Conditions	**10**	**(2.3)**
Asthenia	1	(0.2)
Disease Progression	3	(0.7)
Fatigue	1	(0.2)
Gait Disturbance	1	(0.2)
Malaise	1	(0.2)
Multiple Organ Dysfunction Syndrome	1	(0.2)
Pyrexia	2	(0.5)
Hepatobiliary Disorders	**2**	**(0.5)**
Hepatic Function Abnormal	1	(0.2)
Hyperbilirubinaemia	1	(0.2)
Immune System Disorders	**2**	**(0.5)**
Drug Hypersensitivity	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 428	
Transplant Rejection	1	(0.2)
Infections And Infestations	**14**	**(3.3)**
Aspergillus Infection	2	(0.5)
Cerebral Aspergillosis	1	(0.2)
Fungal Sepsis	2	(0.5)
Pneumonia	1	(0.2)
Pneumonia Fungal	4	(0.9)
Sepsis	1	(0.2)
Septic Embolus	1	(0.2)
Septic Shock	1	(0.2)
Sinusitis	1	(0.2)
Sinusitis Fungal	1	(0.2)
Investigations	**7**	**(1.6)**
Alanine Aminotransferase Increased	1	(0.2)
Amylase	1	(0.2)
Blood Pressure Decreased	1	(0.2)
Drug Level Increased	1	(0.2)
Gamma-Glutamyltransferase Increased	1	(0.2)
Hepatic Enzyme Increased	1	(0.2)
Lipase	1	(0.2)
Liver Function Test Increased	1	(0.2)
Pancreatic Enzymes Increased	1	(0.2)
Metabolism And Nutrition Disorders	**4**	**(0.9)**
Cachexia	1	(0.2)
Decreased Appetite	1	(0.2)
Electrolyte Imbalance	1	(0.2)
Lactic Acidosis	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**2**	**(0.5)**
Back Pain	1	(0.2)
Bone Pain	1	(0.2)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**3**	**(0.7)**
Acute Myeloid Leukaemia	1	(0.2)
Lung Neoplasm	1	(0.2)
Non-Hodgkin's Lymphoma	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 428	
Nervous System Disorders	**10**	**(2.3)**
Arachnoiditis	1	(0.2)
Depressed Level Of Consciousness	2	(0.5)
Dizziness	2	(0.5)
Dysgeusia	1	(0.2)
Haemorrhage Intracranial	1	(0.2)
Headache	1	(0.2)
Lethargy	1	(0.2)
Loss Of Consciousness	1	(0.2)
Seizure	1	(0.2)
Psychiatric Disorders	**2**	**(0.5)**
Confusional State	1	(0.2)
Mental Status Changes	1	(0.2)
Renal And Urinary Disorders	**2**	**(0.5)**
Acute Kidney Injury	1	(0.2)
Renal Failure	1	(0.2)
Renal Tubular Acidosis	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**16**	**(3.7)**
Cough	1	(0.2)
Dyspnoea	3	(0.7)
Lung Infiltration	1	(0.2)
Obliterative Bronchiolitis	1	(0.2)
Obstructive Airways Disorder	1	(0.2)
Respiratory Distress	3	(0.7)
Respiratory Failure	6	(1.4)
Wheezing	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**3**	**(0.7)**
Rash	1	(0.2)
Rash Macular	1	(0.2)
Rash Maculo-Papular	1	(0.2)
Surgical And Medical Procedures	**1**	**(0.2)**
Therapeutic Procedure	1	(0.2)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 428	
Vascular Disorders	**4**	**(0.9)**
Aortic Aneurysm	1	(0.2)
Haemorrhage	2	(0.5)
Hypertension	1	(0.2)
Hypotension	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

付録 2.7.4-153　　投与開始 1 ヵ月間に発現した投与中止に至った副作用の発現例数（%）（発現割合 0%超）

ポサコナゾール経口懸濁液の治療試験（P01893 及び P00041 試験）

（All Randomized Subjects）

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 428	
Subjects Reporting Any Adverse Event	**14**	**(3.3)**
Gastrointestinal Disorders	**4**	**(0.9)**
Abdominal Pain	2	(0.5)
Diarrhoea	1	(0.2)
Nausea	3	(0.7)
Pancreatitis	1	(0.2)
Vomiting	2	(0.5)
General Disorders And Administration Site Conditions	**2**	**(0.5)**
Fatigue	1	(0.2)
Malaise	1	(0.2)
Hepatobiliary Disorders	**1**	**(0.2)**
Hepatic Function Abnormal	1	(0.2)
Immune System Disorders	**1**	**(0.2)**
Drug Hypersensitivity	1	(0.2)
Investigations	**5**	**(1.2)**
Alanine Aminotransferase Increased	1	(0.2)
Amylase	1	(0.2)
Gamma-Glutamyltransferase Increased	1	(0.2)
Hepatic Enzyme Increased	1	(0.2)
Lipase	1	(0.2)
Liver Function Test Increased	1	(0.2)
Pancreatic Enzymes Increased	1	(0.2)
Metabolism And Nutrition Disorders	**2**	**(0.5)**
Decreased Appetite	1	(0.2)
Electrolyte Imbalance	1	(0.2)
Musculoskeletal And Connective Tissue Disorders	**2**	**(0.5)**
Back Pain	1	(0.2)
Bone Pain	1	(0.2)
Nervous System Disorders	**4**	**(0.9)**
Dizziness	2	(0.5)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment-Related Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
During the First 30 days of Treatment

	Posaconazole n = 428	
Dysgeusia	1	(0.2)
Seizure	1	(0.2)
Psychiatric Disorders	**1**	**(0.2)**
Mental Status Changes	1	(0.2)
Renal And Urinary Disorders	**1**	**(0.2)**
Acute Kidney Injury	1	(0.2)
Renal Tubular Acidosis	1	(0.2)
Respiratory, Thoracic And Mediastinal Disorders	**1**	**(0.2)**
Dyspnoea	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**3**	**(0.7)**
Rash	1	(0.2)
Rash Macular	1	(0.2)
Rash Maculo-Papular	1	(0.2)

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-154　　投与開始 1 ヵ月間に発現した有害事象の発現例数（%）
（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events during the first 30 days of treatment	76	(98.7)	36	(94.7)
with no adverse events during the first 30 days of treatment	1	(1.3)	2	(5.3)
Blood and lymphatic system disorders	**5**	**(6.5)**	**3**	**(7.9)**
Anaemia	2	(2.6)	2	(5.3)
Eosinophilia	1	(1.3)	0	(0.0)
Febrile neutropenia	1	(1.3)	1	(2.6)
Hypochromic anaemia	1	(1.3)	0	(0.0)
Thrombocytopenia	2	(2.6)	0	(0.0)
Cardiac disorders	**5**	**(6.5)**	**3**	**(7.9)**
Atrioventricular block first degree	0	(0.0)	1	(2.6)
Bundle branch block right	0	(0.0)	1	(2.6)
Cardiac failure	2	(2.6)	0	(0.0)
Cardiac failure congestive	2	(2.6)	0	(0.0)
Cor pulmonale	1	(1.3)	0	(0.0)
Tachycardia	0	(0.0)	1	(2.6)
Ear and labyrinth disorders	**0**	**(0.0)**	**1**	**(2.6)**
Tinnitus	0	(0.0)	1	(2.6)
Eye disorders	**9**	**(11.7)**	**22**	**(57.9)**
Blepharitis	1	(1.3)	0	(0.0)
Colour blindness acquired	0	(0.0)	5	(13.2)
Conjunctival hyperaemia	1	(1.3)	0	(0.0)
Diplopia	1	(1.3)	0	(0.0)
Dyschromatopsia	0	(0.0)	1	(2.6)
Ocular hyperaemia	2	(2.6)	0	(0.0)
Photophobia	4	(5.2)	11	(28.9)
Vision blurred	1	(1.3)	3	(7.9)
Visual impairment	0	(0.0)	5	(13.2)
Gastrointestinal disorders	**22**	**(28.6)**	**15**	**(39.5)**
Abdominal discomfort	2	(2.6)	0	(0.0)
Cheilitis	0	(0.0)	1	(2.6)
Constipation	12	(15.6)	4	(10 5)
Dental caries	1	(1.3)	0	(0.0)
Diarrhoea	5	(6.5)	2	(5.3)
Enterocolitis	1	(1.3)	1	(2.6)
Faeces hard	0	(0.0)	1	(2.6)
Gastrointestinal disorder	0	(0.0)	1	(2.6)

Subjects With Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Gastrointestinal disorders	**22**	**(28.6)**	**15**	**(39.5)**
Gastrointestinal pain	0	(0.0)	1	(2.6)
Haemorrhoids	1	(1.3)	1	(2.6)
Hypoaesthesia oral	1	(1.3)	0	(0.0)
Lip dry	0	(0.0)	2	(5.3)
Melaena	1	(1.3)	0	(0.0)
Nausea	5	(6.5)	1	(2.6)
Oral discomfort	1	(1.3)	1	(2.6)
Oral dysaesthesia	1	(1.3)	0	(0.0)
Stomatitis	3	(3.9)	0	(0.0)
Vomiting	2	(2.6)	1	(2.6)
General disorders and administration site conditions	**33**	**(42.9)**	**6**	**(15.8)**
Chest discomfort	0	(0.0)	1	(2.6)
Chest pain	2	(2.6)	0	(0.0)
Chills	1	(1.3)	0	(0.0)
Fatigue	2	(2.6)	1	(2.6)
Gait disturbance	0	(0.0)	1	(2.6)
Injection site hypoaesthesia	0	(0.0)	1	(2.6)
Malaise	1	(1.3)	1	(2.6)
Oedema	1	(1.3)	0	(0.0)
Oedema peripheral	7	(9.1)	1	(2.6)
Peripheral swelling	1	(1.3)	0	(0.0)
Pyrexia	24	(31.2)	0	(0.0)
Thirst	2	(2.6)	0	(0.0)
Hepatobiliary disorders	**13**	**(16.9)**	**8**	**(21.1)**
Hepatic function abnormal	13	(16.9)	6	(15.8)
Hepatobiliary disease	0	(0.0)	2	(5.3)
Immune system disorders	**1**	**(1.3)**	**0**	**(0.0)**
Cytokine release syndrome	1	(1.3)	0	(0.0)
Infections and infestations	**31**	**(40.3)**	**8**	**(21.1)**
Angular cheilitis	2	(2.6)	1	(2.6)
Bacterial sepsis	1	(1.3)	0	(0.0)
Blister infected	1	(1.3)	1	(2.6)
Bronchiolitis	2	(2.6)	0	(0.0)
Bronchitis	1	(1.3)	1	(2.6)
Bronchopulmonary aspergillosis	1	(1.3)	0	(0.0)
Cellulitis	1	(1.3)	0	(0.0)
Conjunctivitis	3	(3.9)	0	(0.0)
Device related infection	2	(2.6)	0	(0.0)

Subjects With Adverse Events During the First 30 Days of Treatment (Incidence >0% in One or More Treatment Groups) Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Infections and infestations	**31**	**(40.3)**	**8**	**(21.1)**
Influenza	1	(1.3)	0	(0.0)
Lower respiratory tract infection	1	(1.3)	0	(0.0)
Nasopharyngitis	1	(1.3)	4	(10.5)
Oral herpes	1	(1.3)	0	(0.0)
Osteomyelitis	1	(1.3)	0	(0.0)
Periodontitis	1	(1.3)	0	(0.0)
Pharyngitis	2	(2.6)	1	(2.6)
Pneumonia	8	(10.4)	0	(0.0)
Pneumonia bacterial	5	(6.5)	0	(0.0)
Pyelonephritis	1	(1.3)	0	(0.0)
Sepsis	2	(2.6)	0	(0.0)
Staphylococcal bacteraemia	1	(1.3)	0	(0.0)
Tinea pedis	0	(0.0)	1	(2.6)
Upper respiratory tract infection	1	(1.3)	0	(0.0)
Injury, poisoning and procedural complications	**6**	**(7.8)**	**0**	**(0.0)**
Complications of bone marrow transplant	1	(1.3)	0	(0.0)
Contusion	1	(1.3)	0	(0.0)
Fall	1	(1.3)	0	(0.0)
Skin abrasion	1	(1.3)	0	(0.0)
Spinal compression fracture	1	(1.3)	0	(0.0)
Transplantation complication	1	(1.3)	0	(0.0)
Investigations	**22**	**(28.6)**	**13**	**(34.2)**
Alanine aminotransferase increased	6	(7.8)	2	(5.3)
Aspartate aminotransferase increased	8	(10.4)	4	(10.5)
Blood alkaline phosphatase increased	1	(1.3)	4	(10.5)
Blood creatinine increased	3	(3.9)	3	(7.9)
Blood glucose increased	1	(1.3)	0	(0.0)
Blood lactate dehydrogenase increased	1	(1.3)	1	(2.6)
Blood potassium decreased	2	(2.6)	0	(0.0)
Blood pressure increased	1	(1.3)	0	(0.0)
C-reactive protein increased	5	(6.5)	0	(0.0)
Cytomegalovirus test positive	0	(0.0)	1	(2.6)
Electrocardiogram QT prolonged	4	(5.2)	1	(2.6)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Eosinophil count increased	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	3	(7.9)
Liver function test increased	1	(1.3)	2	(5.3)
Neutrophil count decreased	1	(1.3)	0	(0.0)
Platelet count decreased	3	(3.9)	1	(2.6)
Renal function test abnormal	0	(0.0)	1	(2.6)

Subjects With Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Investigations	**22**	**(28.6)**	**13**	**(34.2)**
White blood cell count decreased	1	(1.3)	0	(0.0)
Metabolism and nutrition disorders	**22**	**(28.6)**	**5**	**(13.2)**
Decreased appetite	12	(15.6)	0	(0.0)
Dehydration	0	(0.0)	1	(2.6)
Hyperkalaemia	0	(0.0)	3	(7.9)
Hyperuricaemia	0	(0.0)	1	(2.6)
Hypoalbuminaemia	2	(2.6)	0	(0.0)
Hypoglycaemia	2	(2.6)	0	(0.0)
Hypokalaemia	10	(13.0)	1	(2.6)
Hyponatraemia	2	(2.6)	1	(2.6)
Musculoskeletal and connective tissue disorders	**8**	**(10.4)**	**3**	**(7.9)**
Arthralgia	1	(1.3)	0	(0.0)
Arthritis	1	(1.3)	0	(0.0)
Back pain	1	(1.3)	1	(2.6)
Chondrocalcinosis pyrophosphate	1	(1.3)	0	(0.0)
Flank pain	0	(0.0)	1	(2.6)
Joint effusion	1	(1.3)	0	(0.0)
Muscular weakness	1	(1.3)	0	(0.0)
Musculoskeletal pain	0	(0.0)	1	(2.6)
Pain in extremity	1	(1.3)	1	(2.6)
Periarthritis	1	(1.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(3.9)**	**0**	**(0.0)**
Acute myeloid leukaemia	1	(1.3)	0	(0.0)
Cancer pain	1	(1.3)	0	(0.0)
Lung cancer metastatic	1	(1.3)	0	(0.0)
Squamous cell carcinoma of lung	1	(1.3)	0	(0.0)
Nervous system disorders	**3**	**(3.9)**	**6**	**(15.8)**
Dizziness	1	(1.3)	0	(0.0)
Dysgeusia	0	(0.0)	3	(7.9)
Head discomfort	0	(0.0)	1	(2.6)
Headache	1	(1.3)	0	(0.0)
Hypoaesthesia	1	(1.3)	0	(0.0)
Hypogeusia	0	(0.0)	1	(2.6)
Mental impairment	0	(0.0)	1	(2.6)
Somnolence	0	(0.0)	1	(2.6)
Psychiatric disorders	**5**	**(6.5)**	**10**	**(26.3)**

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Subjects With Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Psychiatric disorders	**5**	**(6.5)**	**10**	**(26.3)**
Anxiety	1	(1.3)	0	(0.0)
Delirium	0	(0.0)	3	(7 9)
Hallucination	0	(0.0)	3	(7 9)
Hallucination, auditory	0	(0.0)	1	(2.6)
Hallucination, visual	0	(0.0)	1	(2.6)
Insomnia	3	(3.9)	4	(10.5)
Mental disorder	1	(1.3)	0	(0.0)
Renal and urinary disorders	**5**	**(6.5)**	**2**	**(5.3)**
Acute kidney injury	1	(1.3)	0	(0.0)
Hypertonic bladder	1	(1.3)	0	(0.0)
Neurogenic bladder	1	(1.3)	1	(2.6)
Renal impairment	2	(2.6)	0	(0.0)
Urethral pain	0	(0.0)	1	(2.6)
Urinary incontinence	0	(0.0)	1	(2.6)
Reproductive system and breast disorders	**2**	**(2.6)**	**0**	**(0.0)**
Benign prostatic hyperplasia	2	(2.6)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**17**	**(22.1)**	**1**	**(2.6)**
Asthma	1	(1.3)	0	(0.0)
Chronic obstructive pulmonary disease	2	(2.6)	0	(0.0)
Epistaxis	1	(1.3)	0	(0.0)
Haemoptysis	3	(3.9)	0	(0.0)
Hypercapnia	1	(1.3)	0	(0.0)
Interstitial lung disease	1	(1.3)	0	(0.0)
Laryngeal pain	1	(1.3)	0	(0.0)
Organising pneumonia	0	(0.0)	1	(2.6)
Oropharyngeal pain	4	(5.2)	0	(0.0)
Pleural effusion	1	(1.3)	0	(0.0)
Pneumonia aspiration	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)
Upper respiratory tract inflammation	1	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**19**	**(24.7)**	**4**	**(10.5)**
Decubitus ulcer	1	(1.3)	0	(0.0)
Dermatitis acneiform	1	(1.3)	0	(0.0)
Dermatitis contact	2	(2.6)	1	(2.6)
Drug eruption	1	(1.3)	0	(0.0)
Dry skin	4	(5.2)	0	(0.0)
Erythema	2	(2.6)	0	(0.0)

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Subjects With Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**19**	**(24.7)**	**4**	**(10.5)**
Erythema nodosum	1	(1.3)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(2.6)
Hyperkeratosis	0	(0.0)	1	(2.6)
Petechiae	1	(1.3)	0	(0.0)
Rash	4	(5.2)	0	(0.0)
Rash maculo-papular	1	(1.3)	0	(0.0)
Rash pruritic	1	(1.3)	0	(0.0)
Skin exfoliation	0	(0.0)	1	(2.6)
Skin irritation	1	(1.3)	0	(0.0)
Vascular disorders	**10**	**(13.0)**	**2**	**(5.3)**
Hypertension	10	(13.0)	1	(2.6)
Thrombophlebitis	0	(0.0)	1	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-155　　投与開始 1 ヵ月間に発現した副作用の発現例数（%）
（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events during the first 30 days of treatment	51	(66.2)	34	(89.5)
with no drug-related adverse events during the first 30 days of treatment	26	(33.8)	4	(10.5)
Blood and lymphatic system disorders	**2**	**(2.6)**	**1**	**(2.6)**
Anaemia	1	(1.3)	1	(2.6)
Thrombocytopenia	2	(2.6)	0	(0.0)
Cardiac disorders	**1**	**(1.3)**	**1**	**(2.6)**
Bundle branch block right	0	(0.0)	1	(2.6)
Cardiac failure	1	(1.3)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**1**	**(2.6)**
Tinnitus	0	(0.0)	1	(2.6)
Eye disorders	**2**	**(2.6)**	**22**	**(57.9)**
Colour blindness acquired	0	(0.0)	5	(13.2)
Diplopia	1	(1.3)	0	(0.0)
Dyschromatopsia	0	(0.0)	1	(2.6)
Photophobia	0	(0.0)	11	(28.9)
Vision blurred	1	(1.3)	3	(7.9)
Visual impairment	0	(0.0)	5	(13.2)
Gastrointestinal disorders	**9**	**(11.7)**	**6**	**(15.8)**
Abdominal discomfort	1	(1.3)	0	(0.0)
Constipation	2	(2.6)	0	(0.0)
Diarrhoea	3	(3.9)	0	(0.0)
Gastrointestinal pain	0	(0.0)	1	(2.6)
Lip dry	0	(0.0)	2	(5.3)
Nausea	4	(5.2)	1	(2.6)
Oral discomfort	0	(0.0)	1	(2.6)
Oral dysaesthesia	1	(1.3)	0	(0.0)
Stomatitis	1	(1.3)	0	(0.0)
Vomiting	0	(0.0)	1	(2.6)
General disorders and administration site conditions	**23**	**(29.9)**	**4**	**(10.5)**
Chest pain	1	(1.3)	0	(0.0)
Fatigue	2	(2.6)	1	(2.6)
Gait disturbance	0	(0.0)	1	(2.6)

Subjects With Drug-Related Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
General disorders and administration site conditions	**23**	**(29.9)**	**4**	**(10.5)**
Injection site hypoaesthesia	0	(0.0)	1	(2.6)
Malaise	1	(1.3)	1	(2.6)
Oedema	1	(1.3)	0	(0.0)
Oedema peripheral	3	(3.9)	0	(0.0)
Pyrexia	17	(22.1)	0	(0.0)
Thirst	1	(1.3)	0	(0.0)
Hepatobiliary disorders	**9**	**(11.7)**	**8**	**(21.1)**
Hepatic function abnormal	9	(11.7)	6	(15.8)
Hepatobiliary disease	0	(0.0)	2	(5.3)
Infections and infestations	**4**	**(5.2)**	**0**	**(0.0)**
Cellulitis	1	(1.3)	0	(0.0)
Pharyngitis	1	(1.3)	0	(0.0)
Pneumonia	3	(3.9)	0	(0.0)
Investigations	**11**	**(14.3)**	**8**	**(21.1)**
Alanine aminotransferase increased	5	(6.5)	2	(5.3)
Aspartate aminotransferase increased	6	(7.8)	3	(7.9)
Blood alkaline phosphatase increased	1	(1.3)	3	(7.9)
Blood creatinine increased	0	(0.0)	1	(2.6)
Blood lactate dehydrogenase increased	1	(1.3)	1	(2.6)
Blood potassium decreased	1	(1.3)	0	(0.0)
C-reactive protein increased	2	(2.6)	0	(0.0)
Electrocardiogram QT prolonged	4	(5.2)	1	(2.6)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	3	(7.9)
Liver function test increased	1	(1.3)	1	(2.6)
Metabolism and nutrition disorders	**15**	**(19.5)**	**2**	**(5.3)**
Decreased appetite	9	(11.7)	0	(0.0)
Hyperkalaemia	0	(0.0)	2	(5.3)
Hypokalaemia	7	(9.1)	0	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(2.6)**	**0**	**(0.0)**
Arthralgia	1	(1.3)	0	(0.0)
Arthritis	1	(1.3)	0	(0.0)
Nervous system disorders	**1**	**(1.3)**	**4**	**(10.5)**
Dizziness	1	(1.3)	0	(0.0)

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Subjects With Drug-Related Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Nervous system disorders	**1**	**(1.3)**	**4**	**(10.5)**
Dysgeusia	0	(0.0)	2	(5.3)
Head discomfort	0	(0.0)	1	(2.6)
Hypogeusia	0	(0.0)	1	(2.6)
Mental impairment	0	(0.0)	1	(2.6)
Psychiatric disorders	**2**	**(2.6)**	**8**	**(21.1)**
Delirium	0	(0.0)	2	(5 3)
Hallucination	0	(0.0)	3	(7 9)
Hallucination, auditory	0	(0.0)	1	(2.6)
Hallucination, visual	0	(0.0)	1	(2.6)
Insomnia	2	(2.6)	2	(5 3)
Renal and urinary disorders	**1**	**(1.3)**	**0**	**(0.0)**
Hypertonic bladder	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**4**	**(5.2)**	**0**	**(0.0)**
Epistaxis	1	(1.3)	0	(0.0)
Oropharyngeal pain	1	(1.3)	0	(0.0)
Pleural effusion	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**9**	**(11.7)**	**1**	**(2.6)**
Dermatitis acneiform	1	(1.3)	0	(0.0)
Dry skin	3	(3.9)	0	(0.0)
Erythema	1	(1.3)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(2.6)
Rash	4	(5.2)	0	(0.0)
Rash maculo-papular	1	(1.3)	0	(0.0)
Vascular disorders	**8**	**(10.4)**	**1**	**(2.6)**
Hypertension	8	(10.4)	1	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-156　　投与開始 1 ヵ月間に発現した重篤な有害事象の発現例数（%）
（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Serious Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more serious adverse events during the first 30 days of treatment	23	(29.9)	3	(7.9)
with no serious adverse events during the first 30 days of treatment	54	(70.1)	35	(92.1)
Blood and lymphatic system disorders	**1**	**(1.3)**	**0**	**(0.0)**
Febrile neutropenia	1	(1.3)	0	(0.0)
Cardiac disorders	**3**	**(3.9)**	**0**	**(0.0)**
Cardiac failure	1	(1.3)	0	(0.0)
Cardiac failure congestive	1	(1.3)	0	(0.0)
Cor pulmonale	1	(1.3)	0	(0.0)
General disorders and administration site conditions	**3**	**(3.9)**	**0**	**(0.0)**
Chest pain	1	(1.3)	0	(0.0)
Pyrexia	2	(2.6)	0	(0.0)
Infections and infestations	**12**	**(15.6)**	**3**	**(7.9)**
Blister infected	0	(0.0)	1	(2.6)
Bronchitis	0	(0.0)	1	(2.6)
Bronchopulmonary aspergillosis	1	(1.3)	0	(0.0)
Nasopharyngitis	0	(0.0)	1	(2.6)
Osteomyelitis	1	(1.3)	0	(0.0)
Pneumonia	6	(7.8)	0	(0.0)
Pneumonia bacterial	2	(2.6)	0	(0.0)
Pyelonephritis	1	(1.3)	0	(0.0)
Sepsis	2	(2.6)	0	(0.0)
Staphylococcal bacteraemia	1	(1.3)	0	(0.0)
Investigations	**1**	**(1.3)**	**0**	**(0.0)**
White blood cell count decreased	1	(1.3)	0	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(2.6)**	**0**	**(0.0)**
Arthritis	1	(1.3)	0	(0.0)
Joint effusion	1	(1.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(2.6)**	**0**	**(0.0)**
Lung cancer metastatic	1	(1.3)	0	(0.0)
Squamous cell carcinoma of lung	1	(1.3)	0	(0.0)

Subjects With Serious Adverse Events During the First 30 Days of Treatment (Incidence >0% in One or More Treatment Groups) Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Renal and urinary disorders	**1**	**(1.3)**	**0**	**(0.0)**
Acute kidney injury	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(7.8)**	**0**	**(0.0)**
Chronic obstructive pulmonary disease	2	(2.6)	0	(0.0)
Hypercapnia	1	(1.3)	0	(0.0)
Interstitial lung disease	1	(1.3)	0	(0.0)
Pneumonia aspiration	1	(1.3)	0	(0.0)
Respiratory failure	1	(1.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

Confidential

付録 2.7.4-157　　投与開始 1 ヵ月間に発現した重篤な副作用の発現例数（%）
（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Serious and Drug-Related Adverse Events During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more serious and drug-related adverse events during the first 30 days of treatment	5	(6.5)	0	(0.0)
with no serious and drug-related adverse events during the first 30 days of treatment	72	(93.5)	38	(100.0)
General disorders and administration site conditions	**1**	**(1.3)**	**0**	**(0.0)**
Pyrexia	1	(1.3)	0	(0.0)
Infections and infestations	**2**	**(2.6)**	**0**	**(0.0)**
Pneumonia	2	(2.6)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(1.3)**	**0**	**(0.0)**
Arthritis	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(1.3)**	**0**	**(0.0)**
Respiratory failure	1	(1.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-158　　投与開始 1 ヵ月間に発現した投与中止に至った有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Adverse Events Resulting in Study Medication Discontinuation During the First 30 Days of Treatment (Incidence >0% in One or More Treatment Groups) Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more adverse events resulting in study medication discontinuation during the first 30 days of treatment	21	(27.3)	2	(5.3)
with no adverse events resulting in study medication discontinuation during the first 30 days of treatment	56	(72.7)	36	(94.7)
Cardiac disorders	**1**	**(1.3)**	**0**	**(0.0)**
Cor pulmonale	1	(1.3)	0	(0.0)
General disorders and administration site conditions	**5**	**(6.5)**	**1**	**(2.6)**
Gait disturbance	0	(0.0)	1	(2.6)
Pyrexia	5	(6.5)	0	(0.0)
Hepatobiliary disorders	**2**	**(2.6)**	**0**	**(0.0)**
Hepatic function abnormal	2	(2.6)	0	(0.0)
Infections and infestations	**5**	**(6.5)**	**0**	**(0.0)**
Bronchiolitis	1	(1.3)	0	(0.0)
Pneumonia	3	(3.9)	0	(0.0)
Sepsis	1	(1.3)	0	(0.0)
Investigations	**1**	**(1.3)**	**1**	**(2.6)**
Electrocardiogram QT prolonged	0	(0.0)	1	(2.6)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Metabolism and nutrition disorders	**3**	**(3.9)**	**0**	**(0.0)**
Decreased appetite	1	(1.3)	0	(0.0)
Hypokalaemia	2	(2.6)	0	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(2.6)**	**0**	**(0.0)**
Arthritis	1	(1.3)	0	(0.0)
Joint effusion	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**3**	**(3.9)**	**0**	**(0.0)**
Interstitial lung disease	1	(1.3)	0	(0.0)
Pneumonia aspiration	1	(1.3)	0	(0.0)

Subjects With Adverse Events Resulting in Study Medication Discontinuation During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**3**	**(3.9)**	**0**	**(0.0)**
Respiratory failure	1	(1.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-159　　投与開始 1 ヵ月間に発現した投与中止に至った副作用の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール新錠剤及び静注用溶液の治療試験（P101 試験）（コホート 1 及び 2 併合）（ASaT）

Subjects With Drug-Related Adverse Events Resulting in Study Medication Discontinuation During the First 30 Days of Treatment
(Incidence >0% in One or More Treatment Groups)
Cohort 1 and 2 (ASaT)

	MK-5592		Voriconazole	
	n	(%)	n	(%)
Subjects in population	77		38	
with one or more drug-related adverse events resulting in study medication discontinuation during the first 30 days of treatment	14	(18.2)	2	(5.3)
with no drug-related adverse events resulting in study medication discontinuation during the first 30 days of treatment	63	(81.8)	36	(94.7)
General disorders and administration site conditions	**5**	**(6.5)**	**1**	**(2.6)**
Gait disturbance	0	(0.0)	1	(2.6)
Pyrexia	5	(6.5)	0	(0.0)
Hepatobiliary disorders	**2**	**(2.6)**	**0**	**(0.0)**
Hepatic function abnormal	2	(2.6)	0	(0.0)
Infections and infestations	**2**	**(2.6)**	**0**	**(0.0)**
Pneumonia	2	(2.6)	0	(0.0)
Investigations	**1**	**(1.3)**	**1**	**(2.6)**
Electrocardiogram QT prolonged	0	(0.0)	1	(2.6)
Electrocardiogram ST segment elevation	1	(1.3)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(2.6)**	**0**	**(0.0)**
Decreased appetite	1	(1.3)	0	(0.0)
Hypokalaemia	1	(1.3)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(1.3)**	**0**	**(0.0)**
Arthritis	1	(1.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(1.3)**	**0**	**(0.0)**
Respiratory failure	1	(1.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA Version 20.1

Source:　[P101MK5592: analysis-adsl] [P101MK5592: tabulations-aeplus]

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付録 2.7.4-160　　年齢別の有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）

ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）

（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Subjects Reporting Any Adverse Event	**12 (100.0)**	**521 (98.3)**	**62 (98.4)**	**16 (100.0)**	**452 (98.3)**	**63 (100.0)**	**0**	**49 (100.0)**	**9 (100.0)**
Blood And Lymphatic System Disorders	**7 (58.3)**	**323 (60.9)**	**50 (79.4)**	**9 (56.3)**	**282 (61.3)**	**39 (61.9)**	**0**	**33 (67.3)**	**8 (88.9)**
Anaemia	2 (16.7)	142 (26.8)	17 (27.0)	4 (25.0)	117 (25.4)	15 (23.8)	0	15 (30.6)	4 (44.4)
Bone Marrow Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Bone Marrow Failure	0	4 (0.8)	1 (1.6)	0	0	0	0	0	0
Coagulation Factor Deficiency	0	0	1 (1.6)	0	0	0	0	0	0
Coagulopathy	0	9 (1.7)	3 (4.8)	0	11 (2.4)	3 (4.8)	0	1 (2.0)	0
Disseminated Intravascular Coagulation	0	2 (0.4)	1 (1.6)	0	5 (1.1)	0	0	0	0
Eosinophilia	0	1 (0.2)	0	0	0	0	0	0	0
Febrile Neutropenia	4 (33.3)	91 (17.2)	23 (36.5)	4 (25.0)	63 (13.7)	18 (28.6)	0	19 (38.8)	4 (44.4)
Granulocytopenia	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Haemolysis	0	5 (0.9)	0	0	3 (0.7)	1 (1.6)	0	0	0
Haemolytic Anaemia	0	0	0	0	1 (0.2)	0	0	0	0
Haemolytic Uraemic Syndrome	0	6 (1.1)	0	0	3 (0.7)	0	0	0	0
Haemorrhagic Diathesis	0	1 (0.2)	1 (1.6)	0	4 (0.9)	0	0	0	0
Haemorrhagic Disorder	0	0	1 (1.6)	0	0	0	0	0	0
Hypercoagulation	0	1 (0.2)	0	0	0	0	0	0	0
Hypofibrinogenaemia	1 (8.3)	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Hypoglobulinaemia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hypoprothrombinaemia	0	2 (0.4)	0	0	4 (0.9)	1 (1.6)	0	0	0
Increased Tendency To Bruise	0	0	0	0	2 (0.4)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Iron Deficiency Anaemia	0	0	0	0	1 (0.2)	0	0	0	0
Leukocytosis	0	2 (0.4)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0
Leukopenia	1 (8.3)	33 (6.2)	2 (3.2)	2 (12.5)	37 (8.0)	2 (3.2)	0	4 (8.2)	1 (11.1)
Lymph Node Pain	0	3 (0.6)	0	0	0	0	0	1 (2.0)	0
Lymphadenitis	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Lymphadenopathy	0	9 (1.7)	2 (3.2)	0	8 (1.7)	1 (1.6)	0	2 (4.1)	0
Lymphopenia	0	0	0	0	1 (0.2)	0	0	0	1 (11 1)
Macrocytosis	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Microangiopathic Haemolytic Anaemia	0	0	0	0	1 (0.2)	0	0	0	0
Monocytosis	0	0	0	0	1 (0.2)	0	0	0	0
Neutropenia	2 (16.7)	124 (23.4)	19 (30.2)	6 (37.5)	110 (23.9)	11 (17.5)	0	19 (38.8)	4 (44.4)
Pancytopenia	0	16 (3.0)	2 (3.2)	0	18 (3.9)	3 (4.8)	0	1 (2.0)	0
Polychromasia	0	0	0	0	1 (0.2)	0	0	0	0
Polycythaemia	0	0	0	1 (6.3)	0	0	0	0	0
Protein Deficiency Anaemia	0	1 (0.2)	0	0	0	0	0	0	0
Red Cell Fragmentation Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Retroperitoneal Lymphadenopathy	0	1 (0.2)	0	0	0	0	0	0	0
Splenomegaly	0	10 (1.9)	1 (1.6)	0	7 (1.5)	0	0	0	0
Thrombocytopenia	2 (16.7)	160 (30.2)	27 (42.9)	2 (12.5)	135 (29.3)	24 (38.1)	0	17 (34.7)	4 (44.4)
Thrombocytosis	0	0	0	0	2 (0.4)	0	0	1 (2.0)	0
Thrombotic Microangiopathy	0	0	0	0	1 (0.2)	0	0	0	0
Thrombotic Thrombocytopenic Purpura	0	9 (1.7)	0	0	3 (0.7)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Cardiac Disorders	**2 (16.7)**	**126 (23.8)**	**16 (25.4)**	**0**	**116 (25.2)**	**23 (36.5)**	**0**	**9 (18.4)**	**5 (55.6)**
Acute Myocardial Infarction	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Angina Pectoris	0	4 (0.8)	0	0	0	4 (6.3)	0	0	0
Aortic Valve Incompetence	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Arrhythmia	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Arrhythmia Supraventricular	0	0	0	0	0	1 (1.6)	0	0	0
Arteriosclerosis Coronary Artery	0	1 (0.2)	0	0	0	0	0	0	0
Atrial Fibrillation	0	9 (1.7)	2 (3.2)	0	9 (2.0)	8 (12.7)	0	2 (4.1)	0
Atrial Flutter	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Atrial Hypertrophy	0	1 (0.2)	0	0	0	0	0	0	0
Atrial Tachycardia	0	1 (0.2)	0	0	0	0	0	0	0
Atrioventricular Block	0	0	0	0	1 (0.2)	0	0	0	0
Atrioventricular Block Complete	0	1 (0.2)	0	0	0	0	0	0	0
Atrioventricular Block Second Degree	0	1 (0.2)	0	0	0	0	0	0	0
Bradycardia	0	10 (1.9)	0	0	6 (1.3)	2 (3.2)	0	1 (2.0)	1 (11 1)
Bundle Branch Block	0	0	0	0	1 (0.2)	0	0	0	0
Bundle Branch Block Left	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Bundle Branch Block Right	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Cardiac Arrest	0	6 (1.1)	1 (1.6)	0	6 (1.3)	0	0	1 (2.0)	0
Cardiac Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Cardiac Failure	0	3 (0.6)	1 (1.6)	0	4 (0.9)	0	0	0	0
Cardiac Failure Congestive	0	2 (0.4)	1 (1.6)	0	2 (0.4)	3 (4.8)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Cardiac Flutter	0	0	0	0	1 (0.2)	0	0	0	0
Cardiac Hypertrophy	0	2 (0.4)	0	0	0	0	0	0	0
Cardiac Tamponade	0	0	0	0	1 (0.2)	0	0	0	0
Cardio-Respiratory Arrest	0	2 (0.4)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0
Cardiomegaly	0	4 (0.8)	2 (3.2)	0	0	0	0	1 (2.0)	0
Cardiomyopathy	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Cardiopulmonary Failure	0	1 (0.2)	0	0	0	0	0	0	0
Cardiotoxicity	0	0	0	0	0	1 (1.6)	0	0	0
Cardiovascular Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Cardiovascular Insufficiency	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Congestive Cardiomyopathy	0	1 (0.2)	0	0	0	0	0	0	0
Cor Pulmonale	0	0	0	0	1 (0.2)	0	0	0	0
Coronary Artery Stenosis	0	1 (0.2)	0	0	0	0	0	0	0
Cyanosis	0	0	0	0	1 (0.2)	0	0	0	0
Defect Conduction Intraventricular	0	0	0	0	1 (0.2)	0	0	0	0
Endocarditis Noninfective	0	0	0	0	1 (0.2)	0	0	0	0
Extrasystoles	0	0	1 (1.6)	0	2 (0.4)	2 (3.2)	0	0	0
Intracardiac Mass	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Left Atrial Dilatation	0	1 (0.2)	0	0	0	0	0	0	0
Left Ventricular Dysfunction	0	3 (0.6)	1 (1.6)	0	3 (0.7)	2 (3.2)	0	0	0
Left Ventricular Hypertrophy	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Mitral Valve Disease	0	1 (0.2)	0	0	0	0	0	0	0
Mitral Valve Incompetence	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Myocardial Infarction	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Myocardial Ischaemia	0	2 (0.4)	0	0	0	0	0	0	0
Myocarditis	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Palpitations	1 (8.3)	3 (0.6)	1 (1.6)	0	6 (1.3)	0	0	1 (2.0)	0
Pericardial Effusion	0	7 (1.3)	1 (1.6)	0	16 (3.5)	1 (1.6)	0	1 (2.0)	0
Pericardial Mass	0	0	0	0	1 (0.2)	0	0	0	0
Pericardial Rub	0	0	0	0	1 (0.2)	0	0	0	0
Pericarditis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Restrictive Cardiomyopathy	0	1 (0.2)	0	0	0	0	0	0	0
Right Atrial Enlargement	0	0	0	0	0	1 (1.6)	0	0	0
Right Ventricular Enlargement	0	0	0	0	0	1 (1.6)	0	0	0
Right Ventricular Hypertrophy	0	0	0	0	1 (0.2)	0	0	0	0
Sinus Arrhythmia	0	1 (0.2)	0	0	0	0	0	0	0
Sinus Bradycardia	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	1 (11 1)
Sinus Tachycardia	0	10 (1.9)	1 (1.6)	0	8 (1.7)	2 (3.2)	0	1 (2.0)	1 (11 1)
Subendocardial Ischaemia	0	0	0	0	2 (0.4)	0	0	0	0
Supraventricular Extrasystoles	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Supraventricular Tachycardia	0	4 (0.8)	0	0	3 (0.7)	0	0	1 (2.0)	0
Tachycardia	1 (8.3)	58 (10.9)	6 (9.5)	0	60 (13.0)	9 (14.3)	0	3 (6.1)	2 (22.2)
Tachycardia Paroxysmal	0	0	0	0	1 (0.2)	0	0	0	0
Torsade De Pointes	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Tricuspid Valve Incompetence	0	2 (0.4)	0	0	0	0	0	0	0
Ventricular Dysfunction	0	0	0	0	0	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Ventricular Extrasystoles	0	7 (1.3)	2 (3.2)	0	1 (0.2)	0	0	1 (2.0)	0
Ventricular Hypertrophy	0	0	0	0	1 (0.2)	0	0	0	0
Ventricular Hypokinesia	0	0	0	0	1 (0.2)	0	0	0	0
Ventricular Tachycardia	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Congenital, Familial And Genetic Disorders	**0**	**2 (0.4)**	**1 (1.6)**	**0**	**1 (0.2)**	**0**	**0**	**0**	**0**
Antithrombin III Deficiency	0	0	0	0	1 (0.2)	0	0	0	0
Chimerism	0	1 (0.2)	0	0	0	0	0	0	0
Epidermolysis	0	1 (0.2)	0	0	0	0	0	0	0
Factor II Deficiency	0	0	1 (1.6)	0	0	0	0	0	0
Ear And Labyrinth Disorders	**0**	**44 (8.3)**	**8 (12.7)**	**1 (6.3)**	**30 (6.5)**	**5 (7.9)**	**0**	**4 (8.2)**	**0**
Deafness	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Ear Congestion	0	0	0	0	3 (0.7)	0	0	1 (2.0)	0
Ear Discomfort	0	4 (0.8)	0	0	3 (0.7)	1 (1.6)	0	0	0
Ear Disorder	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Ear Haemorrhage	0	1 (0.2)	1 (1.6)	0	0	1 (1.6)	0	0	0
Ear Pain	0	13 (2.5)	4 (6.3)	1 (6.3)	10 (2.2)	1 (1.6)	0	1 (2.0)	0
Ear Pruritus	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Ear Swelling	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Eustachian Tube Obstruction	0	0	0	0	0	0	0	1 (2.0)	0
Excessive Cerumen Production	0	1 (0.2)	0	0	0	0	0	0	0
Hypoacusis	0	6 (1.1)	2 (3.2)	0	1 (0.2)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Middle Ear Effusion	0	2 (0.4)	0	0	0	0	0	0	0
Otorrhoea	0	2 (0.4)	0	0	0	0	0	0	0
Sudden Hearing Loss	0	1 (0.2)	0	0	0	0	0	0	0
Tinnitus	0	5 (0.9)	0	0	3 (0.7)	0	0	0	0
Vertigo	0	9 (1.7)	1 (1.6)	0	8 (1.7)	1 (1.6)	0	0	0
Endocrine Disorders	**0**	**31 (5.8)**	**1 (1.6)**	**0**	**33 (7.2)**	**2 (3.2)**	**0**	**1 (2.0)**	**0**
Addison's Disease	0	1 (0.2)	0	0	0	0	0	0	0
Adrenal Insufficiency	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Adrenal Mass	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Adrenomegaly	0	0	0	0	1 (0.2)	0	0	0	0
Androgen Deficiency	0	1 (0.2)	0	0	0	0	0	0	0
Cushing's Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Cushingoid	0	23 (4.3)	1 (1.6)	0	26 (5.7)	0	0	0	0
Euthyroid Sick Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Goitre	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hypogonadism	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Hypothyroidism	0	0	0	0	2 (0.4)	0	0	0	0
Inappropriate Antidiuretic Hormone Secretion	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Steroid Withdrawal Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Thyroid Cyst	0	1 (0.2)	0	0	0	0	0	0	0
Eye Disorders	**0**	**115 (21.7)**	**10 (15.9)**	**1 (6.3)**	**123 (26.7)**	**11 (17.5)**	**0**	**9 (18.4)**	**1 (11.1)**

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Abnormal Sensation In Eye	0	1 (0.2)	0	0	0	0	0	0	0
Blepharitis	0	0	0	0	0	0	0	1 (2.0)	0
Cataract	0	2 (0.4)	1 (1.6)	0	4 (0.9)	0	0	0	0
Choroiditis	0	0	0	0	1 (0.2)	0	0	0	0
Conjunctival Deposit	0	0	0	0	0	0	0	1 (2.0)	0
Conjunctival Discolouration	0	0	0	0	1 (0.2)	0	0	0	0
Conjunctival Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Conjunctival Haemorrhage	0	7 (1.3)	1 (1.6)	1 (6.3)	12 (2.6)	1 (1.6)	0	1 (2.0)	0
Conjunctival Hyperaemia	0	2 (0.4)	0	0	0	0	0	0	0
Conjunctival Irritation	0	0	0	0	1 (0.2)	0	0	0	0
Conjunctival Oedema	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Conjunctivitis Allergic	0	0	0	0	1 (0.2)	0	0	0	0
Corneal Degeneration	0	0	0	0	1 (0.2)	0	0	0	0
Corneal Irritation	0	0	0	0	1 (0.2)	0	0	0	0
Corneal Oedema	0	0	0	0	1 (0.2)	0	0	0	0
Diabetic Retinopathy	0	0	0	0	0	1 (1.6)	0	0	0
Diplopia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Dry Eye	0	22 (4.2)	0	0	25 (5.4)	1 (1.6)	0	0	1 (11 1)
Episcleritis	0	0	0	0	1 (0.2)	0	0	0	0
Erythema Of Eyelid	0	2 (0.4)	0	0	0	0	0	0	0
Exophthalmos	0	0	0	0	1 (0.2)	0	0	0	0
Eye Discharge	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Eye Disorder	0	0	0	0	1 (0.2)	0	0	0	0

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Eye Haemorrhage	0	3 (0.6)	0	0	5 (1.1)	2 (3.2)	0	2 (4.1)	0
Eye Inflammation	0	0	0	0	0	1 (1.6)	0	0	0
Eye Irritation	0	12 (2.3)	0	0	5 (1.1)	1 (1.6)	0	1 (2.0)	0
Eye Movement Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Eye Oedema	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Eye Pain	0	9 (1.7)	0	1 (6.3)	9 (2.0)	1 (1.6)	0	1 (2.0)	0
Eye Pruritus	0	4 (0.8)	0	0	4 (0.9)	1 (1.6)	0	0	0
Eye Swelling	0	4 (0.8)	0	0	2 (0.4)	0	0	1 (2.0)	0
Eyelid Oedema	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Eyelid Pain	0	0	0	0	0	0	0	1 (2.0)	0
Foreign Body Sensation In Eyes	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Glaucoma	0	1 (0.2)	0	0	0	0	0	0	0
Halo Vision	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Iridocyclitis	0	0	0	0	1 (0.2)	0	0	0	0
Iritis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Keratitis	0	0	1 (1.6)	0	0	0	0	0	0
Lacrimation Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Lacrimation Increased	0	5 (0.9)	1 (1.6)	0	9 (2.0)	0	0	1 (2.0)	0
Mydriasis	0	0	1 (1.6)	0	2 (0.4)	0	0	0	0
Myopia	0	1 (0.2)	0	0	0	0	0	0	0
Ocular Discomfort	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Ocular Hyperaemia	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	2 (4.1)	0
Ophthalmoplegia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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Orbital Oedema	0	0	0	0	1 (0.2)	0	0	0	0
Periorbital Oedema	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Photophobia	0	6 (1.1)	0	0	7 (1.5)	0	0	0	0
Photopsia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Punctate Keratitis	0	0	0	0	1 (0.2)	0	0	0	0
Pupils Unequal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Retinal Exudates	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Retinal Haemorrhage	0	5 (0.9)	0	0	3 (0.7)	0	0	1 (2.0)	0
Retinal Oedema	0	1 (0.2)	0	0	0	0	0	0	0
Retinopathy Haemorrhagic	0	0	0	0	1 (0.2)	0	0	0	0
Scleral Discolouration	0	0	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Scleral Haemorrhage	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Scleral Oedema	0	0	0	0	1 (0.2)	0	0	0	0
Vision Blurred	0	24 (4.5)	2 (3.2)	0	29 (6.3)	2 (3.2)	0	3 (6.1)	0
Visual Acuity Reduced	0	3 (0.6)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	0	0
Visual Impairment	0	8 (1.5)	1 (1.6)	0	9 (2.0)	0	0	3 (6.1)	0
Vitreous Detachment	0	0	0	0	0	1 (1.6)	0	0	0
Vitreous Floaters	0	2 (0.4)	0	0	1 (0.2)	0	0	1 (2.0)	0
Vitreous Haemorrhage	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Gastrointestinal Disorders	**8 (66.7)**	**422 (79.6)**	**58 (92.1)**	**12 (75.0)**	**363 (78.9)**	**54 (85.7)**	**0**	**46 (93.9)**	**9 (100.0)**
Abdominal Compartment Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Abdominal Discomfort	0	21 (4.0)	5 (7.9)	0	7 (1.5)	1 (1.6)	0	2 (4.1)	0

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Abdominal Distension	1 (8.3)	36 (6.8)	3 (4.8)	0	36 (7.8)	8 (12.7)	0	3 (6.1)	1 (11.1)
Abdominal Hernia	0	1 (0.2)	0	0	0	0	0	0	0
Abdominal Mass	0	0	0	0	1 (0.2)	0	0	0	0
Abdominal Pain	0	108 (20.4)	5 (7.9)	1 (6.3)	105 (22.8)	6 (9.5)	0	15 (30.6)	0
Abdominal Pain Lower	0	10 (1.9)	1 (1.6)	0	6 (1.3)	1 (1.6)	0	0	0
Abdominal Pain Upper	0	37 (7.0)	7 (11.1)	1 (6.3)	38 (8.3)	4 (6.3)	0	14 (28.6)	0
Abdominal Rigidity	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Abdominal Tenderness	0	8 (1.5)	2 (3.2)	0	9 (2.0)	2 (3.2)	0	2 (4.1)	0
Acute Abdomen	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Anal Fissure	2 (16.7)	7 (1.3)	0	0	2 (0.4)	0	0	2 (4.1)	0
Anal Fistula	0	0	0	0	0	0	0	1 (2.0)	0
Anal Haemorrhage	0	1 (0.2)	0	0	0	0	0	2 (4.1)	0
Anal Incontinence	0	5 (0.9)	1 (1.6)	0	9 (2.0)	3 (4.8)	0	0	0
Anal Inflammation	0	0	0	1 (6.3)	0	0	0	0	0
Anal Pruritus	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Anal Ulcer	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Anorectal Discomfort	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Aphthous Ulcer	0	4 (0.8)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	2 (4.1)	0
Aptyalism	0	2 (0.4)	0	0	0	0	0	0	0
Ascites	0	20 (3.8)	3 (4.8)	0	13 (2.8)	2 (3.2)	0	1 (2.0)	0
Breath Odour	0	1 (0.2)	0	0	0	0	0	0	0
Change Of Bowel Habit	0	1 (0.2)	0	0	0	0	0	0	0
Chapped Lips	0	3 (0.6)	0	0	4 (0.9)	0	0	1 (2.0)	1 (11 1)

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Cheilitis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Colitis	0	14 (2.6)	1 (1.6)	1 (6.3)	7 (1.5)	3 (4.8)	0	1 (2.0)	2 (22 2)
Colitis Ulcerative	0	2 (0.4)	0	0	0	0	0	0	0
Constipation	1 (8.3)	104 (19.6)	20 (31.7)	0	81 (17.6)	14 (22.2)	0	5 (10.2)	1 (11.1)
Crohn's Disease	0	1 (0.2)	0	0	0	0	0	0	0
Dental Alveolar Anomaly	0	0	0	0	1 (0.2)	0	0	0	0
Diarrhoea	2 (16.7)	215 (40.6)	34 (54.0)	3 (18.8)	181 (39.3)	29 (46.0)	0	31 (63.3)	5 (55.6)
Diarrhoea Haemorrhagic	0	4 (0.8)	0	0	6 (1.3)	2 (3.2)	0	0	0
Diverticulum	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Diverticulum Intestinal	0	1 (0.2)	0	0	0	0	0	0	0
Dry Mouth	0	28 (5.3)	4 (6.3)	0	26 (5.7)	1 (1.6)	0	1 (2.0)	1 (11 1)
Duodenal Perforation	0	1 (0.2)	0	0	0	0	0	0	0
Duodenitis	0	5 (0.9)	0	0	2 (0.4)	0	0	1 (2.0)	0
Duodenitis Haemorrhagic	0	0	0	0	1 (0.2)	0	0	0	0
Dyschezia	1 (8.3)	2 (0.4)	0	0	0	0	0	0	0
Dyspepsia	0	47 (8.9)	4 (6.3)	0	44 (9.6)	6 (9.5)	0	3 (6.1)	2 (22 2)
Dysphagia	0	6 (1.1)	3 (4.8)	0	15 (3.3)	5 (7.9)	0	4 (8.2)	0
Enteritis	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Enterocolitis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Epigastric Discomfort	0	3 (0.6)	1 (1.6)	0	3 (0.7)	0	0	0	0
Erosive Oesophagitis	0	1 (0.2)	0	0	0	0	0	0	0
Eructation	0	3 (0.6)	0	0	0	0	0	0	0
Faecal Volume Increased	0	1 (0.2)	0	0	0	0	0	0	0

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Faecaloma	0	0	0	0	0	1 (1.6)	0	0	0
Faeces Discoloured	0	1 (0.2)	0	0	0	0	0	0	0
Faeces Hard	0	0	0	0	0	0	0	1 (2.0)	0
Flatulence	0	16 (3.0)	2 (3.2)	0	25 (5.4)	3 (4.8)	0	2 (4.1)	0
Frequent Bowel Movements	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gastric Disorder	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	4 (8.2)	1 (11.1)
Gastric Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Gastric Ulcer	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Gastric Ulcer Haemorrhage	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Gastric Varices	0	1 (0.2)	0	0	0	0	0	0	0
Gastritis	0	23 (4.3)	1 (1.6)	0	21 (4.6)	0	0	1 (2.0)	0
Gastritis Erosive	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gastritis Haemorrhagic	0	1 (0.2)	0	0	0	0	0	0	0
Gastroenteritis Eosinophilic	0	0	0	0	1 (0.2)	0	0	0	0
Gastrointestinal Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Gastrointestinal Haemorrhage	0	20 (3.8)	3 (4.8)	0	18 (3.9)	1 (1.6)	0	0	0
Gastrointestinal Hypomotility	0	1 (0.2)	0	0	0	0	0	0	0
Gastrointestinal Inflammation	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Gastrointestinal Obstruction	0	1 (0.2)	0	0	0	0	0	0	0
Gastrointestinal Pain	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Gastrointestinal Sounds Abnormal	0	4 (0.8)	0	0	4 (0.9)	3 (4.8)	0	0	0
Gastrointestinal Ulcer Haemorrhage	0	2 (0.4)	0	0	0	0	0	0	0
Gastrooesophageal Reflux Disease	0	18 (3.4)	2 (3.2)	0	11 (2.4)	2 (3.2)	0	0	0

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Gingival Bleeding	2 (16.7)	21 (4.0)	2 (3.2)	0	9 (2.0)	2 (3.2)	0	1 (2.0)	0
Gingival Erosion	0	0	0	0	0	0	0	1 (2.0)	0
Gingival Hypertrophy	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gingival Pain	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	0	0
Gingival Swelling	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Gingival Ulceration	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Glossitis	0	0	0	0	1 (0.2)	0	0	0	0
Glossodynia	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	0	0
Haematemesis	0	13 (2.5)	1 (1.6)	0	7 (1.5)	1 (1.6)	0	0	0
Haematochezia	0	15 (2.8)	2 (3.2)	0	9 (2.0)	0	0	1 (2.0)	1 (11 1)
Haemorrhoidal Haemorrhage	0	8 (1.5)	1 (1.6)	0	2 (0.4)	2 (3.2)	0	0	0
Haemorrhoids	0	35 (6.6)	3 (4.8)	1 (6.3)	26 (5.7)	5 (7.9)	0	10 (20.4)	1 (11.1)
Haemorrhoids Thrombosed	0	0	1 (1.6)	0	0	0	0	0	0
Hiatus Hernia	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Hyperchlorhydria	0	1 (0.2)	0	0	0	0	0	0	0
Hypoaesthesia Oral	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Ileus	0	4 (0.8)	0	0	5 (1.1)	0	0	0	0
Ileus Paralytic	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Impaired Gastric Emptying	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Inguinal Hernia	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Intestinal Angioedema	0	0	0	0	1 (0.2)	0	0	0	0
Intestinal Haemorrhage	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Intestinal Infarction	0	1 (0.2)	0	0	0	0	0	0	0

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Intestinal Ischaemia	0	1 (0.2)	0	0	0	0	0	0	0
Intestinal Mass	0	0	0	0	1 (0.2)	0	0	0	0
Intestinal Obstruction	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Intestinal Ulcer	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Intra-Abdominal Fluid Collection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Intra-Abdominal Haematoma	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Irritable Bowel Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Leukoplakia Oral	0	2 (0.4)	0	0	4 (0.9)	0	0	0	0
Lip Blister	0	2 (0.4)	0	0	0	0	0	0	0
Lip Dry	0	3 (0.6)	0	0	7 (1.5)	3 (4.8)	0	0	0
Lip Exfoliation	0	1 (0.2)	0	0	0	0	0	0	0
Lip Haematoma	0	0	0	0	1 (0.2)	0	0	0	0
Lip Haemorrhage	0	0	0	0	2 (0.4)	0	0	1 (2.0)	0
Lip Pain	0	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	0	0
Lip Swelling	0	1 (0.2)	0	0	0	0	0	0	0
Lip Ulceration	0	2 (0.4)	2 (3.2)	0	1 (0.2)	1 (1.6)	0	0	0
Loose Tooth	0	0	0	0	2 (0.4)	0	0	0	0
Lower Gastrointestinal Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Malabsorption	0	0	1 (1.6)	0	0	0	0	0	0
Melaena	0	13 (2.5)	1 (1.6)	2 (12.5)	8 (1.7)	2 (3.2)	0	1 (2.0)	0
Mouth Haemorrhage	0	13 (2.5)	4 (6.3)	0	1 (0.2)	3 (4.8)	0	2 (4.1)	0
Mouth Ulceration	0	19 (3.6)	3 (4.8)	0	16 (3.5)	0	0	4 (8.2)	0
Mucous Stools	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Nausea	2 (16.7)	210 (39.6)	31 (49.2)	5 (31.3)	172 (37.4)	26 (41.3)	0	28 (57.1)	5 (55.6)
Neutropenic Colitis	0	6 (1.1)	0	0	1 (0.2)	0	0	1 (2.0)	1 (11 1)
Odynophagia	0	6 (1.1)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Oedema Mouth	0	0	0	0	1 (0.2)	0	0	0	0
Oesophageal Pain	0	0	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Oesophageal Ulcer	0	2 (0.4)	0	0	0	0	0	0	0
Oesophagitis	0	11 (2.1)	0	0	4 (0.9)	2 (3.2)	0	0	0
Oesophagitis Ulcerative	0	1 (0.2)	0	0	0	0	0	0	0
Oral Discomfort	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Oral Disorder	0	12 (2.3)	0	0	6 (1.3)	2 (3.2)	0	1 (2.0)	0
Oral Mucosal Blistering	0	4 (0.8)	1 (1.6)	0	1 (0.2)	0	0	2 (4.1)	0
Oral Mucosal Discolouration	0	0	0	0	1 (0.2)	0	0	0	0
Oral Mucosal Erythema	0	5 (0.9)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Oral Mucosal Exfoliation	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Oral Mucosal Hypertrophy	0	0	0	0	1 (0.2)	0	0	0	0
Oral Pain	0	20 (3.8)	6 (9.5)	0	20 (4.3)	4 (6.3)	0	3 (6.1)	0
Palatal Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Palatal Swelling	0	1 (0.2)	0	0	0	0	0	0	0
Pancreatitis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Pancreatitis Acute	0	1 (0.2)	0	0	0	0	0	0	0
Paraesthesia Oral	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Parotid Gland Enlargement	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Perianal Erythema	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Periodontal Disease	0	1 (0.2)	0	0	0	0	0	0	0
Pneumoperitoneum	0	1 (0.2)	0	0	0	0	0	0	0
Proctalgia	2 (16.7)	5 (0.9)	2 (3.2)	2 (12.5)	14 (3.0)	1 (1.6)	0	5 (10.2)	0
Proctitis	0	2 (0.4)	0	0	1 (0.2)	0	0	1 (2.0)	0
Proctitis Ulcerative	0	0	0	0	1 (0.2)	0	0	0	0
Rectal Discharge	0	0	0	0	1 (0.2)	0	0	0	0
Rectal Fissure	0	1 (0.2)	0	0	0	0	0	0	0
Rectal Haemorrhage	0	13 (2.5)	2 (3.2)	0	7 (1.5)	0	0	2 (4.1)	0
Rectal Lesion	0	0	0	0	1 (0.2)	0	0	0	0
Rectal Prolapse	0	0	0	0	1 (0.2)	0	0	0	0
Rectal Tenesmus	0	1 (0.2)	0	0	0	0	0	0	0
Rectal Ulcer	0	0	0	0	1 (0.2)	0	0	0	0
Retching	0	6 (1.1)	0	0	4 (0.9)	1 (1.6)	0	0	0
Retroperitoneal Haemorrhage	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Saliva Altered	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Salivary Gland Calculus	0	0	0	0	1 (0.2)	0	0	0	0
Salivary Gland Mass	0	1 (0.2)	0	0	0	0	0	0	0
Salivary Gland Pain	0	0	0	0	1 (0.2)	0	0	0	0
Salivary Hypersecretion	0	1 (0.2)	0	0	2 (0.4)	0	0	0	1 (11 1)
Sensitivity Of Teeth	0	1 (0.2)	0	0	0	0	0	0	0
Small Intestinal Obstruction	0	2 (0.4)	0	0	0	1 (1.6)	0	0	0
Small Intestinal Stenosis	0	0	0	0	1 (0.2)	0	0	0	0
Stomach Mass	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Stomatitis	0	16 (3.0)	2 (3.2)	1 (6.3)	6 (1.3)	2 (3.2)	0	6 (12.2)	0
Subileus	0	1 (0.2)	0	0	0	0	0	0	0
Swollen Tongue	0	0	0	0	1 (0.2)	0	0	0	0
Tongue Blistering	0	0	1 (1.6)	0	0	0	0	0	0
Tongue Coated	0	9 (1.7)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Tongue Discolouration	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Tongue Discomfort	0	0	1 (1.6)	0	0	0	0	0	0
Tongue Disorder	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Tongue Erythema	1 (8.3)	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Tongue Haematoma	0	1 (0.2)	1 (1.6)	0	0	0	0	1 (2.0)	0
Tongue Haemorrhage	0	0	1 (1.6)	0	0	0	0	0	0
Tongue Ulceration	0	4 (0.8)	0	1 (6.3)	6 (1.3)	2 (3.2)	0	3 (6.1)	0
Tooth Discolouration	0	1 (0.2)	0	0	0	0	0	0	0
Tooth Loss	0	0	0	0	0	2 (3.2)	0	0	0
Toothache	2 (16.7)	5 (0.9)	2 (3.2)	0	10 (2.2)	3 (4.8)	0	1 (2.0)	1 (11 1)
Trichoglossia	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Umbilical Hernia	0	1 (0.2)	0	0	0	0	0	0	0
Upper Gastrointestinal Haemorrhage	0	3 (0.6)	1 (1.6)	0	0	0	0	0	0
Uvulitis	0	1 (0.2)	0	0	0	0	0	0	0
Vomiting	3 (25.0)	159 (30.0)	16 (25.4)	6 (37.5)	150 (32.6)	19 (30.2)	0	18 (36.7)	6 (66.7)
General Disorders And Administration Site Conditions	**8 (66.7)**	**404 (76.2)**	**54 (85.7)**	**11 (68 8)**	**344 (74.8)**	**58 (92.1)**	**0**	**47 (95.9)**	**8 (88.9)**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Adverse Drug Reaction	0	0	1 (1.6)	0	0	0	0	0	0
Application Site Burn	0	1 (0.2)	0	0	0	0	0	0	0
Application Site Discomfort	0	0	1 (1.6)	0	0	0	0	0	0
Asthenia	1 (8.3)	52 (9.8)	7 (11.1)	0	55 (12.0)	5 (7.9)	0	1 (2.0)	2 (22.2)
Atrophy	0	0	0	0	1 (0.2)	0	0	0	0
Axillary Pain	0	0	0	0	1 (0.2)	0	0	0	0
Catheter Site Bruise	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Catheter Site Discharge	0	3 (0.6)	0	0	0	0	0	1 (2.0)	0
Catheter Site Erosion	0	0	0	0	1 (0.2)	0	0	0	0
Catheter Site Erythema	0	35 (6.6)	4 (6.3)	0	27 (5.9)	5 (7.9)	0	9 (18.4)	2 (22 2)
Catheter Site Haematoma	0	3 (0.6)	0	0	3 (0.7)	2 (3.2)	0	0	0
Catheter Site Haemorrhage	0	14 (2.6)	1 (1.6)	0	4 (0.9)	2 (3.2)	0	0	1 (11 1)
Catheter Site Inflammation	0	7 (1.3)	1 (1.6)	0	3 (0.7)	0	0	5 (10.2)	2 (22 2)
Catheter Site Oedema	0	0	0	0	2 (0.4)	0	0	0	0
Catheter Site Pain	1 (8.3)	28 (5.3)	4 (6.3)	1 (6.3)	28 (6.1)	4 (6.3)	0	3 (6.1)	0
Catheter Site Phlebitis	0	1 (0.2)	1 (1.6)	0	0	2 (3.2)	0	0	0
Catheter Site Pruritus	0	3 (0.6)	0	0	1 (0.2)	0	0	1 (2.0)	0
Catheter Site Rash	0	1 (0.2)	0	0	0	0	0	0	0
Catheter Site Related Reaction	0	4 (0.8)	0	0	3 (0.7)	2 (3.2)	0	0	0
Catheter Site Swelling	0	2 (0.4)	1 (1.6)	0	0	1 (1.6)	0	0	0
Chest Discomfort	0	8 (1.5)	0	0	6 (1.3)	0	0	3 (6.1)	0
Chest Pain	0	43 (8.1)	9 (14.3)	1 (6.3)	25 (5.4)	9 (14.3)	0	3 (6.1)	0
Chills	1 (8.3)	101 (19.1)	15 (23.8)	0	64 (13.9)	17 (27.0)	0	14 (28.6)	3 (33.3)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Complication Associated With Device	0	3 (0.6)	1 (1.6)	0	6 (1.3)	0	0	0	0
Crepitations	0	2 (0.4)	2 (3.2)	0	3 (0.7)	2 (3.2)	0	0	0
Death	0	0	0	0	1 (0.2)	0	0	0	0
Device Related Thrombosis	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Disease Progression	0	2 (0.4)	2 (3.2)	1 (6.3)	3 (0.7)	1 (1.6)	0	0	0
Drug Interaction	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Drug Intolerance	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Drug Withdrawal Syndrome	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Early Satiety	0	0	0	0	3 (0.7)	0	0	0	0
Effusion	0	1 (0.2)	0	0	0	0	0	0	0
Exercise Tolerance Decreased	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Face Oedema	0	6 (1.1)	0	1 (6.3)	7 (1.5)	0	0	0	0
Facial Pain	0	3 (0.6)	0	1 (6.3)	3 (0.7)	1 (1.6)	0	0	0
Fatigue	0	86 (16.2)	18 (28.6)	1 (6.3)	93 (20.2)	9 (14.3)	0	2 (4.1)	1 (11.1)
Feeling Cold	0	3 (0.6)	1 (1.6)	0	7 (1.5)	1 (1.6)	0	0	0
Feeling Hot	0	1 (0.2)	0	0	0	0	0	0	0
Feeling Jittery	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Gait Disturbance	0	8 (1.5)	1 (1.6)	0	10 (2.2)	1 (1.6)	0	0	0
Gait Inability	0	0	0	0	1 (0.2)	0	0	0	0
General Physical Health Deterioration	0	1 (0.2)	2 (3.2)	0	1 (0.2)	0	0	0	0
General Symptom	0	1 (0.2)	0	0	0	0	0	0	0
Generalised Oedema	0	10 (1.9)	5 (7.9)	0	15 (3.3)	4 (6.3)	0	0	1 (11 1)
Granuloma	0	3 (0.6)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Gravitational Oedema	0	0	0	0	0	1 (1.6)	0	0	0
Hyperpyrexia	0	0	0	0	0	0	0	0	1 (11 1)
Hyperthermia	0	2 (0.4)	2 (3.2)	0	1 (0.2)	0	0	3 (6.1)	0
Hypothermia	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	0	0
Impaired Healing	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Induration	0	2 (0.4)	0	0	0	1 (1.6)	0	0	0
Inflammation	0	2 (0.4)	0	0	0	0	0	0	0
Influenza Like Illness	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Infusion Site Erythema	0	0	0	0	1 (0.2)	0	0	0	0
Infusion Site Extravasation	0	0	0	0	2 (0.4)	0	0	0	0
Infusion Site Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Infusion Site Inflammation	0	1 (0.2)	0	0	0	0	0	0	0
Infusion Site Pain	0	4 (0.8)	2 (3.2)	0	0	0	0	0	0
Infusion Site Swelling	0	0	0	0	1 (0.2)	0	0	0	0
Infusion Site Vesicles	0	1 (0.2)	0	0	0	0	0	0	0
Injection Site Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Injection Site Inflammation	0	0	0	0	1 (0.2)	0	0	0	0
Injection Site Irritation	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Injection Site Nodule	0	0	0	0	1 (0.2)	0	0	0	0
Injection Site Pain	0	0	0	0	1 (0.2)	0	0	0	0
Injection Site Reaction	0	0	0	0	1 (0.2)	0	0	0	0
Injection Site Vesicles	0	0	0	0	0	0	0	0	1 (11.1)
Localised Oedema	0	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	1 (2.0)	0

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All Randomized Subjects
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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Malaise	0	15 (2.8)	0	0	8 (1.7)	2 (3.2)	0	1 (2.0)	1 (11 1)
Mass	0	2 (0.4)	0	0	0	0	0	0	0
Mucosa Vesicle	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Mucosal Haemorrhage	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Mucosal Hyperaemia	0	1 (0.2)	0	0	0	0	0	0	0
Mucosal Inflammation	2 (16.7)	80 (15.1)	17 (27.0)	5 (31.3)	46 (10.0)	14 (22.2)	0	12 (24.5)	2 (22.2)
Mucous Membrane Disorder	0	0	1 (1.6)	0	0	0	0	0	0
Multi-Organ Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	0	14 (2.6)	1 (1.6)	0	8 (1.7)	1 (1.6)	0	2 (4.1)	0
Necrosis	0	3 (0.6)	0	0	0	0	0	0	0
Nodule	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Non-Cardiac Chest Pain	0	0	0	0	0	0	0	1 (2.0)	0
Obstruction	0	1 (0.2)	0	0	0	0	0	3 (6.1)	0
Oedema	1 (8.3)	34 (6.4)	4 (6.3)	1 (6.3)	39 (8.5)	8 (12.7)	0	4 (8.2)	0
Oedema Mucosal	0	0	0	0	1 (0.2)	0	0	0	0
Oedema Peripheral	0	79 (14.9)	17 (27.0)	0	71 (15.4)	8 (12.7)	0	9 (18.4)	3 (33.3)
Pain	1 (8.3)	38 (7.2)	3 (4.8)	1 (6.3)	23 (5.0)	2 (3.2)	0	5 (10.2)	0
Paradoxical Drug Reaction	0	0	0	0	0	1 (1.6)	0	0	0
Performance Status Decreased	0	0	2 (3.2)	0	0	0	0	0	0
Peripheral Swelling	1 (8.3)	15 (2.8)	0	0	11 (2.4)	1 (1.6)	0	0	1 (11 1)
Puncture Site Pain	0	3 (0.6)	0	0	0	0	0	0	0
Puncture Site Reaction	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Pyrexia	6 (50.0)	236 (44.5)	24 (38.1)	6 (37.5)	207 (45.0)	38 (60.3)	0	27 (55.1)	4 (44.4)

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All Randomized Subjects
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Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Secretion Discharge	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Sudden Death	0	0	0	0	0	1 (1.6)	0	0	0
Swelling	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Tenderness	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Therapeutic Product Ineffective	0	0	0	0	1 (0.2)	0	0	0	0
Therapy Non-Responder	0	2 (0.4)	2 (3.2)	0	3 (0.7)	0	0	0	0
Thirst	0	4 (0.8)	1 (1.6)	0	4 (0.9)	0	0	0	0
Ulcer	0	2 (0.4)	0	0	0	0	0	0	0
Ulcer Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Vessel Puncture Site Inflammation	0	0	0	0	1 (0.2)	0	0	0	0
Vessel Puncture Site Pain	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Xerosis	0	1 (0.2)	0	0	0	0	0	0	0
Hepatobiliary Disorders	**2 (16.7)**	**85 (16.0)**	**9 (14.3)**	**2 (12.5)**	**67 (14.6)**	**8 (12.7)**	**0**	**9 (18.4)**	**3 (33 3)**
Acute Hepatic Failure	0	1 (0.2)	0	0	0	0	0	0	0
Cholecystitis	0	1 (0.2)	0	0	2 (0.4)	0	0	1 (2.0)	0
Cholecystitis Acute	0	0	0	0	0	0	0	1 (2.0)	0
Cholelithiasis	0	5 (0.9)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	2 (4.1)	0
Cholestasis	0	5 (0.9)	0	0	2 (0.4)	0	0	0	0
Drug-Induced Liver Injury	0	0	0	0	1 (0.2)	0	0	0	0
Gallbladder Enlargement	0	0	0	0	1 (0.2)	0	0	0	0
Gallbladder Polyp	0	2 (0.4)	0	0	0	0	0	0	0
Hepatic Cyst	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Hepatic Failure	0	7 (1.3)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Hepatic Function Abnormal	0	3 (0.6)	0	0	7 (1.5)	1 (1.6)	0	0	0
Hepatic Lesion	0	4 (0.8)	0	0	0	0	0	0	0
Hepatic Necrosis	0	1 (0.2)	0	0	0	0	0	0	0
Hepatic Steatosis	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Hepatitis	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Hepatitis Acute	0	1 (0.2)	0	0	0	0	0	0	0
Hepatocellular Injury	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Hepatomegaly	0	8 (1.5)	2 (3.2)	0	4 (0.9)	1 (1.6)	0	1 (2.0)	0
Hepatosplenomegaly	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Hepatotoxicity	0	4 (0.8)	0	0	4 (0.9)	0	0	0	0
Hyperbilirubinaemia	2 (16.7)	22 (4.2)	4 (6.3)	1 (6.3)	21 (4.6)	4 (6.3)	0	5 (10.2)	3 (33.3)
Hypertransaminasaemia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Jaundice	0	23 (4.3)	4 (6.3)	1 (6.3)	19 (4.1)	4 (6.3)	0	1 (2.0)	0
Jaundice Cholestatic	0	1 (0.2)	0	0	0	0	0	0	0
Liver Disorder	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Liver Injury	0	2 (0.4)	0	0	0	0	0	0	0
Ocular Icterus	0	10 (1.9)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Perihepatic Discomfort	0	1 (0.2)	0	0	0	0	0	0	0
Portal Hypertension	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Portal Vein Thrombosis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Venoocclusive Liver Disease	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Immune System Disorders	**0**	**107 (20.2)**	**4 (6.3)**	**2 (12.5)**	**106 (23.0)**	**3 (4.8)**	**0**	**3 (6.1)**	**0**
Acute Graft Versus Host Disease In Liver	0	0	0	0	1 (0.2)	0	0	0	0
Acute Graft Versus Host Disease In Skin	0	0	0	0	1 (0.2)	0	0	0	0
Anaphylactic Reaction	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Chronic Graft Versus Host Disease	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Contrast Media Allergy	0	1 (0.2)	0	0	0	0	0	0	0
Drug Hypersensitivity	0	10 (1.9)	4 (6.3)	0	6 (1.3)	1 (1.6)	0	3 (6.1)	0
Graft Versus Host Disease	0	61 (11.5)	0	2 (12.5)	52 (11.3)	1 (1.6)	0	0	0
Graft Versus Host Disease In Gastrointestinal Tract	0	27 (5.1)	0	0	20 (4.3)	1 (1.6)	0	0	0
Graft Versus Host Disease In Liver	0	14 (2.6)	0	0	10 (2.2)	0	0	0	0
Graft Versus Host Disease In Lung	0	0	0	0	5 (1.1)	0	0	0	0
Graft Versus Host Disease In Skin	0	25 (4.7)	0	1 (6.3)	25 (5.4)	1 (1.6)	0	0	0
Hypersensitivity	0	1 (0.2)	0	0	4 (0.9)	1 (1.6)	0	0	0
Hypogammaglobulinaemia	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Immune System Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Sarcoidosis	0	1 (0.2)	0	0	0	0	0	0	0
Seasonal Allergy	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Transplant Rejection	0	3 (0.6)	0	0	0	0	0	0	0
Infections And Infestations	**8 (66.7)**	**386 (72.8)**	**43 (68.3)**	**14 (87.5)**	**354 (77.0)**	**46 (73.0)**	**0**	**42 (85.7)**	**9 (100.0)**
Abscess Fungal	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
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Abscess Jaw	0	0	0	0	1 (0.2)	0	0	0	0
Abscess Limb	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Abscess Neck	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Acarodermatitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Acid Fast Bacilli Infection	0	1 (0.2)	0	0	0	0	0	0	0
Acinetobacter Bacteraemia	0	0	0	0	1 (0.2)	0	0	0	0
Acinetobacter Infection	0	0	0	1 (6.3)	3 (0.7)	0	0	0	0
Acute Sinusitis	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Adenovirus Infection	0	0	0	1 (6.3)	2 (0.4)	0	0	0	0
Alpha Haemolytic Streptococcal Infection	0	1 (0.2)	0	1 (6.3)	4 (0.9)	0	0	0	0
Amoebic Dysentery	0	1 (0.2)	0	0	0	0	0	0	0
Anal Abscess	0	4 (0.8)	1 (1.6)	0	3 (0.7)	2 (3.2)	0	0	0
Anal Infection	0	0	0	1 (6.3)	0	0	0	0	0
Angular Cheilitis	0	0	0	0	1 (0.2)	0	0	0	0
Anorectal Cellulitis	0	0	0	0	0	1 (1.6)	0	0	0
Anorectal Infection	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Aspergilloma	0	0	0	0	1 (0.2)	0	0	0	0
Aspergillus Infection	0	4 (0.8)	1 (1.6)	0	11 (2.4)	3 (4.8)	0	1 (2.0)	0
Atypical Pneumonia	0	1 (0.2)	0	0	0	0	0	0	0
Bacillus Bacteraemia	0	1 (0.2)	0	0	0	0	0	0	0
Bacillus Infection	0	1 (0.2)	0	0	0	0	0	0	0
Bacteraemia	0	49 (9.2)	7 (11.1)	1 (6.3)	38 (8.3)	6 (9.5)	0	6 (12.2)	2 (22.2)
Bacterial Disease Carrier	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Bacterial Infection	0	13 (2.5)	1 (1.6)	1 (6.3)	8 (1.7)	3 (4.8)	0	1 (2.0)	0
Bacterial Sepsis	0	5 (0.9)	0	0	4 (0.9)	1 (1.6)	0	1 (2.0)	0
Bacteriuria	0	0	0	0	0	1 (1.6)	0	0	0
Bartholin's Abscess	0	1 (0.2)	0	0	0	0	0	0	0
Bartholinitis	0	1 (0.2)	0	0	0	0	0	0	0
Bk Virus Infection	0	0	1 (1.6)	0	0	0	0	0	0
Body Tinea	0	0	0	0	2 (0.4)	0	0	0	0
Bronchiolitis	0	4 (0.8)	0	0	0	0	0	0	0
Bronchitis	0	13 (2.5)	1 (1.6)	2 (12.5)	7 (1.5)	1 (1.6)	0	0	0
Bronchopulmonary Aspergillosis	0	3 (0.6)	0	0	8 (1.7)	1 (1.6)	0	2 (4.1)	0
Campylobacter Infection	0	1 (0.2)	0	0	0	0	0	0	0
Candida Infection	0	8 (1.5)	1 (1.6)	0	8 (1.7)	1 (1.6)	0	1 (2.0)	0
Candida Sepsis	0	0	1 (1.6)	0	0	0	0	0	0
Catheter Site Cellulitis	0	4 (0.8)	0	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Catheter Site Infection	0	9 (1.7)	1 (1.6)	0	8 (1.7)	1 (1.6)	0	1 (2.0)	0
Cavernous Sinus Thrombosis	0	0	0	0	1 (0.2)	0	0	0	0
Cellulitis	1 (8.3)	13 (2.5)	1 (1.6)	1 (6.3)	13 (2.8)	3 (4.8)	0	1 (2.0)	0
Cellulitis Staphylococcal	0	1 (0.2)	0	0	0	0	0	0	0
Cerebral Fungal Infection	0	0	0	0	1 (0.2)	0	0	0	0
Cerebral Toxoplasmosis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Chlamydial Infection	0	0	0	0	1 (0.2)	0	0	0	0
Chronic Sinusitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Citrobacter Infection	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Clostridial Infection	0	5 (0.9)	0	0	0	0	0	0	0
Clostridium Bacteraemia	0	0	0	0	0	1 (1.6)	0	0	0
Clostridium Colitis	0	1 (0.2)	0	0	0	0	0	0	0
Clostridium Difficile Colitis	0	7 (1.3)	1 (1.6)	0	9 (2.0)	1 (1.6)	0	1 (2.0)	0
Clostridium Difficile Infection	0	8 (1.5)	1 (1.6)	0	6 (1.3)	1 (1.6)	0	1 (2.0)	0
Conjunctivitis	0	21 (4.0)	2 (3.2)	1 (6.3)	19 (4.1)	2 (3.2)	0	0	0
Corynebacterium Bacteraemia	0	0	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Corynebacterium Infection	0	0	0	0	3 (0.7)	0	0	0	0
Corynebacterium Sepsis	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Cystitis	0	8 (1.5)	2 (3.2)	1 (6.3)	2 (0.4)	1 (1.6)	0	0	0
Cystitis Escherichia	0	0	0	1 (6.3)	0	0	0	0	0
Cystitis Klebsiella	0	0	1 (1.6)	0	0	0	0	0	0
Cytomegalovirus Colitis	0	5 (0.9)	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Enteritis	0	1 (0.2)	0	0	0	0	0	0	0
Cytomegalovirus Enterocolitis	0	0	0	0	1 (0.2)	0	0	0	0
Cytomegalovirus Gastritis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Cytomegalovirus Gastroenteritis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Hepatitis	0	0	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Infection	0	40 (7.5)	0	1 (6.3)	27 (5.9)	1 (1.6)	0	0	0
Cytomegalovirus Viraemia	0	12 (2.3)	0	0	7 (1.5)	0	0	0	0
Device Related Infection	0	25 (4.7)	4 (6.3)	0	32 (7.0)	1 (1.6)	0	3 (6.1)	0
Device Related Sepsis	0	4 (0.8)	0	0	2 (0.4)	1 (1.6)	0	0	1 (11 1)
Ear Infection	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Emphysematous Cystitis	0	1 (0.2)	0	0	0	0	0	0	0
Encephalitis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Encephalitis Viral	0	0	0	0	1 (0.2)	0	0	0	0
Enterobacter Bacteraemia	1 (8.3)	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Enterobacter Infection	0	3 (0.6)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Enterobacter Sepsis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Enterococcal Bacteraemia	0	6 (1.1)	2 (3.2)	0	3 (0.7)	0	0	2 (4.1)	1 (11 1)
Enterococcal Infection	0	3 (0.6)	0	0	9 (2.0)	1 (1.6)	0	0	0
Enterococcal Sepsis	0	0	0	0	2 (0.4)	0	0	0	0
Enterovirus Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Epididymitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Epiglottitis	0	1 (0.2)	0	0	0	0	0	0	0
Epstein-Barr Virus Infection	0	4 (0.8)	0	0	4 (0.9)	0	0	0	0
Erysipelas	0	0	0	0	1 (0.2)	0	0	0	1 (11 1)
Escherichia Bacteraemia	1 (8.3)	10 (1.9)	0	0	4 (0.9)	1 (1.6)	0	0	0
Escherichia Infection	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Escherichia Sepsis	0	2 (0.4)	0	1 (6.3)	1 (0.2)	0	0	0	0
Escherichia Urinary Tract Infection	0	3 (0.6)	0	0	1 (0.2)	1 (1.6)	0	0	0
Eye Infection	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Eye Infection Staphylococcal	0	0	0	0	1 (0.2)	0	0	0	0
Eyelid Infection	0	0	0	0	1 (0.2)	0	0	0	0
Febrile Infection	0	0	0	0	0	1 (1.6)	0	0	0
Folliculitis	0	11 (2.1)	0	0	12 (2.6)	1 (1.6)	0	2 (4.1)	1 (11 1)

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Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Fungaemia	0	0	0	0	0	1 (1.6)	0	0	0
Fungal Infection	0	11 (2.1)	2 (3.2)	0	14 (3.0)	3 (4.8)	0	3 (6.1)	0
Fungal Oesophagitis	0	1 (0.2)	0	0	0	0	0	0	0
Fungal Rhinitis	0	0	0	0	1 (0.2)	0	0	0	0
Fungal Sepsis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Fungal Skin Infection	1 (8.3)	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Furuncle	0	0	0	0	0	1 (1.6)	0	0	0
Fusobacterium Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gangrene	0	0	0	0	2 (0.4)	0	0	0	0
Gastroenteritis	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Gastroenteritis Cryptosporidial	0	1 (0.2)	0	0	0	0	0	0	0
Gastroenteritis Pseudomonas	0	1 (0.2)	0	0	0	0	0	0	0
Gastroenteritis Rotavirus	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gastroenteritis Viral	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Gastrointestinal Candidiasis	0	0	0	0	1 (0.2)	0	0	0	0
Gastrointestinal Infection	0	1 (0.2)	0	0	0	0	0	0	0
Genital Herpes	0	5 (0.9)	0	0	1 (0.2)	0	0	0	0
Genital Herpes Simplex	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Genital Infection Bacterial	0	1 (0.2)	0	0	0	0	0	0	0
Giardiasis	0	1 (0.2)	0	0	0	0	0	0	0
Gingivitis	0	4 (0.8)	0	0	4 (0.9)	2 (3.2)	0	1 (2.0)	0
Haemophilus Infection	1 (8.3)	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hepatitis B	0	1 (0.2)	0	0	0	0	0	0	0

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Herpes Dermatitis	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Herpes Oesophagitis	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Herpes Pharyngitis	0	0	0	0	1 (0.2)	0	0	0	0
Herpes Simplex	0	12 (2.3)	2 (3.2)	1 (6.3)	13 (2.8)	2 (3.2)	0	0	0
Herpes Virus Infection	0	15 (2.8)	1 (1.6)	1 (6.3)	6 (1.3)	1 (1.6)	0	2 (4.1)	1 (11.1)
Herpes Zoster	0	20 (3.8)	1 (1.6)	1 (6.3)	9 (2.0)	0	0	0	1 (11 1)
Herpes Zoster Disseminated	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hookworm Infection	0	0	0	0	1 (0.2)	0	0	0	0
Hordeolum	0	0	0	0	1 (0.2)	0	0	0	0
Human Herpesvirus 6 Infection	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Impetigo	0	0	0	0	1 (0.2)	0	0	0	0
Infected Skin Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Infection	0	8 (1.5)	0	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Infectious Disease Carrier	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Influenza	0	5 (0.9)	0	1 (6.3)	2 (0.4)	1 (1.6)	0	0	0
Infusion Site Infection	0	0	0	0	1 (0.2)	0	0	0	0
Klebsiella Bacteraemia	0	4 (0.8)	0	0	5 (1.1)	1 (1.6)	0	1 (2.0)	0
Klebsiella Infection	0	2 (0.4)	0	0	6 (1.3)	0	0	0	0
Klebsiella Sepsis	0	1 (0.2)	0	0	0	0	0	0	0
Lactobacillus Infection	0	0	0	0	1 (0.2)	0	0	0	0
Laryngitis	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Leptotrichia Infection	0	0	0	0	1 (0.2)	0	0	0	0
Lip Infection	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Liver Abscess	0	0	0	0	1 (0.2)	0	0	0	0
Localised Infection	0	2 (0.4)	1 (1.6)	0	4 (0.9)	0	0	0	0
Lower Respiratory Tract Infection	1 (8.3)	7 (1.3)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	0	0
Lower Respiratory Tract Infection Fungal	0	0	0	0	1 (0.2)	0	0	0	0
Lung Abscess	0	1 (0.2)	0	0	0	0	0	0	0
Lung Infection	0	0	0	0	0	0	0	0	1 (11 1)
Lymphangitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Mastitis	0	1 (0.2)	0	0	0	0	0	0	0
Mastoiditis	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	0	0
Meningitis Listeria	0	0	0	0	1 (0.2)	0	0	0	0
Meningococcal Infection	0	0	0	0	1 (0.2)	0	0	0	0
Micrococcus Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Mycobacterial Infection	0	0	0	0	1 (0.2)	0	0	0	0
Mycobacterium Avium Complex Infection	0	0	0	0	0	1 (1.6)	0	0	0
Myelitis	0	1 (0.2)	0	0	0	0	0	0	0
Nail Infection	0	1 (0.2)	0	0	0	0	0	0	0
Nasopharyngitis	1 (8.3)	12 (2.3)	1 (1.6)	0	17 (3.7)	1 (1.6)	0	3 (6.1)	0
Neisseria Infection	0	0	0	0	1 (0.2)	0	0	0	0
Neutropenic Sepsis	1 (8.3)	5 (0.9)	0	0	1 (0.2)	0	0	4 (8.2)	1 (11.1)
Nocardia Sepsis	0	0	0	0	1 (0.2)	0	0	0	0
Nocardiosis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Oesophageal Candidiasis	0	0	0	0	2 (0.4)	0	0	0	0
Onychomycosis	0	1 (0.2)	0	0	0	0	0	0	1 (11 1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Ophthalmic Herpes Simplex	0	0	0	0	1 (0.2)	0	0	0	0
Oral Candidiasis	1 (8.3)	14 (2.6)	2 (3.2)	1 (6.3)	17 (3.7)	0	0	2 (4.1)	0
Oral Fungal Infection	0	0	0	0	0	0	0	1 (2.0)	0
Oral Herpes	1 (8.3)	49 (9.2)	6 (9.5)	0	29 (6.3)	4 (6.3)	0	7 (14.3)	1 (11 1)
Oral Infection	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Oropharyngeal Candidiasis	0	0	0	0	3 (0.7)	0	0	1 (2.0)	0
Osteomyelitis	0	0	0	0	1 (0.2)	0	0	0	0
Otitis Externa	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Otitis Media	0	2 (0.4)	0	0	4 (0.9)	0	0	0	0
Parainfluenzae Virus Infection	0	1 (0.2)	0	1 (6.3)	3 (0.7)	0	0	0	0
Paronychia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Parotitis	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Pericoronitis	0	1 (0.2)	0	0	0	0	0	0	0
Perineal Abscess	0	1 (0.2)	0	0	0	0	0	0	0
Periodontitis	1 (8.3)	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Periorbital Cellulitis	0	0	0	0	0	0	0	1 (2.0)	0
Perirectal Abscess	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Peritonitis	0	0	0	0	1 (0.2)	0	0	0	0
Peritonitis Bacterial	0	0	0	0	1 (0.2)	0	0	0	0
Pharyngitis	0	10 (1.9)	0	1 (6.3)	7 (1.5)	0	0	1 (2.0)	0
Pharyngitis Bacterial	0	1 (0.2)	0	0	0	0	0	0	0
Pilonidal Cyst	0	1 (0.2)	0	0	0	0	0	0	0
Pneumococcal Bacteraemia	0	0	1 (1.6)	0	0	0	0	1 (2.0)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Pneumocystis Jirovecii Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pneumocystis Jirovecii Pneumonia	0	2 (0.4)	0	0	2 (0.4)	0	0	0	1 (11 1)
Pneumonia	0	52 (9.8)	3 (4.8)	1 (6.3)	46 (10.0)	6 (9.5)	0	4 (8.2)	3 (33.3)
Pneumonia Bacterial	0	6 (1.1)	1 (1.6)	0	0	0	0	0	0
Pneumonia Cytomegaloviral	0	6 (1.1)	0	0	0	0	0	0	0
Pneumonia Fungal	0	3 (0.6)	1 (1.6)	0	4 (0.9)	2 (3.2)	0	0	1 (11 1)
Pneumonia Klebsiella	0	4 (0.8)	0	0	5 (1.1)	0	0	0	0
Pneumonia Necrotising	0	0	0	0	1 (0.2)	0	0	0	0
Pneumonia Pseudomonal	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Pneumonia Staphylococcal	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Pneumonia Streptococcal	0	0	0	0	1 (0.2)	0	0	0	0
Pneumonia Viral	0	1 (0.2)	0	0	0	0	0	0	0
Polyomavirus-Associated Nephropathy	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Progressive Multifocal Leukoencephalopathy	0	0	0	0	1 (0.2)	0	0	0	0
Pseudomembranous Colitis	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Pseudomonal Bacteraemia	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Pseudomonal Sepsis	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Pseudomonas Infection	1 (8.3)	6 (1.1)	2 (3.2)	0	4 (0.9)	2 (3.2)	0	0	0
Pulmonary Mycosis	0	2 (0.4)	1 (1.6)	0	3 (0.7)	2 (3.2)	0	0	0
Pulmonary Tuberculosis	0	1 (0.2)	0	0	0	0	0	0	0
Purulent Discharge	0	1 (0.2)	0	0	0	0	0	0	0
Pyoderma	0	1 (0.2)	0	0	0	0	0	0	0
Pyuria	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Rash Pustular	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Relapsing Fever	0	0	0	0	1 (0.2)	0	0	0	0
Respiratory Moniliasis	0	0	0	0	1 (0.2)	0	0	0	0
Respiratory Syncytial Virus Infection	0	6 (1.1)	0	1 (6.3)	3 (0.7)	0	0	0	0
Respiratory Tract Infection	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Rhinitis	0	9 (1.7)	1 (1.6)	1 (6.3)	9 (2.0)	0	0	1 (2.0)	0
Rhinovirus Infection	0	0	0	0	0	0	0	1 (2.0)	0
Rotavirus Infection	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Salmonellosis	0	1 (0.2)	0	0	0	0	0	0	0
Scedosporium Infection	0	0	0	0	1 (0.2)	0	0	0	0
Sepsis	0	15 (2.8)	4 (6.3)	1 (6.3)	21 (4.6)	1 (1.6)	0	2 (4.1)	1 (11.1)
Sepsis Syndrome	0	0	1 (1.6)	0	0	0	0	0	0
Septic Embolus	0	1 (0.2)	0	0	0	0	0	0	0
Septic Rash	0	0	1 (1.6)	0	0	0	0	0	0
Septic Shock	0	14 (2.6)	2 (3.2)	2 (12.5)	13 (2.8)	1 (1.6)	0	4 (8.2)	2 (22.2)
Serratia Infection	0	3 (0.6)	0	0	0	0	0	0	0
Sialoadenitis	0	1 (0.2)	0	0	0	0	0	0	0
Sinusitis	0	24 (4.5)	0	0	24 (5.2)	1 (1.6)	0	2 (4.1)	0
Sinusitis Bacterial	1 (8.3)	1 (0.2)	0	0	0	0	0	0	0
Sinusitis Fungal	0	0	0	0	0	0	0	0	1 (11.1)
Skin Bacterial Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Skin Candida	0	0	0	0	1 (0.2)	0	0	0	0
Skin Infection	0	0	0	0	4 (0.9)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Soft Tissue Infection	0	0	0	0	0	0	0	1 (2.0)	0
Sputum Purulent	0	0	0	0	1 (0.2)	0	0	0	0
Staphylococcal Abscess	0	0	0	0	1 (0.2)	0	0	0	0
Staphylococcal Bacteraemia	1 (8.3)	19 (3.6)	5 (7.9)	0	25 (5.4)	3 (4.8)	0	3 (6.1)	0
Staphylococcal Infection	0	24 (4.5)	2 (3.2)	0	17 (3.7)	3 (4.8)	0	2 (4.1)	0
Staphylococcal Sepsis	0	5 (0.9)	2 (3.2)	1 (6.3)	3 (0.7)	1 (1.6)	0	1 (2.0)	0
Staphylococcal Skin Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Stenotrophomonas Infection	0	1 (0.2)	0	0	0	0	0	0	0
Streptococcal Bacteraemia	0	6 (1.1)	0	0	10 (2.2)	1 (1.6)	0	1 (2.0)	0
Streptococcal Infection	0	4 (0.8)	0	0	4 (0.9)	1 (1.6)	0	0	0
Streptococcal Sepsis	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Strongyloidiasis	0	0	0	0	1 (0.2)	0	0	0	0
Subcutaneous Abscess	0	2 (0.4)	1 (1.6)	1 (6.3)	1 (0.2)	0	0	0	0
Superinfection	0	1 (0.2)	0	0	0	0	0	0	0
Systemic Candida	0	4 (0.8)	1 (1.6)	0	2 (0.4)	0	0	0	0
Systemic Mycosis	1 (8.3)	0	0	0	4 (0.9)	0	0	1 (2.0)	0
Tinea Infection	0	0	0	0	1 (0.2)	0	0	0	0
Tonsillitis	0	0	0	0	3 (0.7)	0	0	2 (4.1)	0
Tooth Abscess	0	4 (0.8)	0	0	1 (0.2)	0	0	1 (2.0)	0
Tooth Infection	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Toxoplasmosis	0	0	0	0	1 (0.2)	0	0	0	0
Tracheobronchitis	0	5 (0.9)	0	0	3 (0.7)	1 (1.6)	0	0	0
Tracheobronchitis Viral	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Trichomoniasis	0	1 (0.2)	0	0	0	0	0	0	0
Tuberculosis	0	0	0	0	1 (0.2)	0	0	0	0
Upper Respiratory Tract Infection	0	27 (5.1)	2 (3.2)	1 (6.3)	33 (7.2)	1 (1.6)	0	0	0
Urethritis	0	0	0	0	1 (0.2)	0	0	0	0
Urinary Tract Infection	1 (8.3)	21 (4.0)	3 (4.8)	1 (6.3)	23 (5.0)	2 (3.2)	0	4 (8.2)	0
Urinary Tract Infection Enterococcal	0	0	0	0	1 (0.2)	0	0	0	0
Urinary Tract Infection Fungal	0	1 (0.2)	0	0	0	0	0	0	0
Urinary Tract Infection Pseudomonal	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Urinary Tract Infection Staphylococcal	0	1 (0.2)	0	0	0	0	0	0	0
Urinary Tract Infection Viral	0	0	0	0	1 (0.2)	0	0	0	0
Varicella	0	1 (0.2)	0	0	0	0	0	0	0
Varicella Zoster Pneumonia	0	1 (0.2)	0	0	0	0	0	0	0
Varicella Zoster Virus Infection	0	3 (0.6)	0	0	0	0	0	0	0
Viral Haemorrhagic Cystitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Viral Infection	0	2 (0.4)	0	0	5 (1.1)	0	0	0	0
Vulval Abscess	0	0	0	0	0	1 (1.6)	0	0	0
Vulvitis	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Vulvovaginal Candidiasis	0	0	0	0	4 (0.9)	0	0	0	0
Vulvovaginal Mycotic Infection	0	1 (0.2)	0	0	0	0	0	0	0
Vulvovaginitis	0	1 (0.2)	0	0	0	0	0	0	0
Wound Infection	0	0	0	0	0	0	0	1 (2.0)	0

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Injury, Poisoning And Procedural Complications	**1 (8.3)**	**121 (22.8)**	**16 (25.4)**	**1 (6.3)**	**103 (22.4)**	**19 (30.2)**	**0**	**19 (38.8)**	**2 (22.2)**
Accidental Overdose	0	0	0	0	1 (0.2)	0	0	0	0
Allergic Transfusion Reaction	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Anal Injury	0	2 (0.4)	0	0	0	0	0	0	0
Animal Bite	0	0	0	0	0	0	0	1 (2.0)	0
Arthropod Bite	0	1 (0.2)	0	0	0	0	0	0	0
Back Injury	0	1 (0.2)	0	0	0	0	0	0	0
Brain Herniation	0	0	0	0	0	0	0	1 (2.0)	0
Chemical Eye Injury	0	0	0	0	1 (0.2)	0	0	0	0
Complications Of Transplant Surgery	0	1 (0.2)	0	0	0	0	0	0	0
Compression Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Contusion	0	15 (2.8)	1 (1.6)	0	15 (3.3)	3 (4.8)	0	1 (2.0)	0
Eschar	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Excoriation	0	3 (0.6)	0	0	0	2 (3.2)	0	0	0
Eye Burns	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Eye Injury	0	0	0	0	0	1 (1.6)	0	0	0
Fall	0	19 (3.6)	1 (1.6)	0	17 (3.7)	2 (3.2)	0	4 (8.2)	1 (11 1)
Femoral Neck Fracture	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Foreign Body	0	0	0	0	1 (0.2)	0	0	0	0
Gastrointestinal Stoma Complication	0	0	0	0	1 (0.2)	0	0	0	0
Haematuria Traumatic	0	0	0	0	1 (0.2)	0	0	0	0

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Haemodilution	0	0	0	0	0	1 (1.6)	0	0	0
Hand Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Head Injury	0	0	1 (1.6)	0	2 (0.4)	0	0	0	0
Hip Fracture	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Incision Site Erythema	0	0	0	0	0	0	0	1 (2.0)	0
Incision Site Haemorrhage	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Incision Site Pain	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Inflammation Of Wound	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Infusion Related Reaction	0	6 (1.1)	1 (1.6)	0	10 (2.2)	1 (1.6)	0	0	0
Injury	0	0	0	0	1 (0.2)	0	0	0	0
Injury Corneal	0	0	0	0	1 (0.2)	0	0	0	0
Joint Injury	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Keratorhexis	0	0	0	0	0	1 (1.6)	0	0	0
Laceration	0	8 (1.5)	1 (1.6)	0	4 (0.9)	4 (6.3)	0	0	0
Ligament Sprain	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Lip Injury	0	1 (0.2)	0	0	0	0	0	0	0
Lumbar Vertebral Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Mouth Injury	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Muscle Rupture	0	0	0	0	1 (0.2)	0	0	0	0
Muscle Strain	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Overdose	0	0	0	0	1 (0.2)	0	0	0	0
Periorbital Haematoma	0	0	0	0	1 (0.2)	0	0	0	0
Pneumothorax Traumatic	0	0	0	0	1 (0.2)	0	0	0	0

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Post Lumbar Puncture Syndrome	0	2 (0.4)	0	0	0	0	0	0	0
Post Procedural Complication	0	1 (0.2)	1 (1.6)	0	0	0	0	0	1 (11 1)
Post Procedural Discomfort	0	0	0	0	1 (0.2)	0	0	0	0
Post Procedural Haematoma	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Post Procedural Haemorrhage	0	2 (0.4)	1 (1.6)	0	4 (0.9)	2 (3.2)	0	0	0
Post Procedural Oedema	0	1 (0.2)	0	0	0	0	0	0	0
Post-Traumatic Pain	0	1 (0.2)	0	0	0	0	0	0	0
Postoperative Fever	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Procedural Hypertension	0	1 (0.2)	0	0	0	0	0	0	0
Procedural Pain	0	18 (3.4)	0	0	16 (3.5)	0	0	0	0
Rib Fracture	0	0	1 (1.6)	0	0	0	0	0	0
Road Traffic Accident	0	0	0	0	1 (0.2)	0	0	0	0
Scratch	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Sedation Complication	0	1 (0.2)	0	0	0	0	0	0	0
Skin Abrasion	0	5 (0.9)	0	0	4 (0.9)	0	0	0	0
Skin Injury	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Spinal Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Stoma Site Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Stoma Site Pain	0	0	0	0	1 (0.2)	0	0	0	0
Subarachnoid Haemorrhage	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Subcutaneous Haematoma	0	0	0	0	0	0	0	0	1 (11.1)
Subdural Haematoma	0	2 (0.4)	0	0	2 (0.4)	1 (1.6)	0	0	0
Thermal Burn	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Tooth Fracture	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Toxicity To Various Agents	0	8 (1.5)	0	0	7 (1.5)	0	0	0	0
Transfusion Reaction	1 (8.3)	26 (4.9)	7 (11.1)	1 (6.3)	16 (3.5)	4 (6.3)	0	10 (20.4)	0
Transplant Failure	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Traumatic Haematoma	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Vaginal Laceration	0	0	0	0	1 (0.2)	0	0	0	0
Vascular Injury	0	0	0	0	1 (0.2)	0	0	0	0
Wound	0	3 (0.6)	0	0	7 (1.5)	3 (4.8)	0	0	0
Wound Complication	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Wound Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Wound Secretion	0	0	0	0	1 (0.2)	0	0	0	0
Investigations	**7 (58.3)**	**284 (53.6)**	**37 (58.7)**	**10 (62.5)**	**247 (53.7)**	**30 (47.6)**	**0**	**28 (57.1)**	**5 (55.6)**
Activated Partial Thromboplastin Time Prolonged	0	0	0	0	3 (0.7)	0	0	0	0
Activated Partial Thromboplastin Time Shortened	0	0	0	0	0	1 (1.6)	0	0	0
Alanine Aminotransferase Abnormal	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Alanine Aminotransferase Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Alanine Aminotransferase Increased	1 (8.3)	32 (6.0)	4 (6.3)	0	24 (5.2)	2 (3.2)	0	1 (2.0)	2 (22.2)
Ammonia Increased	0	1 (0.2)	0	0	0	0	0	0	0
Amylase Increased	0	0	0	0	1 (0.2)	0	0	0	0
Antithrombin III Decreased	0	1 (0.2)	0	0	0	0	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Aspartate Aminotransferase Abnormal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Aspartate Aminotransferase Increased	0	17 (3.2)	2 (3.2)	0	15 (3.3)	2 (3.2)	0	3 (6.1)	0
Aspergillus Test Positive	0	0	0	0	2 (0.4)	0	0	0	0
Aspiration Bronchial	0	1 (0.2)	0	0	0	0	0	0	0
Aspiration Tracheal	0	0	0	0	0	1 (1.6)	0	0	0
Aspiration Tracheal Abnormal	0	0	0	0	0	1 (1.6)	0	0	0
Atrial Pressure Increased	0	0	0	0	0	1 (1.6)	0	0	0
Bacterial Test Positive	0	10 (1.9)	2 (3.2)	0	16 (3.5)	2 (3.2)	0	0	0
Basophil Count Increased	0	1 (0.2)	0	0	0	0	0	0	0
Bilirubin Conjugated Increased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Blast Cells Present	0	1 (0.2)	0	0	0	0	0	0	0
Bleeding Time Prolonged	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Blood Albumin Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Blood Albumin Decreased	0	5 (0.9)	1 (1.6)	0	6 (1.3)	0	0	1 (2.0)	0
Blood Albumin Increased	0	0	0	0	2 (0.4)	0	0	0	0
Blood Alkaline Phosphatase Decreased	0	0	0	0	0	0	0	1 (2.0)	0
Blood Alkaline Phosphatase Increased	0	14 (2.6)	2 (3.2)	0	17 (3.7)	2 (3.2)	0	1 (2.0)	0
Blood Bicarbonate Decreased	0	2 (0.4)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	1 (2.0)	0
Blood Bilirubin Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Blood Bilirubin Increased	1 (8.3)	27 (5.1)	1 (1.6)	2 (12.5)	22 (4.8)	2 (3.2)	0	4 (8.2)	0
Blood Calcium Decreased	0	1 (0.2)	1 (1.6)	1 (6.3)	5 (1.1)	1 (1.6)	0	0	0
Blood Chloride Increased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Cholesterol Increased	0	5 (0.9)	0	0	1 (0.2)	0	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
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Blood Creatine Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Creatine Increased	0	2 (0.4)	0	0	0	0	0	0	0
Blood Creatine Phosphokinase Increased	0	0	1 (1.6)	0	0	0	0	0	0
Blood Creatinine Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Creatinine Increased	0	33 (6.2)	1 (1.6)	2 (12.5)	40 (8.7)	6 (9.5)	0	2 (4.1)	0
Blood Culture Positive	0	16 (3.0)	1 (1.6)	1 (6.3)	8 (1.7)	0	0	1 (2.0)	0
Blood Electrolytes Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Blood Gastrin Increased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Glucose Increased	0	4 (0.8)	1 (1.6)	0	6 (1.3)	0	0	0	0
Blood Immunoglobulin G Decreased	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Blood Lactate Dehydrogenase	0	0	0	0	1 (0.2)	0	0	0	0
Blood Lactate Dehydrogenase Increased	0	16 (3.0)	2 (3.2)	0	17 (3.7)	0	0	0	0
Blood Magnesium Decreased	0	9 (1.7)	2 (3.2)	1 (6.3)	7 (1.5)	0	0	0	0
Blood Magnesium Increased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Phosphorus Decreased	0	3 (0.6)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Blood Phosphorus Increased	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Blood Potassium	0	1 (0.2)	0	0	0	0	0	0	0
Blood Potassium Abnormal	0	0	0	0	0	0	0	1 (2.0)	0
Blood Potassium Decreased	0	6 (1.1)	2 (3.2)	1 (6.3)	5 (1.1)	2 (3.2)	0	1 (2.0)	0
Blood Potassium Increased	0	0	0	0	2 (0.4)	0	0	0	0
Blood Pressure Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Pressure Diastolic Increased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Pressure Increased	0	5 (0.9)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Blood Pressure Orthostatic	0	2 (0.4)	0	0	0	0	0	0	0
Blood Sodium Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Testosterone Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Blood Thyroid Stimulating Hormone Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Triglycerides Increased	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Blood Urea Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Urea Increased	1 (8.3)	4 (0.8)	0	0	11 (2.4)	2 (3.2)	0	0	0
Blood Uric Acid Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Uric Acid Increased	0	5 (0.9)	0	0	5 (1.1)	0	0	0	0
Blood Urine Present	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Body Temperature	0	1 (0.2)	0	0	0	0	0	0	0
Body Temperature Increased	0	3 (0.6)	1 (1.6)	0	0	0	0	0	0
Breath Sounds Abnormal	0	13 (2.5)	5 (7.9)	0	10 (2.2)	1 (1.6)	0	0	0
Bronchoscopy	0	0	0	0	1 (0.2)	0	0	0	0
C-Reactive Protein Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
C-Reactive Protein Increased	0	3 (0.6)	1 (1.6)	0	3 (0.7)	0	0	2 (4.1)	0
Carbon Dioxide Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Carbon Monoxide Diffusing Capacity Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Cardiac Murmur	0	11 (2.1)	3 (4.8)	0	6 (1.3)	1 (1.6)	0	0	0
Central Venous Pressure Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Chest X-Ray Abnormal	0	5 (0.9)	1 (1.6)	0	6 (1.3)	0	0	0	0

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All Randomized Subjects
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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Clostridium Test	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Clostridium Test Positive	0	7 (1.3)	0	0	5 (1.1)	1 (1.6)	0	0	0
Coagulation Factor Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Coagulation Factor XIII Level Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Coagulation Test Abnormal	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Coagulation Time Prolonged	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Coagulation Time Shortened	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Colour Vision Tests Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Computerised Tomogram Abnormal	0	1 (0.2)	0	0	4 (0.9)	0	0	1 (2.0)	0
Creatinine Renal Clearance Decreased	0	2 (0.4)	0	0	6 (1.3)	0	0	0	0
Culture	0	1 (0.2)	0	0	0	0	0	0	0
Culture Positive	0	1 (0.2)	0	0	0	0	0	0	0
Culture Stool Positive	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Culture Urine Positive	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Culture Wound Positive	0	0	0	0	1 (0.2)	0	0	0	0
Cytomegalovirus Test	0	5 (0.9)	0	0	6 (1.3)	0	0	0	0
Cytomegalovirus Test Positive	1 (8.3)	26 (4.9)	0	0	22 (4.8)	0	0	0	0
Drug Level Changed	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Drug Level Increased	0	5 (0.9)	0	0	3 (0.7)	0	0	0	0
Echocardiogram Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Ejection Fraction Decreased	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Electrocardiogram Abnormal	0	2 (0.4)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Electrocardiogram Qt Interval	0	0	0	0	0	0	0	1 (2.0)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Electrocardiogram Qt Prolonged	1 (8.3)	20 (3.8)	3 (4.8)	1 (6.3)	12 (2.6)	6 (9.5)	0	3 (6.1)	2 (22.2)
Electrocardiogram Repolarisation Abnormality	0	1 (0.2)	0	0	0	0	0	0	0
Electrocardiogram St Segment Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Electrocardiogram St-T Change	0	1 (0.2)	0	0	0	0	0	0	0
Electrocardiogram St-T Segment Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Electrocardiogram T Wave Abnormal	0	4 (0.8)	0	0	0	0	0	0	0
Electrocardiogram T Wave Inversion	0	1 (0.2)	0	0	0	0	0	0	0
Electroencephalogram Abnormal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Eosinophil Count Increased	0	1 (0.2)	0	0	0	0	0	0	0
Fibrinolysis	0	0	0	0	1 (0.2)	0	0	0	0
Fungal Test	0	0	0	0	0	0	0	0	1 (11.1)
Fungal Test Positive	0	3 (0.6)	0	0	0	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Gamma-Glutamyltransferase Increased	1 (8.3)	34 (6.4)	6 (9.5)	1 (6.3)	37 (8.0)	0	0	3 (6.1)	1 (11 1)
Gastric Ph Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
General Physical Condition	0	0	1 (1.6)	0	0	0	0	0	0
Glucose Urine	0	1 (0.2)	0	0	0	0	0	0	0
Haematocrit Decreased	0	0	0	0	2 (0.4)	0	0	0	0
Haemoglobin Decreased	0	7 (1.3)	1 (1.6)	0	2 (0.4)	0	0	1 (2.0)	0
Heart Rate Increased	0	0	0	0	2 (0.4)	0	0	0	0
Heart Rate Irregular	0	3 (0.6)	2 (3.2)	0	2 (0.4)	1 (1.6)	0	0	0
Heart Sounds Abnormal	0	1 (0.2)	0	0	0	0	0	0	0

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Hepatic Enzyme Abnormal	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hepatic Enzyme Increased	1 (8.3)	8 (1.5)	0	0	12 (2.6)	0	0	0	0
Herpes Simplex Test Positive	0	1 (0.2)	0	0	0	0	0	0	0
High Density Lipoprotein Increased	0	1 (0.2)	0	0	0	0	0	0	0
Immunoglobulins Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Immunosuppressant Drug Level Decreased	0	0	0	0	1 (0.2)	0	0	0	0
International Normalised Ratio Abnormal	0	2 (0.4)	0	0	0	0	0	0	0
International Normalised Ratio Increased	0	1 (0.2)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Liver Function Test Abnormal	0	1 (0.2)	1 (1.6)	0	3 (0.7)	0	0	0	0
Liver Function Test Increased	0	18 (3.4)	0	0	14 (3.0)	2 (3.2)	0	1 (2.0)	0
Lymphocyte Count Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Lymphocyte Count Increased	0	0	0	0	1 (0.2)	0	0	0	0
Microbiology Test Normal	0	1 (0.2)	0	0	0	0	0	0	0
Neurological Examination Abnormal	0	0	0	0	0	1 (1.6)	0	0	0
Neutrophil Count Abnormal	0	2 (0.4)	0	0	0	0	0	0	0
Neutrophil Count Decreased	0	3 (0.6)	0	0	1 (0.2)	0	0	1 (2.0)	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Nuclear Magnetic Resonance Imaging Brain Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Nutritional Condition Abnormal	0	0	0	0	2 (0.4)	0	0	0	0
Occult Blood Positive	0	7 (1.3)	0	0	3 (0.7)	4 (6.3)	0	1 (2.0)	0
Oxygen Consumption Decreased	0	0	0	0	1 (0.2)	0	0	0	0

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Oxygen Saturation Decreased	0	8 (1.5)	1 (1.6)	0	7 (1.5)	2 (3.2)	0	0	0
Parvovirus B19 Test Positive	0	1 (0.2)	0	0	0	0	0	0	0
Pedal Pulse Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Platelet Count Decreased	0	9 (1.7)	0	0	6 (1.3)	0	0	1 (2.0)	0
Po2 Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Protein Total Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Protein Total Increased	0	0	0	0	1 (0.2)	0	0	0	0
Prothrombin Time Prolonged	1 (8.3)	3 (0.6)	1 (1.6)	2 (12.5)	7 (1.5)	3 (4.8)	0	2 (4.1)	1 (11.1)
Prothrombin Time Ratio Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Prothrombin Time Shortened	0	3 (0.6)	0	0	2 (0.4)	0	0	1 (2.0)	0
Pulmonary Function Test Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pulse Absent	0	0	0	0	1 (0.2)	0	0	0	0
Qrs Axis Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Red Blood Cell Count Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Red Blood Cell Schistocytes Present	0	0	0	0	1 (0.2)	0	0	0	0
Respiratory Rate Increased	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Romberg Test Positive	0	0	0	0	1 (0.2)	0	0	0	0
Rotavirus Test Positive	0	0	0	0	1 (0.2)	0	0	0	0
Salmonella Test Positive	0	1 (0.2)	0	0	0	0	0	0	0
Scan Bone Marrow Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Serum Ferritin Increased	0	1 (0.2)	0	0	0	0	0	0	0
Sputum Abnormal	0	0	1 (1.6)	0	0	0	0	0	0
Sputum Culture Positive	0	0	0	0	1 (0.2)	0	0	0	0

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Thrombin Time Prolonged	0	1 (0.2)	0	0	0	0	0	0	0
Thyroid Function Test Abnormal	0	0	0	0	0	1 (1.6)	0	0	0
Total Lung Capacity Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Toxoplasma Serology Positive	0	1 (0.2)	0	0	0	0	0	0	0
Transaminases Increased	1 (8.3)	11 (2.1)	1 (1.6)	0	13 (2.8)	1 (1.6)	0	0	0
Troponin I Increased	0	0	0	0	1 (0.2)	0	0	0	0
Troponin Increased	0	0	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Urine Output Decreased	0	2 (0.4)	1 (1.6)	0	0	1 (1.6)	0	0	0
Urine Output Increased	0	1 (0.2)	0	0	0	0	0	0	0
Viral Test Positive	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Vitamin K Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Volume Blood Decreased	0	0	0	0	0	0	0	0	1 (11.1)
Weight Decreased	3 (25.0)	34 (6.4)	4 (6.3)	2 (12.5)	43 (9.3)	5 (7.9)	0	3 (6.1)	1 (11.1)
Weight Increased	0	10 (1.9)	2 (3.2)	0	8 (1.7)	1 (1.6)	0	5 (10.2)	0
White Blood Cell Count Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
White Blood Cell Count Decreased	0	1 (0.2)	0	0	3 (0.7)	0	0	1 (2.0)	0
White Blood Cell Count Increased	0	2 (0.4)	0	0	0	0	0	0	0
X-Ray Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Metabolism And Nutrition Disorders	**6 (50.0)**	**308 (58.1)**	**40 (63.5)**	**7 (43.8)**	**261 (56.7)**	**46 (73.0)**	**0**	**38 (77.6)**	**7 (77.8)**
Acidosis	0	11 (2.1)	0	0	5 (1.1)	1 (1.6)	0	2 (4.1)	0
Appetite Disorder	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Cachexia	0	2 (0.4)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Calcium Deficiency	0	0	0	0	1 (0.2)	0	0	0	0
Decreased Appetite	1 (8.3)	80 (15.1)	7 (11.1)	0	75 (16.3)	12 (19.0)	0	13 (26.5)	4 (44.4)
Dehydration	0	23 (4.3)	3 (4.8)	0	23 (5.0)	4 (6.3)	0	2 (4.1)	0
Diabetes Mellitus	0	17 (3.2)	0	0	7 (1.5)	0	0	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	0	0	0	0	1 (11 1)
Electrolyte Depletion	0	1 (0.2)	0	0	0	0	0	0	0
Electrolyte Imbalance	0	6 (1.1)	0	0	3 (0.7)	0	0	3 (6.1)	1 (11 1)
Enzyme Abnormality	0	0	0	0	1 (0.2)	0	0	0	0
Failure To Thrive	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Feeding Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Fluid Imbalance	0	0	0	0	1 (0.2)	0	0	0	0
Fluid Overload	0	24 (4.5)	3 (4.8)	0	13 (2.8)	4 (6.3)	0	2 (4.1)	0
Fluid Retention	0	17 (3.2)	1 (1.6)	0	21 (4.6)	3 (4.8)	0	3 (6.1)	0
Food Aversion	0	0	1 (1.6)	0	0	0	0	0	0
Food Craving	0	1 (0.2)	0	0	0	0	0	0	0
Food Intolerance	0	1 (0.2)	0	0	0	0	0	0	0
Glucose Tolerance Impaired	0	0	0	0	1 (0.2)	0	0	0	0
Gout	0	2 (0.4)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Haemochromatosis	0	0	0	0	1 (0.2)	0	0	0	0
Haemosiderosis	0	0	0	0	1 (0.2)	0	0	0	0
Hypercalcaemia	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Hyperchloraemia	0	1 (0.2)	0	0	0	0	0	0	0
Hypercholesterolaemia	0	4 (0.8)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Hypercreatininaemia	0	0	1 (1.6)	0	0	0	0	0	0
Hyperferritinaemia	0	0	0	0	0	1 (1.6)	0	0	0
Hyperglycaemia	1 (8.3)	59 (11.1)	6 (9.5)	1 (6.3)	62 (13.5)	8 (12.7)	0	2 (4.1)	0
Hyperhomocysteinaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperinsulinaemic Hypoglycaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperkalaemia	0	12 (2.3)	3 (4.8)	0	21 (4.6)	2 (3.2)	0	1 (2.0)	1 (11 1)
Hyperlipidaemia	0	0	0	0	1 (0.2)	0	0	0	0
Hypermagnesaemia	1 (8.3)	3 (0.6)	2 (3.2)	0	3 (0.7)	0	0	1 (2.0)	2 (22 2)
Hypernatraemia	0	6 (1.1)	0	0	3 (0.7)	1 (1.6)	0	2 (4.1)	0
Hyperosmolar State	0	1 (0.2)	0	0	0	0	0	0	0
Hyperphagia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperphosphataemia	0	5 (0.9)	1 (1.6)	0	5 (1.1)	3 (4.8)	0	0	0
Hypertriglyceridaemia	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Hyperuricaemia	0	4 (0.8)	0	2 (12.5)	7 (1.5)	1 (1.6)	0	0	0
Hypervolaemia	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Hypoalbuminaemia	0	27 (5.1)	1 (1.6)	1 (6.3)	16 (3.5)	1 (1.6)	0	2 (4.1)	0
Hypocalcaemia	0	44 (8.3)	9 (14.3)	1 (6.3)	41 (8.9)	4 (6.3)	0	4 (8.2)	1 (11.1)
Hypochloraemia	0	0	0	0	0	1 (1.6)	0	0	0
Hypoglycaemia	0	10 (1.9)	0	0	7 (1.5)	2 (3.2)	0	0	0
Hypokalaemia	5 (41.7)	140 (26.4)	27 (42.9)	3 (18.8)	106 (23.0)	27 (42.9)	0	24 (49.0)	5 (55.6)
Hypomagnesaemia	2 (16.7)	80 (15.1)	16 (25.4)	0	62 (13.5)	13 (20.6)	0	8 (16.3)	3 (33.3)
Hyponatraemia	0	27 (5.1)	3 (4.8)	0	24 (5.2)	5 (7.9)	0	3 (6.1)	0
Hypophagia	0	6 (1.1)	4 (6.3)	0	8 (1.7)	3 (4.8)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Hypophosphataemia	0	35 (6.6)	12 (19.0)	0	31 (6.7)	6 (9.5)	0	6 (12.2)	0
Hypoproteinaemia	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	1 (2.0)	0
Hypovitaminosis	0	2 (0.4)	0	0	0	0	0	0	0
Hypovolaemia	0	2 (0.4)	1 (1.6)	0	4 (0.9)	0	0	0	0
Lactose Intolerance	0	0	0	0	1 (0.2)	0	0	0	0
Magnesium Deficiency	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Malnutrition	0	5 (0.9)	0	0	13 (2.8)	2 (3.2)	0	0	0
Metabolic Acidosis	0	10 (1.9)	0	0	5 (1.1)	1 (1.6)	0	1 (2.0)	1 (11 1)
Metabolic Alkalosis	0	0	0	0	2 (0.4)	0	0	0	0
Obesity	0	0	0	0	2 (0.4)	0	0	0	0
Phosphorus Metabolism Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Polydipsia	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Vitamin B12 Deficiency	0	1 (0.2)	0	0	0	0	0	0	0
Vitamin B6 Deficiency	0	0	0	0	1 (0.2)	0	0	0	0
Vitamin C Deficiency	0	0	0	0	1 (0.2)	0	0	0	0
Vitamin K Deficiency	0	1 (0.2)	0	1 (6.3)	1 (0.2)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders	**3 (25.0)**	**226 (42.6)**	**20 (31.7)**	**5 (31.3)**	**208 (45.2)**	**33 (52.4)**	**0**	**16 (32.7)**	**4 (44.4)**
Arthralgia	0	52 (9.8)	6 (9.5)	1 (6.3)	52 (11.3)	3 (4.8)	0	2 (4.1)	1 (11.1)
Arthritis	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	0	1 (11 1)
Axillary Mass	0	1 (0.2)	0	0	0	0	0	0	0
Back Pain	0	53 (10.0)	8 (12.7)	1 (6.3)	54 (11.7)	11 (17.5)	0	4 (8.2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Bone Pain	0	26 (4.9)	0	0	11 (2.4)	0	0	3 (6.1)	0
Bursitis	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Chondritis	0	1 (0.2)	0	0	0	0	0	0	0
Clubbing	0	0	0	0	1 (0.2)	0	0	0	0
Coccydynia	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Flank Pain	0	7 (1.3)	2 (3.2)	0	5 (1.1)	2 (3.2)	0	1 (2.0)	0
Groin Pain	0	2 (0.4)	0	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Haemarthrosis	0	2 (0.4)	0	0	0	1 (1.6)	0	0	0
Inguinal Mass	0	2 (0.4)	0	0	0	0	0	0	0
Intervertebral Disc Degeneration	0	0	0	0	1 (0.2)	0	0	0	0
Intervertebral Disc Protrusion	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Joint Contracture	0	1 (0.2)	0	0	0	0	0	0	0
Joint Effusion	0	3 (0.6)	0	0	0	0	0	0	0
Joint Stiffness	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Joint Swelling	0	7 (1.3)	2 (3.2)	0	6 (1.3)	0	0	0	0
Kyphoscoliosis	0	1 (0.2)	0	0	0	0	0	0	0
Limb Discomfort	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Mobility Decreased	0	0	1 (1.6)	0	0	0	0	0	0
Muscle Atrophy	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Muscle Contracture	0	1 (0.2)	0	0	0	0	0	0	0
Muscle Fatigue	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Muscle Spasms	1 (8.3)	29 (5.5)	1 (1.6)	0	34 (7.4)	4 (6.3)	0	0	0
Muscle Swelling	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Muscle Tightness	0	1 (0.2)	0	0	0	0	0	0	0
Muscle Twitching	0	3 (0.6)	1 (1.6)	0	3 (0.7)	0	0	0	0
Muscular Weakness	0	27 (5.1)	1 (1.6)	0	25 (5.4)	3 (4.8)	0	1 (2.0)	0
Musculoskeletal Chest Pain	0	11 (2.1)	1 (1.6)	0	9 (2.0)	3 (4.8)	0	0	0
Musculoskeletal Discomfort	0	4 (0.8)	0	0	3 (0.7)	0	0	0	0
Musculoskeletal Pain	0	15 (2.8)	1 (1.6)	0	15 (3.3)	5 (7.9)	0	3 (6.1)	1 (11 1)
Musculoskeletal Stiffness	0	5 (0.9)	0	0	9 (2.0)	1 (1.6)	0	1 (2.0)	0
Myalgia	0	27 (5.1)	4 (6.3)	0	29 (6.3)	4 (6.3)	0	1 (2.0)	0
Myopathy	0	20 (3.8)	0	0	11 (2.4)	0	0	0	0
Myositis	0	0	1 (1.6)	0	0	0	0	0	0
Neck Mass	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Neck Pain	0	7 (1.3)	2 (3.2)	0	15 (3.3)	5 (7.9)	0	1 (2.0)	0
Nuchal Rigidity	0	0	0	0	1 (0.2)	0	0	0	0
Osteoarthritis	0	0	0	0	1 (0.2)	0	0	0	0
Osteolysis	0	0	0	0	1 (0.2)	0	0	0	0
Osteonecrosis	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Osteopenia	0	2 (0.4)	0	0	0	0	0	0	0
Osteoporosis	0	0	0	0	2 (0.4)	0	0	0	0
Pain In Extremity	2 (16.7)	49 (9.2)	7 (11.1)	3 (18.8)	37 (8.0)	8 (12.7)	0	4 (8.2)	1 (11.1)
Pain In Jaw	0	6 (1.1)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Pathological Fracture	0	0	0	0	1 (0.2)	0	0	0	0
Plantar Fasciitis	0	1 (0.2)	0	0	0	0	0	0	0
Polychondritis	0	0	0	0	0	0	0	1 (2.0)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Scoliosis	0	1 (0.2)	0	0	0	0	0	0	0
Sjogren's Syndrome	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Soft Tissue Disorder	0	0	0	0	2 (0.4)	1 (1.6)	0	0	0
Spinal Osteoarthritis	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Spinal Pain	0	0	0	0	1 (0.2)	0	0	0	0
Temporomandibular Joint Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Tendon Pain	0	0	0	0	1 (0.2)	0	0	0	0
Tendonitis	0	3 (0.6)	0	0	0	0	0	1 (2.0)	1 (11.1)
Tenosynovitis	0	1 (0.2)	0	0	0	0	0	0	0
Torticollis	0	1 (0.2)	0	0	0	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**2 (16.7)**	**51 (9.6)**	**8 (12.7)**	**2 (12.5)**	**50 (10.9)**	**5 (7.9)**	**0**	**2 (4.1)**	**1 (11 1)**
Acute Lymphocytic Leukaemia Recurrent	0	0	0	1 (6.3)	5 (1.1)	0	0	0	0
Acute Myeloid Leukaemia	2 (16.7)	6 (1.1)	5 (7.9)	0	6 (1.3)	3 (4.8)	0	0	1 (11 1)
Acute Myeloid Leukaemia Recurrent	0	11 (2.1)	1 (1.6)	0	6 (1.3)	0	0	0	0
Adenoma Benign	0	0	0	0	1 (0.2)	0	0	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	0	0	1 (0.2)	0	0	0	0
Angiomyolipoma	0	0	0	0	1 (0.2)	0	0	0	0
Anogenital Warts	0	1 (0.2)	0	0	0	0	0	0	0
B-Cell Lymphoma	0	0	0	0	1 (0.2)	0	0	0	0
Basal Cell Carcinoma	0	0	0	0	1 (0.2)	0	0	0	0
Bowen's Disease	0	1 (0.2)	0	0	0	0	0	0	0

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Breast Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0
Chloroma	0	1 (0.2)	0	0	0	0	0	0	0
Chronic Lymphocytic Leukaemia Recurrent	0	0	0	0	1 (0.2)	0	0	0	0
Chronic Myeloid Leukaemia	0	1 (0.2)	0	0	0	0	0	0	0
Colon Adenoma	0	1 (0.2)	0	0	0	0	0	0	0
Haemangioma Of Liver	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hodgkin's Disease	0	0	0	0	1 (0.2)	0	0	0	0
Hodgkin's Disease Recurrent	0	0	0	0	1 (0.2)	0	0	0	0
Leukaemia	0	4 (0.8)	0	0	2 (0.4)	1 (1.6)	0	0	0
Leukaemia Cutis	0	0	0	0	0	0	0	1 (2.0)	0
Leukaemia Recurrent	0	5 (0.9)	1 (1.6)	1 (6.3)	4 (0.9)	0	0	0	0
Lipoma	0	2 (0.4)	0	0	0	0	0	0	0
Lymphoma	0	5 (0.9)	1 (1.6)	0	2 (0.4)	0	0	0	0
Malignant Melanoma	0	0	0	0	1 (0.2)	0	0	0	0
Melanocytic Naevus	0	0	0	0	1 (0.2)	0	0	0	0
Meningioma	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Metastases To Kidney	0	0	0	0	1 (0.2)	0	0	0	0
Metastases To Liver	0	0	0	0	1 (0.2)	0	0	0	0
Metastatic Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0
Myelodysplastic Syndrome	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Nasal Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0
Neoplasm Malignant	0	1 (0.2)	0	0	2 (0.4)	1 (1.6)	0	0	0
Neuroma	0	1 (0.2)	0	0	0	0	0	0	0

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	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Non-Hodgkin's Lymphoma	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	0	0	2 (0.4)	0	0	0	0
Plasma Cell Myeloma	0	0	0	0	1 (0.2)	0	0	0	0
Post Transplant Lymphoproliferative Disorder	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pyogenic Granuloma	0	0	0	0	1 (0.2)	0	0	0	0
Renal Cancer	0	1 (0.2)	0	0	0	0	0	0	0
Renal Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0
Seborrhoeic Keratosis	0	0	0	0	1 (0.2)	0	0	0	0
Skin Papilloma	0	1 (0.2)	0	0	0	0	0	0	0
Squamous Cell Carcinoma	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Thyroid Adenoma	0	1 (0.2)	0	0	0	0	0	0	0
Tumour Associated Fever	0	0	0	0	0	0	0	1 (2.0)	0
Tumour Pain	0	2 (0.4)	0	0	0	0	0	0	0
Uterine Leiomyoma	0	2 (0.4)	0	0	0	0	0	0	0
Vaginal Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0
Nervous System Disorders	**6 (50.0)**	**264 (49.8)**	**25 (39.7)**	**8 (50.0)**	**246 (53.5)**	**32 (50.8)**	**0**	**26 (53.1)**	**5 (55.6)**
Ageusia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Akathisia	0	0	0	0	1 (0.2)	0	0	0	0
Akinesia	0	0	0	0	0	1 (1.6)	0	0	0
Amnesia	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Aphasia	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Areflexia	0	2 (0.4)	0	0	0	0	0	0	0
Asterixis	0	1 (0.2)	0	0	0	0	0	0	0
Ataxia	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Athetosis	0	0	0	0	1 (0.2)	0	0	0	0
Balance Disorder	0	5 (0.9)	0	0	3 (0.7)	1 (1.6)	0	0	0
Brachial Plexopathy	0	0	0	0	1 (0.2)	0	0	0	0
Brain Compression	0	0	0	0	0	0	0	1 (2.0)	0
Brain Oedema	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Burning Sensation	0	8 (1.5)	0	0	2 (0.4)	0	0	0	0
Central Nervous System Lesion	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Cerebellar Haemorrhage	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Cerebral Haemorrhage	0	4 (0.8)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	0	0
Cerebral Hypoperfusion	0	0	0	0	1 (0.2)	0	0	0	0
Cerebral Infarction	0	1 (0.2)	0	0	2 (0.4)	1 (1.6)	0	0	0
Cerebrovascular Accident	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Clonus	0	1 (0.2)	0	0	0	0	0	0	0
Cluster Headache	0	1 (0.2)	0	0	0	0	0	0	0
Cognitive Disorder	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Coma	0	3 (0.6)	0	0	5 (1.1)	0	0	0	0
Demyelination	0	4 (0.8)	0	0	0	0	0	0	0
Depressed Level Of Consciousness	0	2 (0.4)	1 (1.6)	0	3 (0.7)	0	0	0	1 (11 1)
Disturbance In Attention	0	0	0	0	6 (1.3)	0	0	0	0
Dizziness	1 (8.3)	56 (10.6)	4 (6.3)	1 (6.3)	39 (8.5)	12 (19.0)	0	4 (8.2)	1 (11.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Dizziness Postural	0	3 (0.6)	1 (1.6)	0	3 (0.7)	0	0	0	0
Dysaesthesia	0	1 (0.2)	0	0	0	0	0	0	0
Dysarthria	0	2 (0.4)	0	0	3 (0.7)	0	0	1 (2.0)	0
Dysgeusia	0	9 (1.7)	0	0	8 (1.7)	1 (1.6)	0	0	0
Encephalopathy	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	0	0
Epilepsy	0	0	0	0	1 (0.2)	0	0	0	0
Extrapyramidal Disorder	0	2 (0.4)	0	0	0	0	0	0	0
Facial Paralysis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Facial Paresis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Generalised Tonic-Clonic Seizure	0	0	0	0	2 (0.4)	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Haemorrhage Intracranial	1 (8.3)	1 (0.2)	0	0	6 (1.3)	0	0	0	0
Haemorrhagic Stroke	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Head Discomfort	0	1 (0.2)	0	0	0	0	0	0	0
Headache	5 (41.7)	151 (28.5)	15 (23.8)	7 (43.8)	113 (24.6)	19 (30.2)	0	17 (34.7)	5 (55.6)
Hemiparesis	0	0	0	0	7 (1.5)	0	0	0	0
Hemiplegia	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Hydrocephalus	0	0	0	0	0	0	0	1 (2.0)	0
Hyperreflexia	0	0	0	0	2 (0.4)	0	0	0	0
Hypertonia	0	0	0	0	2 (0.4)	1 (1.6)	0	0	0
Hypoaesthesia	0	6 (1.1)	0	0	12 (2.6)	1 (1.6)	0	3 (6.1)	0
Hypogeusia	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Hypoglycaemic Coma	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

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Hypokinesia	0	0	0	0	1 (0.2)	0	0	0	0
Hyporeflexia	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Hypotonia	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Incoherent	0	0	0	0	1 (0.2)	0	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	0	0	0	1 (2.0)	0
Intention Tremor	0	0	0	0	0	1 (1.6)	0	0	0
Intercostal Neuralgia	0	0	0	0	1 (0.2)	0	0	0	0
Intracranial Aneurysm	0	0	0	0	0	1 (1.6)	0	0	0
Lethargy	1 (8.3)	17 (3.2)	1 (1.6)	0	19 (4.1)	3 (4.8)	0	3 (6.1)	0
Leukoencephalopathy	0	2 (0.4)	0	0	0	0	0	0	0
Loss Of Consciousness	0	3 (0.6)	1 (1.6)	0	5 (1.1)	0	0	1 (2.0)	0
Memory Impairment	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Meningism	0	1 (0.2)	0	0	0	0	0	0	0
Mental Impairment	0	0	0	0	1 (0.2)	0	0	0	0
Metabolic Encephalopathy	0	3 (0.6)	0	0	0	0	0	0	0
Migraine	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Myoclonus	0	1 (0.2)	1 (1.6)	0	0	1 (1.6)	0	0	0
Nerve Compression	0	1 (0.2)	0	0	0	0	0	0	0
Nervous System Disorder	0	2 (0.4)	0	0	0	0	0	0	0
Neuralgia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Neurological Symptom	0	0	1 (1.6)	0	0	0	0	0	0
Neuropathy Peripheral	0	9 (1.7)	0	0	11 (2.4)	1 (1.6)	0	0	0
Neurotoxicity	0	0	0	0	2 (0.4)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Nystagmus	0	0	0	0	2 (0.4)	0	0	1 (2.0)	0
Paraesthesia	0	17 (3.2)	0	0	19 (4.1)	2 (3.2)	0	1 (2.0)	0
Paralysis	0	2 (0.4)	0	0	0	0	0	0	0
Paresis	0	0	0	0	1 (0.2)	0	0	0	0
Parosmia	0	1 (0.2)	0	0	0	0	0	0	0
Peripheral Sensory Neuropathy	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Peroneal Nerve Palsy	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Polyneuropathy	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Poor Quality Sleep	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Post Herpetic Neuralgia	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Presyncope	0	2 (0.4)	1 (1.6)	0	0	0	0	2 (4.1)	0
Psychomotor Hyperactivity	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Reflexes Abnormal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Sciatica	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Sedation	0	1 (0.2)	0	0	0	0	0	0	0
Seizure	0	7 (1.3)	2 (3.2)	0	7 (1.5)	0	0	0	0
Sensory Disturbance	0	1 (0.2)	0	0	0	0	0	0	0
Sensory Loss	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Sinus Headache	0	3 (0.6)	0	0	0	0	0	0	0
Somnolence	0	13 (2.5)	4 (6.3)	1 (6.3)	9 (2.0)	2 (3.2)	0	0	0
Speech Disorder	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Stupor	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Syncope	0	16 (3.0)	0	0	4 (0.9)	1 (1.6)	0	1 (2.0)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Tension Headache	0	0	0	0	2 (0.4)	0	0	1 (2.0)	0
Tonic Convulsion	0	1 (0.2)	0	0	0	0	0	0	0
Toxic Neuropathy	0	1 (0.2)	0	0	0	0	0	0	0
Transient Ischaemic Attack	0	1 (0.2)	0	0	0	0	0	0	0
Tremor	0	44 (8.3)	4 (6.3)	1 (6.3)	39 (8.5)	4 (6.3)	0	2 (4.1)	0
Trigeminal Neuralgia	0	0	0	0	1 (0.2)	0	0	0	0
Unresponsive To Stimuli	0	1 (0.2)	0	0	2 (0.4)	1 (1.6)	0	0	0
Visual Field Defect	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Pregnancy, Puerperium And Perinatal Conditions	**0**	**1 (0.2)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Pregnancy	0	1 (0.2)	0	0	0	0	0	0	0
Product Issues	**0**	**11 (2.1)**	**5 (7.9)**	**1 (6.3)**	**11 (2.4)**	**2 (3.2)**	**0**	**0**	**0**
Device Breakage	0	0	0	1 (6.3)	0	0	0	0	0
Device Leakage	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Device Occlusion	0	8 (1.5)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	0	0
Thrombosis In Device	0	1 (0.2)	2 (3.2)	0	4 (0.9)	1 (1.6)	0	0	0
Psychiatric Disorders	**2 (16.7)**	**188 (35.5)**	**30 (47.6)**	**2 (12.5)**	**166 (36.1)**	**32 (50.8)**	**0**	**25 (51.0)**	**2 (22 2)**
Abnormal Behaviour	0	0	0	0	1 (0.2)	0	0	0	0
Abnormal Dreams	0	0	0	0	1 (0.2)	0	0	0	0
Adjustment Disorder With Depressed Mood	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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Affect Lability	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Affective Disorder	0	2 (0.4)	0	0	0	0	0	0	0
Aggression	0	1 (0.2)	0	0	0	0	0	0	0
Agitated Depression	0	1 (0.2)	0	0	0	0	0	0	0
Agitation	0	13 (2.5)	3 (4.8)	0	11 (2.4)	3 (4.8)	0	0	0
Anger	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Anxiety	0	49 (9.2)	4 (6.3)	0	46 (10.0)	10 (15.9)	0	9 (18.4)	0
Aversion	0	0	0	0	0	0	0	1 (2.0)	0
Claustrophobia	0	0	0	0	1 (0.2)	0	0	0	0
Confusional State	0	24 (4.5)	5 (7.9)	0	18 (3.9)	10 (15.9)	0	2 (4.1)	1 (11.1)
Delirium	0	3 (0.6)	2 (3.2)	0	1 (0.2)	1 (1.6)	0	0	0
Depressed Mood	0	5 (0.9)	0	0	3 (0.7)	1 (1.6)	0	1 (2.0)	0
Depression	0	46 (8.7)	5 (7.9)	1 (6.3)	36 (7.8)	8 (12.7)	0	2 (4.1)	1 (11.1)
Depression Suicidal	0	0	0	0	1 (0.2)	0	0	0	0
Disorientation	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Disturbance In Social Behaviour	0	1 (0.2)	0	0	0	0	0	0	0
Eating Disorder	0	0	0	0	2 (0.4)	0	0	0	0
Emotional Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Emotional Distress	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Euphoric Mood	0	2 (0.4)	0	0	0	0	0	0	0
Fear	0	0	0	0	1 (0.2)	0	0	0	0
Feeling Of Despair	0	1 (0.2)	0	0	0	0	0	0	0
Flat Affect	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0

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Frustration Tolerance Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Generalised Anxiety Disorder	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hallucination	0	5 (0.9)	1 (1.6)	0	3 (0.7)	2 (3.2)	0	1 (2.0)	0
Hallucination, Visual	0	2 (0.4)	0	0	0	1 (1.6)	0	2 (4.1)	0
Hypomania	0	1 (0.2)	0	0	0	0	0	0	0
Insomnia	2 (16.7)	81 (15.3)	18 (28.6)	1 (6.3)	85 (18.5)	8 (12.7)	0	12 (24.5)	0
Irritability	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Mania	0	0	0	0	2 (0.4)	0	0	0	0
Mental Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Mental Status Changes	0	7 (1.3)	3 (4.8)	0	11 (2.4)	0	0	0	0
Mood Altered	0	6 (1.1)	0	0	3 (0.7)	0	0	0	0
Mood Swings	0	0	0	0	3 (0.7)	0	0	0	0
Nervousness	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Nightmare	0	3 (0.6)	0	0	1 (0.2)	1 (1.6)	0	0	0
Obsessive-Compulsive Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Paranoia	0	0	0	0	2 (0.4)	0	0	0	0
Phonophobia	0	0	0	0	1 (0.2)	0	0	0	0
Posturing	0	0	0	0	1 (0.2)	0	0	0	0
Psychotic Disorder	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Restlessness	0	5 (0.9)	0	0	2 (0.4)	0	0	3 (6.1)	0
Sleep Disorder	0	3 (0.6)	0	0	4 (0.9)	0	0	0	0
Sleep Disorder Due To General Medical Condition, Insomnia Type	0	0	1 (1.6)	0	0	0	0	0	0

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Stress	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Substance-Induced Psychotic Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Suicidal Ideation	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Tachyphrenia	0	0	0	0	1 (0.2)	0	0	0	0
Tearfulness	0	0	0	0	1 (0.2)	0	0	0	0
Renal And Urinary Disorders	**1 (8.3)**	**143 (27.0)**	**24 (38.1)**	**1 (6.3)**	**134 (29.1)**	**20 (31.7)**	**0**	**11 (22.4)**	**4 (44.4)**
Acute Kidney Injury	0	12 (2.3)	2 (3.2)	0	9 (2.0)	3 (4.8)	0	2 (4.1)	0
Acute Prerenal Failure	0	1 (0.2)	0	0	0	0	0	0	0
Anuria	0	3 (0.6)	1 (1.6)	0	0	1 (1.6)	0	0	0
Azotaemia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Bilirubinuria	0	0	0	0	1 (0.2)	0	0	0	0
Bladder Dilatation	0	0	0	0	1 (0.2)	0	0	0	0
Bladder Pain	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Bladder Spasm	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	0	0
Choluria	0	0	1 (1.6)	0	0	0	0	0	0
Chromaturia	0	1 (0.2)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Chronic Kidney Disease	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Costovertebral Angle Tenderness	0	1 (0.2)	0	0	0	0	0	0	0
Cystitis Haemorrhagic	0	11 (2.1)	0	0	11 (2.4)	0	0	0	0
Dysuria	0	33 (6.2)	3 (4.8)	1 (6.3)	25 (5.4)	3 (4.8)	0	0	1 (11 1)
Glycosuria	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Haematuria	0	35 (6.6)	4 (6.3)	1 (6.3)	34 (7.4)	3 (4.8)	0	4 (8.2)	3 (33.3)

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Hydronephrosis	0	2 (0.4)	0	0	0	0	0	0	1 (11.1)
Incontinence	0	0	1 (1.6)	0	0	0	0	0	0
Kidney Enlargement	0	0	0	0	1 (0.2)	0	0	0	0
Micturition Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Micturition Frequency Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Micturition Urgency	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Nephrolithiasis	0	4 (0.8)	0	0	0	0	0	0	0
Nephropathy	0	0	0	0	1 (0.2)	0	0	0	0
Nocturia	0	2 (0.4)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	0	0
Obstructive Nephropathy	0	0	0	0	1 (0.2)	0	0	0	0
Oliguria	0	8 (1.5)	2 (3.2)	0	3 (0.7)	0	0	0	1 (11 1)
Pollakiuria	0	14 (2.6)	3 (4.8)	0	10 (2.2)	2 (3.2)	0	0	0
Polyuria	0	5 (0.9)	3 (4.8)	0	1 (0.2)	0	0	0	0
Proteinuria	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Renal Cyst	0	1 (0.2)	0	0	2 (0.4)	0	0	1 (2.0)	0
Renal Disorder	0	2 (0.4)	0	0	0	0	0	0	0
Renal Failure	1 (8.3)	36 (6.8)	3 (4.8)	0	54 (11.7)	9 (14.3)	0	2 (4.1)	0
Renal Haematoma	0	1 (0.2)	0	0	0	0	0	0	0
Renal Hypertension	0	0	0	0	0	1 (1.6)	0	0	0
Renal Impairment	0	11 (2.1)	1 (1.6)	0	15 (3.3)	1 (1.6)	0	1 (2.0)	0
Renal Mass	0	0	0	0	0	0	0	1 (2.0)	0
Renal Pain	0	1 (0.2)	0	0	0	0	0	0	0
Renal Tubular Necrosis	0	0	0	0	2 (0.4)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Renal Vein Thrombosis	0	1 (0.2)	0	0	0	0	0	0	0
Stress Urinary Incontinence	0	2 (0.4)	0	0	0	0	0	0	0
Tubulointerstitial Nephritis	0	0	0	0	2 (0.4)	0	0	0	0
Urethral Discharge	0	0	0	0	1 (0.2)	0	0	0	0
Urethral Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Urinary Hesitation	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Urinary Incontinence	0	7 (1.3)	5 (7.9)	0	9 (2.0)	2 (3.2)	0	0	0
Urinary Retention	0	4 (0.8)	4 (6.3)	0	6 (1.3)	3 (4.8)	0	2 (4.1)	0
Urine Abnormality	0	1 (0.2)	0	0	0	0	0	0	0
Urine Odour Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Urogenital Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Reproductive System And Breast Disorders	**1 (8.3)**	**56 (10.6)**	**5 (7.9)**	**4 (25.0)**	**49 (10.7)**	**6 (9.5)**	**0**	**8 (16.3)**	**0**
Adnexa Uteri Cyst	0	1 (0.2)	0	0	0	0	0	0	0
Balanoposthitis	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Bartholin's Cyst	0	1 (0.2)	0	0	0	0	0	0	0
Benign Prostatic Hyperplasia	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Breast Mass	0	1 (0.2)	0	0	0	0	0	0	0
Breast Pain	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Dysfunctional Uterine Bleeding	0	1 (0.2)	0	0	0	0	0	0	0
Dysmenorrhoea	0	2 (0.4)	0	0	4 (0.9)	0	0	0	0
Dyspareunia	0	1 (0.2)	0	0	0	0	0	0	0
Epididymal Disorder	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
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Number (%) of Subjects

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Erectile Dysfunction	0	1 (0.2)	0	1 (6.3)	0	0	0	0	0
Genital Erosion	0	0	0	0	0	1 (1.6)	0	0	0
Genital Erythema	0	0	0	0	0	2 (3.2)	0	0	0
Genital Lesion	0	0	0	0	2 (0.4)	0	0	0	0
Genital Swelling	0	0	0	0	1 (0.2)	0	0	2 (4.1)	0
Genital Ulceration	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gynaecomastia	0	1 (0.2)	0	0	0	0	0	0	0
Menopausal Symptoms	0	2 (0.4)	0	0	0	0	0	0	0
Menorrhagia	0	2 (0.4)	0	0	5 (1.1)	0	0	1 (2.0)	0
Menstrual Disorder	0	2 (0.4)	0	0	1 (0.2)	0	0	1 (2.0)	0
Metrorrhagia	0	5 (0.9)	0	0	6 (1.3)	0	0	0	0
Pelvic Discomfort	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pelvic Haematoma	0	1 (0.2)	0	0	0	0	0	0	0
Pelvic Pain	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Penile Discharge	0	0	0	0	1 (0.2)	0	0	0	0
Penile Haemorrhage	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Penile Necrosis	0	1 (0.2)	0	0	0	0	0	0	0
Penile Oedema	0	0	1 (1.6)	0	0	1 (1.6)	0	0	0
Penile Pain	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Perineal Pain	0	1 (0.2)	0	0	0	0	0	0	0
Postmenopausal Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Prostatism	0	1 (0.2)	0	0	0	0	0	0	0
Prostatitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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All Randomized Subjects
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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Pruritus Genital	0	2 (0.4)	0	0	0	0	0	0	0
Scrotal Oedema	0	1 (0.2)	1 (1.6)	0	0	3 (4.8)	0	0	0
Scrotal Pain	0	0	0	0	1 (0.2)	0	0	0	0
Scrotal Swelling	0	0	1 (1.6)	0	0	1 (1.6)	0	0	0
Sexual Dysfunction	0	0	0	0	1 (0.2)	0	0	0	0
Testicular Pain	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Testicular Swelling	0	1 (0.2)	0	0	0	0	0	0	0
Uterine Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Uterine Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Vaginal Discharge	0	0	0	0	2 (0.4)	0	0	1 (2.0)	0
Vaginal Dysplasia	0	0	0	0	1 (0.2)	0	0	0	0
Vaginal Haemorrhage	1 (8.3)	22 (4.2)	1 (1.6)	3 (18.8)	17 (3.7)	0	0	3 (6.1)	0
Vulval Oedema	0	0	1 (1.6)	0	0	0	0	0	0
Vulval Ulceration	0	0	0	0	1 (0.2)	0	0	0	0
Vulvovaginal Burning Sensation	0	2 (0.4)	0	0	0	0	0	0	0
Vulvovaginal Discomfort	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Vulvovaginal Dryness	0	1 (0.2)	0	0	0	0	0	0	0
Vulvovaginal Pain	0	1 (0.2)	0	0	0	0	0	0	0
Vulvovaginal Pruritus	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**7 (58.3)**	**306 (57.7)**	**49 (77.8)**	**8 (50.0)**	**270 (58.7)**	**48 (76.2)**	**0**	**37 (75.5)**	**7 (77.8)**

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	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Acute Promyelocytic Leukaemia Differentiation Syndrome	0	0	1 (1.6)	0	0	0	0	1 (2.0)	0
Acute Pulmonary Oedema	1 (8.3)	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Acute Respiratory Distress Syndrome	0	6 (1.1)	0	0	6 (1.3)	1 (1.6)	0	1 (2.0)	0
Acute Respiratory Failure	0	5 (0.9)	0	0	1 (0.2)	0	0	0	0
Apnoea	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Asthma	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Atelectasis	0	25 (4.7)	0	0	9 (2.0)	3 (4.8)	0	3 (6.1)	0
Bronchial Hyperreactivity	0	0	0	0	1 (0.2)	0	0	0	0
Bronchial Obstruction	0	0	0	1 (6.3)	1 (0.2)	0	0	0	0
Bronchial Wall Thickening	0	1 (0.2)	0	0	0	0	0	0	0
Bronchitis Chronic	0	0	0	0	1 (0.2)	0	0	0	0
Bronchopneumopathy	0	1 (0.2)	0	0	0	0	0	0	0
Bronchospasm	0	7 (1.3)	2 (3.2)	1 (6.3)	6 (1.3)	2 (3.2)	0	0	0
Chronic Obstructive Pulmonary Disease	0	2 (0.4)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Cough	5 (41.7)	133 (25.1)	18 (28.6)	7 (43.8)	112 (24.3)	19 (30.2)	0	12 (24.5)	4 (44.4)
Diaphragmalgia	0	1 (0.2)	0	0	0	0	0	0	0
Diaphragmatic Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Diffuse Alveolar Damage	0	0	0	0	1 (0.2)	0	0	0	0
Dry Throat	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Dysphonia	0	5 (0.9)	1 (1.6)	0	8 (1.7)	0	0	0	0
Dyspnoea	0	85 (16.0)	16 (25.4)	2 (12.5)	82 (17.8)	22 (34.9)	0	13 (26.5)	0
Dyspnoea Exertional	0	21 (4.0)	2 (3.2)	0	17 (3.7)	1 (1.6)	0	1 (2.0)	0

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Dyspnoea Paroxysmal Nocturnal	0	0	0	0	1 (0.2)	0	0	0	0
Emphysema	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Epiglottis Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Epistaxis	2 (16.7)	61 (11.5)	17 (27.0)	2 (12.5)	57 (12.4)	13 (20.6)	0	8 (16.3)	4 (44.4)
Haemoptysis	0	21 (4.0)	1 (1.6)	0	16 (3.5)	4 (6.3)	0	2 (4.1)	1 (11 1)
Haemothorax	0	0	0	0	2 (0.4)	0	0	0	0
Hiccups	0	11 (2.1)	1 (1.6)	0	3 (0.7)	4 (6.3)	0	1 (2.0)	0
Hydrothorax	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hypercapnia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperventilation	1 (8.3)	2 (0.4)	0	0	0	0	0	0	0
Hypocapnia	0	1 (0.2)	0	0	0	0	0	0	0
Hypoxia	0	19 (3.6)	3 (4.8)	0	23 (5.0)	11 (17.5)	0	7 (14.3)	0
Increased Bronchial Secretion	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Increased Upper Airway Secretion	0	2 (0.4)	0	0	4 (0.9)	0	0	0	0
Increased Viscosity Of Bronchial Secretion	0	2 (0.4)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Interstitial Lung Disease	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Laryngeal Infiltration	0	0	0	0	1 (0.2)	0	0	0	0
Laryngeal Oedema	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Lung Consolidation	0	2 (0.4)	0	0	2 (0.4)	0	0	2 (4.1)	0
Lung Disorder	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	1 (2.0)	0
Lung Infiltration	0	20 (3.8)	1 (1.6)	0	20 (4.3)	3 (4.8)	0	0	0
Nasal Congestion	1 (8.3)	22 (4.2)	2 (3.2)	1 (6.3)	19 (4.1)	1 (1.6)	0	2 (4.1)	0
Nasal Discomfort	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0

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Nasal Dryness	0	1 (0.2)	0	0	2 (0.4)	2 (3.2)	0	0	0
Nasal Inflammation	0	0	0	0	1 (0.2)	0	0	0	0
Nasal Necrosis	0	0	0	0	1 (0.2)	0	0	0	0
Nasal Obstruction	0	2 (0.4)	0	1 (6.3)	0	0	0	0	0
Nasal Septum Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Nasal Ulcer	0	0	0	0	1 (0.2)	0	0	0	0
Nocturnal Dyspnoea	0	1 (0.2)	0	0	0	0	0	0	0
Obliterative Bronchiolitis	0	0	0	0	2 (0.4)	0	0	0	0
Obstructive Airways Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Organising Pneumonia	0	2 (0.4)	0	0	0	0	0	0	0
Oropharyngeal Pain	2 (16.7)	53 (10.0)	9 (14.3)	1 (6.3)	46 (10.0)	7 (11.1)	0	10 (20.4)	1 (11.1)
Oropharyngeal Swelling	0	1 (0.2)	0	0	0	0	0	0	0
Orthopnoea	0	0	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0
Painful Respiration	0	2 (0.4)	0	0	0	0	0	0	0
Paranasal Sinus Discomfort	0	3 (0.6)	0	0	0	0	0	0	0
Paranasal Sinus Hypersecretion	0	1 (0.2)	0	0	0	0	0	0	0
Pharyngeal Erythema	0	4 (0.8)	1 (1.6)	0	2 (0.4)	0	0	1 (2.0)	0
Pharyngeal Lesion	0	1 (0.2)	0	0	0	0	0	0	0
Pharyngeal Ulceration	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Pleural Effusion	0	42 (7.9)	5 (7.9)	0	32 (7.0)	7 (11.1)	0	3 (6.1)	1 (11.1)
Pleural Rub	0	0	0	0	1 (0.2)	0	0	0	0
Pleurisy	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pleuritic Pain	0	4 (0.8)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	0	0

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Pneumomediastinum	0	0	0	0	1 (0.2)	0	0	0	0
Pneumonia Aspiration	0	3 (0.6)	0	0	2 (0.4)	1 (1.6)	0	0	0
Pneumonitis	1 (8.3)	6 (1.1)	0	0	4 (0.9)	0	0	0	0
Pneumothorax	0	5 (0.9)	0	0	5 (1.1)	0	0	1 (2.0)	0
Productive Cough	0	23 (4.3)	7 (11.1)	1 (6.3)	31 (6.7)	1 (1.6)	0	2 (4.1)	0
Prolonged Expiration	0	0	1 (1.6)	0	0	0	0	0	0
Pulmonary Alveolar Haemorrhage	0	3 (0.6)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Pulmonary Congestion	0	1 (0.2)	2 (3.2)	0	0	1 (1.6)	0	0	0
Pulmonary Embolism	0	7 (1.3)	0	0	1 (0.2)	1 (1.6)	0	0	0
Pulmonary Fibrosis	0	0	0	0	1 (0.2)	0	0	0	0
Pulmonary Haemorrhage	0	7 (1.3)	0	0	6 (1.3)	0	0	0	0
Pulmonary Haemosiderosis	0	0	0	0	1 (0.2)	0	0	0	0
Pulmonary Hypertension	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Pulmonary Mass	0	8 (1.5)	0	0	6 (1.3)	2 (3.2)	0	0	0
Pulmonary Oedema	0	13 (2.5)	3 (4.8)	0	16 (3.5)	3 (4.8)	0	3 (6.1)	0
Rales	0	25 (4.7)	10 (15.9)	2 (12.5)	23 (5.0)	5 (7.9)	0	3 (6.1)	2 (22.2)
Respiratory Acidosis	0	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	0	0
Respiratory Alkalosis	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Respiratory Arrest	0	1 (0.2)	0	0	0	0	0	0	0
Respiratory Disorder	0	2 (0.4)	0	0	1 (0.2)	0	0	1 (2.0)	0
Respiratory Distress	0	10 (1.9)	0	0	6 (1.3)	1 (1.6)	0	2 (4.1)	0
Respiratory Failure	0	25 (4.7)	0	0	34 (7.4)	3 (4.8)	0	1 (2.0)	1 (11 1)
Respiratory Tract Congestion	0	3 (0.6)	1 (1.6)	0	1 (0.2)	0	0	1 (2.0)	0

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Respiratory Tract Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Restrictive Pulmonary Disease	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Rhinalgia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Rhinitis Allergic	0	0	0	0	1 (0.2)	0	0	0	0
Rhinorrhoea	0	27 (5.1)	3 (4.8)	1 (6.3)	18 (3.9)	3 (4.8)	0	3 (6.1)	1 (11.1)
Rhonchi	0	7 (1.3)	0	0	7 (1.5)	3 (4.8)	0	0	0
Sinus Congestion	0	16 (3.0)	1 (1.6)	0	13 (2.8)	1 (1.6)	0	0	0
Sinus Disorder	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Sinus Pain	0	4 (0.8)	0	0	9 (2.0)	1 (1.6)	0	0	0
Sinus Polyp	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Sleep Apnoea Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Sneezing	0	2 (0.4)	0	0	3 (0.7)	0	0	1 (2.0)	0
Sputum Discoloured	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Sputum Increased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Tachypnoea	0	14 (2.6)	4 (6.3)	1 (6.3)	12 (2.6)	2 (3.2)	0	4 (8.2)	1 (11.1)
Throat Irritation	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Throat Lesion	0	0	1 (1.6)	0	0	0	0	0	0
Throat Tightness	0	0	1 (1.6)	0	0	1 (1.6)	0	0	0
Tonsillar Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Tonsillar Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Upper-Airway Cough Syndrome	0	8 (1.5)	1 (1.6)	0	4 (0.9)	0	0	0	0
Vocal Cord Inflammation	0	1 (0.2)	0	0	0	0	0	0	0
Wheezing	0	15 (2.8)	4 (6.3)	1 (6.3)	21 (4.6)	1 (1.6)	0	6 (12.2)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Skin And Subcutaneous Tissue Disorders	**6 (50.0)**	**260 (49.1)**	**42 (66.7)**	**9 (56.3)**	**218 (47.4)**	**40 (63.5)**	**0**	**35 (71.4)**	**7 (77.8)**
Acne	0	2 (0.4)	0	2 (12.5)	6 (1.3)	0	0	0	0
Actinic Cheilitis	0	1 (0.2)	0	0	0	0	0	0	0
Acute Febrile Neutrophilic Dermatosis	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Alopecia	1 (8.3)	25 (4.7)	5 (7.9)	0	22 (4.8)	2 (3.2)	0	2 (4.1)	1 (11 1)
Alopecia Totalis	0	1 (0.2)	0	0	0	0	0	0	0
Angioedema	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Blister	0	8 (1.5)	2 (3.2)	0	3 (0.7)	2 (3.2)	0	0	0
Blood Blister	0	4 (0.8)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	2 (4.1)	0
Cold Sweat	0	2 (0.4)	0	0	0	0	0	0	0
Cutaneous Vasculitis	0	1 (0.2)	0	0	0	0	0	0	0
Decubitus Ulcer	0	5 (0.9)	0	0	6 (1.3)	2 (3.2)	0	0	0
Dermal Cyst	0	0	0	0	0	1 (1.6)	0	0	0
Dermatitis	0	7 (1.3)	0	0	4 (0.9)	1 (1.6)	0	1 (2.0)	0
Dermatitis Acneiform	0	1 (0.2)	0	0	0	0	0	0	0
Dermatitis Allergic	0	11 (2.1)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0
Dermatitis Bullous	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Dermatitis Contact	0	2 (0.4)	0	0	0	0	0	0	1 (11 1)
Dermatitis Exfoliative	0	0	0	0	1 (0.2)	0	0	0	0
Drug Eruption	0	4 (0.8)	1 (1.6)	1 (6.3)	5 (1.1)	1 (1.6)	0	1 (2.0)	1 (11 1)
Dry Skin	0	12 (2.3)	4 (6.3)	0	11 (2.4)	2 (3.2)	0	1 (2.0)	0
Ecchymosis	0	7 (1.3)	1 (1.6)	0	10 (2.2)	7 (11.1)	0	3 (6.1)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Eczema	0	3 (0.6)	1 (1.6)	0	0	0	0	0	0
Erythema	0	33 (6.2)	8 (12.7)	0	25 (5.4)	7 (11.1)	0	5 (10.2)	0
Erythema Multiforme	0	0	0	0	1 (0.2)	0	0	0	0
Erythema Nodosum	0	0	0	0	0	0	0	1 (2.0)	0
Erythrosis	0	1 (0.2)	0	0	0	0	0	0	0
Exfoliative Rash	0	0	0	0	1 (0.2)	0	0	0	0
Generalised Erythema	0	0	1 (1.6)	0	0	0	0	0	0
Hangnail	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hidradenitis	0	3 (0.6)	0	0	0	0	0	0	0
Hirsutism	0	2 (0.4)	0	0	0	0	0	0	0
Hyperhidrosis	0	16 (3.0)	4 (6.3)	0	14 (3.0)	5 (7.9)	0	3 (6.1)	0
Hypersensitivity Vasculitis	0	2 (0.4)	0	0	0	0	0	0	0
Hypertrichosis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Ingrowing Nail	1 (8.3)	3 (0.6)	0	1 (6.3)	0	0	0	0	0
Leukoplakia	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Lichenification	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Lichenoid Keratosis	0	0	0	0	1 (0.2)	0	0	0	0
Lipohypertrophy	0	0	0	0	1 (0.2)	0	0	0	0
Livedo Reticularis	0	0	0	0	1 (0.2)	0	0	0	0
Macule	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Madarosis	0	0	0	0	1 (0.2)	0	0	0	0
Nail Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Neurodermatitis	0	1 (0.2)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Night Sweats	0	16 (3.0)	2 (3.2)	0	9 (2.0)	1 (1.6)	0	0	1 (11 1)
Onychoclasis	0	1 (0.2)	0	0	0	0	0	0	0
Onychomadesis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pain Of Skin	0	4 (0.8)	0	0	4 (0.9)	2 (3.2)	0	0	0
Palmar Erythema	0	2 (0.4)	0	0	2 (0.4)	0	0	1 (2.0)	0
Palmar-Plantar Erythrodysaesthesia Syndrome	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Papule	0	2 (0.4)	0	0	3 (0.7)	0	0	2 (4.1)	1 (11 1)
Penile Ulceration	0	0	0	0	0	1 (1.6)	0	0	0
Petechiae	3 (25.0)	44 (8.3)	12 (19.0)	2 (12.5)	37 (8.0)	13 (20.6)	0	8 (16.3)	1 (11.1)
Photosensitivity Reaction	0	0	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Pigmentation Disorder	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	0	0
Prurigo	0	1 (0.2)	0	0	0	0	0	0	0
Pruritus	2 (16.7)	53 (10.0)	5 (7.9)	5 (31.3)	45 (9.8)	6 (9.5)	0	7 (14.3)	2 (22.2)
Pruritus Allergic	0	0	0	0	2 (0.4)	0	0	0	0
Pruritus Generalised	0	5 (0.9)	1 (1.6)	0	3 (0.7)	0	0	1 (2.0)	0
Psoriasis	0	0	0	0	0	1 (1.6)	0	0	0
Purpura	1 (8.3)	8 (1.5)	1 (1.6)	1 (6.3)	2 (0.4)	2 (3.2)	0	2 (4.1)	0
Purpura Senile	0	1 (0.2)	0	0	0	0	0	0	0
Rash	1 (8.3)	85 (16.0)	14 (22.2)	2 (12.5)	75 (16.3)	11 (17.5)	0	19 (38.8)	4 (44.4)
Rash Erythematous	0	8 (1.5)	0	0	5 (1.1)	1 (1.6)	0	1 (2.0)	0
Rash Follicular	0	1 (0.2)	1 (1.6)	0	3 (0.7)	0	0	0	0
Rash Generalised	0	5 (0.9)	0	0	5 (1.1)	0	0	2 (4.1)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Rash Macular	0	5 (0.9)	0	0	2 (0.4)	0	0	2 (4.1)	0
Rash Maculo-Papular	1 (8.3)	11 (2.1)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	1 (2.0)	0
Rash Papular	0	4 (0.8)	0	0	4 (0.9)	0	0	0	0
Rash Pruritic	0	5 (0.9)	2 (3.2)	1 (6.3)	8 (1.7)	3 (4.8)	0	0	0
Rash Vesicular	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Red Man Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Rosacea	0	1 (0.2)	0	0	0	0	0	0	0
Scab	0	1 (0.2)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Skin Burning Sensation	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Skin Discolouration	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Skin Disorder	0	5 (0.9)	2 (3.2)	0	7 (1.5)	2 (3.2)	0	0	1 (11 1)
Skin Dystrophy	0	0	0	0	1 (0.2)	0	0	0	0
Skin Exfoliation	0	8 (1.5)	0	0	7 (1.5)	2 (3.2)	0	1 (2.0)	0
Skin Fissures	0	0	0	0	1 (0.2)	0	0	0	0
Skin Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Skin Hyperpigmentation	0	7 (1.3)	0	0	3 (0.7)	1 (1.6)	0	0	0
Skin Hypopigmentation	0	1 (0.2)	0	0	0	0	0	0	0
Skin Irritation	0	0	0	0	1 (0.2)	0	0	0	0
Skin Lesion	0	18 (3.4)	2 (3.2)	0	12 (2.6)	2 (3.2)	0	2 (4.1)	1 (11 1)
Skin Mass	0	5 (0.9)	0	0	0	0	0	0	0
Skin Necrosis	0	0	0	0	0	1 (1.6)	0	0	0
Skin Oedema	0	1 (0.2)	0	0	0	0	0	0	0
Skin Striae	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Skin Ulcer	0	5 (0.9)	0	0	2 (0.4)	0	0	0	0
Subcutaneous Emphysema	0	1 (0.2)	0	0	0	0	0	0	0
Swelling Face	0	6 (1.1)	1 (1.6)	0	1 (0.2)	0	0	1 (2.0)	0
Transient Acantholytic Dermatosis	0	1 (0.2)	0	0	0	0	0	0	0
Urticaria	0	11 (2.1)	2 (3.2)	0	8 (1.7)	2 (3.2)	0	1 (2.0)	0
Vascular Skin Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Vitiligo	0	0	0	0	1 (0.2)	0	0	0	0
Xanthomatosis	0	0	0	0	1 (0.2)	0	0	0	0
Social Circumstances	**0**	**2 (0.4)**	**0**	**0**	**2 (0.4)**	**0**	**0**	**0**	**0**
Loss Of Personal Independence In Daily Activities	0	0	0	0	1 (0.2)	0	0	0	0
Menopause	0	1 (0.2)	0	0	0	0	0	0	0
Social Problem	0	1 (0.2)	0	0	0	0	0	0	0
Treatment Noncompliance	0	0	0	0	1 (0.2)	0	0	0	0
Surgical And Medical Procedures	**0**	**16 (3.0)**	**1 (1.6)**	**0**	**15 (3.3)**	**1 (1.6)**	**0**	**3 (6.1)**	**0**
Abscess Drainage	0	0	0	0	1 (0.2)	0	0	0	0
Analgesic Therapy	0	0	0	0	1 (0.2)	0	0	0	0
Artificial Crown Procedure	0	0	0	0	1 (0.2)	0	0	0	0
Astringent Therapy	0	1 (0.2)	0	0	0	0	0	2 (4.1)	0
Blood Stem Cell Harvest	0	1 (0.2)	0	0	0	0	0	0	0
Bone Marrow Transplant	0	2 (0.4)	0	0	0	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Central Venous Catheter Removal	0	0	0	0	0	1 (1.6)	0	0	0
Central Venous Catheterisation	0	0	0	0	1 (0.2)	0	0	0	0
Chemotherapy	0	0	0	0	2 (0.4)	0	0	0	0
Fluid Replacement	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Incisional Drainage	0	0	0	0	1 (0.2)	0	0	0	0
Mitral Valve Replacement	0	1 (0.2)	0	0	0	0	0	0	0
Oesophageal Dilation Procedure	0	1 (0.2)	0	0	0	0	0	0	0
Oxygen Therapy	0	0	0	0	1 (0.2)	0	0	0	0
Parenteral Nutrition	0	1 (0.2)	0	0	0	0	0	0	0
Prophylaxis	0	0	0	0	1 (0.2)	0	0	0	0
Sinus Operation	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	0	0
Stem Cell Transplant	0	1 (0.2)	0	0	0	0	0	0	0
Surgery	0	0	0	0	0	0	0	1 (2.0)	0
Therapeutic Procedure	0	1 (0.2)	0	0	0	0	0	0	0
Tooth Extraction	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Wisdom Teeth Removal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Vascular Disorders	**2 (16.7)**	**210 (39.6)**	**19 (30.2)**	**4 (25.0)**	**182 (39.6)**	**30 (47.6)**	**0**	**20 (40.8)**	**4 (44.4)**
Air Embolism	0	1 (0.2)	0	0	0	0	0	0	0
Angiodysplasia	0	0	0	0	0	0	0	1 (2.0)	0
Arteriovenous Fistula	0	1 (0.2)	0	0	0	0	0	0	0
Capillary Leak Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Circulatory Collapse	0	2 (0.4)	0	0	5 (1.1)	1 (1.6)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Deep Vein Thrombosis	0	7 (1.3)	0	0	6 (1.3)	2 (3.2)	0	1 (2.0)	0
Diastolic Hypertension	0	0	0	0	1 (0.2)	0	0	0	0
Embolism Arterial	0	0	0	0	1 (0.2)	0	0	0	0
Flushing	0	5 (0.9)	0	0	9 (2.0)	1 (1.6)	0	3 (6.1)	0
Haematoma	0	15 (2.8)	1 (1.6)	0	12 (2.6)	4 (6.3)	0	4 (8.2)	1 (11 1)
Haemodynamic Instability	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Haemorrhage	0	5 (0.9)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	0	0
Haemorrhagic Infarction	0	0	0	0	1 (0.2)	0	0	0	0
Hot Flush	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hyperaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hypertension	0	100 (18.9)	10 (15.9)	0	85 (18.5)	10 (15.9)	0	4 (8.2)	1 (11.1)
Hypertensive Crisis	0	0	1 (1.6)	0	0	1 (1.6)	0	0	0
Hypotension	1 (8.3)	76 (14.3)	7 (11.1)	4 (25.0)	60 (13.0)	15 (23.8)	0	9 (18.4)	2 (22.2)
Hypovolaemic Shock	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	0	0
Intermittent Claudication	0	1 (0.2)	0	0	0	0	0	0	0
Ischaemia	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Jugular Vein Thrombosis	0	0	0	0	1 (0.2)	0	0	0	0
Labile Hypertension	0	0	0	0	1 (0.2)	0	0	0	0
Microangiopathy	0	1 (0.2)	0	0	0	0	0	0	0
Orthostatic Hypotension	0	14 (2.6)	2 (3.2)	0	6 (1.3)	1 (1.6)	0	1 (2.0)	0
Pallor	0	7 (1.3)	0	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Peripheral Circulatory Failure	0	0	1 (1.6)	0	0	0	0	0	0
Peripheral Coldness	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Peripheral Vascular Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Peripheral Venous Disease	0	1 (0.2)	0	0	0	0	0	0	0
Phlebitis	1 (8.3)	6 (1.1)	0	1 (6.3)	5 (1.1)	2 (3.2)	0	1 (2.0)	0
Poor Peripheral Circulation	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Postpartum Venous Thrombosis	0	1 (0.2)	0	0	0	0	0	0	0
Reperfusion Injury	0	0	0	0	1 (0.2)	0	0	0	0
Secondary Hypertension	0	0	0	0	1 (0.2)	0	0	0	0
Shock	0	0	0	1 (6.3)	3 (0.7)	0	0	0	0
Subclavian Vein Thrombosis	0	2 (0.4)	0	0	0	0	0	0	0
Superior Vena Cava Stenosis	0	0	0	0	1 (0.2)	0	0	0	0
Thrombophlebitis	0	5 (0.9)	0	0	5 (1.1)	1 (1.6)	0	0	0
Thrombophlebitis Superficial	0	0	0	0	1 (0.2)	0	0	0	1 (11 1)
Thrombosis	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Varicose Vein	0	1 (0.2)	0	0	0	0	0	0	0
Vasculitis	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Vasodilatation	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Vein Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Vena Cava Embolism	0	0	0	0	1 (0.2)	0	0	0	0
Venous Thrombosis	0	3 (0.6)	0	0	4 (0.9)	2 (3.2)	0	0	0
Venous Thrombosis Limb	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

Every subject is counted a single time for each applicable row and column.
MedDRA Version 20.1

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付録 2.7.4-161　　年齢別の重度／生命を脅かす有害事象の発現例数（%）（いずれかの投与群で発現割合 0%超）
ポサコナゾール経口懸濁液の予防投与試験（C/I98-316 及び P01899 試験）
（All Randomized Subjects）

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

	Posaconazole			Fluconazole			Itraconazole		
	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Subjects Reporting Any Adverse Event	**7 (58.3)**	**390 (73.6)**	**51 (81.0)**	**10 (62.5)**	**326 (70.9)**	**45 (71.4)**	**0**	**39 (79.6)**	**8 (88.9)**
Blood And Lymphatic System Disorders	**4 (33.3)**	**202 (38.1)**	**33 (52.4)**	**5 (31.3)**	**179 (38.9)**	**27 (42.9)**	**0**	**22 (44.9)**	**6 (66.7)**
Anaemia	1 (8.3)	60 (11.3)	6 (9.5)	1 (6.3)	40 (8.7)	7 (11.1)	0	10 (20.4)	2 (22.2)
Bone Marrow Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Bone Marrow Failure	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Coagulopathy	0	0	0	0	4 (0.9)	0	0	1 (2.0)	0
Disseminated Intravascular Coagulation	0	1 (0.2)	1 (1.6)	0	4 (0.9)	0	0	0	0
Febrile Neutropenia	0	39 (7.4)	10 (15.9)	3 (18.8)	28 (6.1)	9 (14.3)	0	6 (12.2)	1 (11.1)
Granulocytopenia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Haemolysis	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Haemolytic Uraemic Syndrome	0	5 (0.9)	0	0	1 (0.2)	0	0	0	0
Haemorrhagic Diathesis	0	0	0	0	2 (0.4)	0	0	0	0
Leukocytosis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Leukopenia	1 (8.3)	18 (3.4)	0	0	18 (3.9)	2 (3.2)	0	4 (8.2)	1 (11 1)
Lymphadenitis	0	0	0	0	0	1 (1.6)	0	0	0
Lymphadenopathy	0	1 (0.2)	0	0	2 (0.4)	0	0	1 (2.0)	0
Lymphopenia	0	0	0	0	1 (0.2)	0	0	0	0
Microangiopathic Haemolytic Anaemia	0	0	0	0	1 (0.2)	0	0	0	0
Neutropenia	2 (16.7)	80 (15.1)	13 (20.6)	2 (12.5)	69 (15.0)	8 (12.7)	0	15 (30.6)	4 (44.4)
Pancytopenia	0	7 (1.3)	2 (3.2)	0	12 (2.6)	1 (1.6)	0	1 (2.0)	0
Splenomegaly	0	0	0	0	1 (0.2)	0	0	0	0

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All Randomized Subjects
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Thrombocytopenia	2 (16.7)	118 (22.3)	23 (36.5)	2 (12.5)	97 (21.1)	18 (28.6)	0	12 (24.5)	4 (44.4)
Thrombocytosis	0	0	0	0	1 (0.2)	0	0	0	0
Thrombotic Microangiopathy	0	0	0	0	1 (0.2)	0	0	0	0
Thrombotic Thrombocytopenic Purpura	0	8 (1.5)	0	0	2 (0.4)	0	0	0	0
Cardiac Disorders	**0**	**40 (7.5)**	**6 (9.5)**	**0**	**34 (7.4)**	**6 (9.5)**	**0**	**5 (10.2)**	**0**
Acute Myocardial Infarction	0	1 (0.2)	0	0	0	0	0	0	0
Angina Pectoris	0	1 (0.2)	0	0	0	0	0	0	0
Arrhythmia	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Arrhythmia Supraventricular	0	0	0	0	0	1 (1.6)	0	0	0
Atrial Fibrillation	0	6 (1.1)	2 (3.2)	0	5 (1.1)	3 (4.8)	0	2 (4.1)	0
Atrial Flutter	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Atrioventricular Block	0	0	0	0	1 (0.2)	0	0	0	0
Atrioventricular Block Complete	0	1 (0.2)	0	0	0	0	0	0	0
Bradycardia	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Bundle Branch Block Left	0	0	0	0	1 (0.2)	0	0	0	0
Bundle Branch Block Right	0	0	0	0	1 (0.2)	0	0	0	0
Cardiac Arrest	0	6 (1.1)	1 (1.6)	0	6 (1.3)	0	0	1 (2.0)	0
Cardiac Failure	0	2 (0.4)	1 (1.6)	0	3 (0.7)	0	0	0	0
Cardiac Failure Congestive	0	1 (0.2)	1 (1.6)	0	2 (0.4)	2 (3.2)	0	0	0
Cardio-Respiratory Arrest	0	2 (0.4)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0
Cardiomegaly	0	1 (0.2)	0	0	0	0	0	0	0
Cardiomyopathy	0	0	0	0	0	0	0	1 (2.0)	0

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Cardiopulmonary Failure	0	1 (0.2)	0	0	0	0	0	0	0
Cardiotoxicity	0	0	0	0	0	1 (1.6)	0	0	0
Cardiovascular Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Cardiovascular Insufficiency	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Congestive Cardiomyopathy	0	1 (0.2)	0	0	0	0	0	0	0
Endocarditis Noninfective	0	0	0	0	1 (0.2)	0	0	0	0
Intracardiac Mass	0	0	0	0	1 (0.2)	0	0	0	0
Left Atrial Dilatation	0	1 (0.2)	0	0	0	0	0	0	0
Left Ventricular Dysfunction	0	1 (0.2)	0	0	0	0	0	0	0
Left Ventricular Hypertrophy	0	1 (0.2)	0	0	0	0	0	0	0
Mitral Valve Incompetence	0	1 (0.2)	0	0	0	0	0	0	0
Myocardial Infarction	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Myocardial Ischaemia	0	1 (0.2)	0	0	0	0	0	0	0
Myocarditis	0	1 (0.2)	0	0	0	0	0	0	0
Palpitations	0	1 (0.2)	0	0	0	0	0	0	0
Pericardial Effusion	0	0	0	0	2 (0.4)	1 (1.6)	0	0	0
Pericarditis	0	1 (0.2)	0	0	0	0	0	0	0
Sinus Tachycardia	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Subendocardial Ischaemia	0	0	0	0	1 (0.2)	0	0	0	0
Supraventricular Tachycardia	0	3 (0.6)	0	0	2 (0.4)	0	0	1 (2.0)	0
Tachycardia	0	4 (0.8)	2 (3.2)	0	4 (0.9)	0	0	3 (6.1)	0
Torsade De Pointes	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Ventricular Extrasystoles	0	2 (0.4)	0	0	0	0	0	0	0

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Ear And Labyrinth Disorders	**0**	**3 (0.6)**	**0**	**0**	**2 (0.4)**	**0**	**0**	**0**	**0**
Deafness	0	0	0	0	1 (0.2)	0	0	0	0
Ear Discomfort	0	0	0	0	1 (0.2)	0	0	0	0
Hypoacusis	0	2 (0.4)	0	0	0	0	0	0	0
Vertigo	0	1 (0.2)	0	0	0	0	0	0	0
Endocrine Disorders	**0**	**1 (0.2)**	**0**	**0**	**0**	**0**	**0**	**1 (2.0)**	**0**
Adrenal Insufficiency	0	0	0	0	0	0	0	1 (2.0)	0
Cushing's Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Eye Disorders	**0**	**4 (0.8)**	**0**	**0**	**13 (2.8)**	**1 (1.6)**	**0**	**0**	**0**
Choroiditis	0	0	0	0	1 (0.2)	0	0	0	0
Conjunctival Haemorrhage	0	0	0	0	2 (0.4)	0	0	0	0
Corneal Degeneration	0	0	0	0	1 (0.2)	0	0	0	0
Diplopia	0	0	0	0	1 (0.2)	0	0	0	0
Dry Eye	0	0	0	0	1 (0.2)	0	0	0	0
Eye Haemorrhage	0	0	0	0	0	1 (1.6)	0	0	0
Eye Oedema	0	0	0	0	1 (0.2)	0	0	0	0
Eye Pain	0	0	0	0	1 (0.2)	0	0	0	0
Eye Pruritus	0	1 (0.2)	0	0	0	0	0	0	0
Glaucoma	0	1 (0.2)	0	0	0	0	0	0	0
Mydriasis	0	0	0	0	2 (0.4)	0	0	0	0

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Photophobia	0	0	0	0	1 (0.2)	0	0	0	0
Pupils Unequal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Scleral Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Vision Blurred	0	1 (0.2)	0	0	0	0	0	0	0
Visual Acuity Reduced	0	0	0	0	1 (0.2)	0	0	0	0
Visual Impairment	0	1 (0.2)	0	0	0	0	0	0	0
Gastrointestinal Disorders	**1 (8.3)**	**98 (18.5)**	**12 (19.0)**	**1 (6.3)**	**91 (19.8)**	**10 (15.9)**	**0**	**11 (22.4)**	**1 (11.1)**
Abdominal Compartment Syndrome	0	0	0	0	1 (0.2)	0	0	0	0
Abdominal Discomfort	0	0	0	0	0	1 (1.6)	0	0	0
Abdominal Distension	0	3 (0.6)	0	0	3 (0.7)	1 (1.6)	0	0	0
Abdominal Pain	0	16 (3.0)	0	0	17 (3.7)	0	0	0	0
Abdominal Pain Lower	0	1 (0.2)	0	0	0	0	0	0	0
Abdominal Pain Upper	0	4 (0.8)	1 (1.6)	0	5 (1.1)	0	0	0	0
Abdominal Rigidity	0	0	0	0	1 (0.2)	0	0	0	0
Abdominal Tenderness	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Acute Abdomen	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Anal Fissure	1 (8.3)	1 (0.2)	0	0	0	0	0	0	0
Anal Fistula	0	0	0	0	0	0	0	1 (2.0)	0
Anal Incontinence	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	0	0
Anal Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Anorectal Discomfort	0	0	1 (1.6)	0	0	0	0	0	0
Ascites	0	4 (0.8)	1 (1.6)	0	5 (1.1)	1 (1.6)	0	0	0

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Change Of Bowel Habit	0	1 (0.2)	0	0	0	0	0	0	0
Colitis	0	2 (0.4)	0	1 (6.3)	3 (0.7)	1 (1.6)	0	0	1 (11 1)
Colitis Ulcerative	0	1 (0.2)	0	0	0	0	0	0	0
Constipation	0	1 (0.2)	0	0	2 (0.4)	0	0	1 (2.0)	0
Crohn's Disease	0	1 (0.2)	0	0	0	0	0	0	0
Diarrhoea	0	19 (3.6)	3 (4.8)	0	24 (5.2)	0	0	3 (6.1)	0
Diarrhoea Haemorrhagic	0	3 (0.6)	0	0	3 (0.7)	2 (3.2)	0	0	0
Dry Mouth	0	1 (0.2)	0	0	0	0	0	0	0
Duodenal Perforation	0	1 (0.2)	0	0	0	0	0	0	0
Duodenitis Haemorrhagic	0	0	0	0	1 (0.2)	0	0	0	0
Dyspepsia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Dysphagia	0	1 (0.2)	1 (1.6)	0	6 (1.3)	0	0	0	0
Enteritis	0	1 (0.2)	0	0	0	0	0	0	0
Erosive Oesophagitis	0	1 (0.2)	0	0	0	0	0	0	0
Gastric Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Gastric Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Gastric Ulcer	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gastric Ulcer Haemorrhage	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Gastritis	0	0	0	0	3 (0.7)	0	0	0	0
Gastritis Erosive	0	1 (0.2)	0	0	0	0	0	0	0
Gastritis Haemorrhagic	0	1 (0.2)	0	0	0	0	0	0	0
Gastrointestinal Haemorrhage	0	12 (2.3)	1 (1.6)	0	13 (2.8)	1 (1.6)	0	0	0
Gastrointestinal Pain	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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Gastrointestinal Sounds Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Gastrointestinal Ulcer Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Gastrooesophageal Reflux Disease	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Gingival Bleeding	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Glossitis	0	0	0	0	1 (0.2)	0	0	0	0
Haematemesis	0	4 (0.8)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Haematochezia	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Haemorrhoidal Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Haemorrhoids	0	4 (0.8)	0	0	0	0	0	1 (2.0)	0
Ileus	0	3 (0.6)	0	0	5 (1.1)	0	0	0	0
Ileus Paralytic	0	0	0	0	2 (0.4)	0	0	0	0
Inguinal Hernia	0	0	0	0	0	1 (1.6)	0	0	0
Intestinal Haemorrhage	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0
Intestinal Infarction	0	1 (0.2)	0	0	0	0	0	0	0
Intestinal Ischaemia	0	1 (0.2)	0	0	0	0	0	0	0
Intestinal Mass	0	0	0	0	1 (0.2)	0	0	0	0
Intestinal Obstruction	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Intestinal Ulcer	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Intra-Abdominal Fluid Collection	0	0	0	0	1 (0.2)	0	0	0	0
Malabsorption	0	0	1 (1.6)	0	0	0	0	0	0
Melaena	0	4 (0.8)	0	0	2 (0.4)	0	0	1 (2.0)	0
Mouth Haemorrhage	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Nausea	0	25 (4.7)	1 (1.6)	0	10 (2.2)	0	0	3 (6.1)	0

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Neutropenic Colitis	0	4 (0.8)	0	0	1 (0.2)	0	0	0	1 (11 1)
Odynophagia	0	0	0	0	1 (0.2)	0	0	0	0
Oesophageal Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Oesophagitis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Oral Mucosal Blistering	0	0	0	0	0	0	0	1 (2.0)	0
Oral Pain	0	2 (0.4)	0	0	2 (0.4)	0	0	1 (2.0)	0
Pancreatitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pancreatitis Acute	0	1 (0.2)	0	0	0	0	0	0	0
Proctalgia	0	0	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Rectal Haemorrhage	0	2 (0.4)	1 (1.6)	0	1 (0.2)	0	0	0	0
Rectal Tenesmus	0	1 (0.2)	0	0	0	0	0	0	0
Small Intestinal Obstruction	0	1 (0.2)	0	0	0	0	0	0	0
Stomatitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Subileus	0	1 (0.2)	0	0	0	0	0	0	0
Swollen Tongue	0	0	0	0	1 (0.2)	0	0	0	0
Upper Gastrointestinal Haemorrhage	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Vomiting	0	14 (2.6)	2 (3.2)	0	14 (3.0)	0	0	0	0
General Disorders And Administration Site Conditions	**2 (16.7)**	**104 (19.6)**	**15 (23.8)**	**3 (18.8)**	**89 (19.3)**	**12 (19.0)**	**0**	**12 (24.5)**	**3 (33 3)**
Adverse Drug Reaction	0	0	1 (1.6)	0	0	0	0	0	0
Asthenia	0	10 (1.9)	2 (3.2)	0	11 (2.4)	1 (1.6)	0	0	1 (11 1)
Catheter Site Bruise	0	0	0	0	1 (0.2)	0	0	0	0

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Catheter Site Erythema	0	0	0	0	0	0	0	1 (2.0)	0
Catheter Site Haematoma	0	1 (0.2)	0	0	0	0	0	0	0
Catheter Site Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Catheter Site Inflammation	0	0	0	0	0	0	0	0	1 (11.1)
Chest Pain	0	4 (0.8)	2 (3.2)	0	6 (1.3)	0	0	0	0
Chills	0	7 (1.3)	1 (1.6)	0	2 (0.4)	0	0	2 (4.1)	0
Death	0	0	0	0	1 (0.2)	0	0	0	0
Disease Progression	0	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	0	0
Drug Interaction	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Drug Intolerance	0	0	0	0	2 (0.4)	0	0	0	0
Fatigue	0	12 (2.3)	4 (6.3)	0	7 (1.5)	1 (1.6)	0	0	0
Gait Disturbance	0	0	0	0	2 (0.4)	0	0	0	0
General Physical Health Deterioration	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Generalised Oedema	0	1 (0.2)	1 (1.6)	0	4 (0.9)	0	0	0	0
Hyperpyrexia	0	0	0	0	0	0	0	0	1 (11 1)
Hyperthermia	0	0	1 (1.6)	0	1 (0.2)	0	0	0	0
Hypothermia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Malaise	0	0	0	0	1 (0.2)	0	0	0	0
Mucosal Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Mucosal Inflammation	1 (8.3)	13 (2.5)	3 (4.8)	3 (18.8)	10 (2.2)	1 (1.6)	0	1 (2.0)	0
Multi-Organ Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	0	14 (2.6)	1 (1.6)	0	8 (1.7)	1 (1.6)	0	2 (4.1)	0
Necrosis	0	1 (0.2)	0	0	0	0	0	0	0

Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Nodule	0	0	0	0	1 (0.2)	0	0	0	0
Oedema	0	1 (0.2)	0	0	3 (0.7)	2 (3.2)	0	0	0
Oedema Peripheral	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Pain	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Performance Status Decreased	0	0	2 (3.2)	0	0	0	0	0	0
Peripheral Swelling	0	2 (0.4)	0	0	0	0	0	0	0
Pyrexia	1 (8.3)	42 (7.9)	2 (3.2)	2 (12.5)	44 (9.6)	6 (9.5)	0	10 (20.4)	0
Sudden Death	0	0	0	0	0	1 (1.6)	0	0	0
Therapy Non-Responder	0	2 (0.4)	2 (3.2)	0	2 (0.4)	0	0	0	0
Thirst	0	0	0	0	1 (0.2)	0	0	0	0
Hepatobiliary Disorders	**0**	**31 (5.8)**	**6 (9.5)**	**0**	**24 (5.2)**	**4 (6.3)**	**0**	**5 (10.2)**	**0**
Acute Hepatic Failure	0	1 (0.2)	0	0	0	0	0	0	0
Cholecystitis	0	0	0	0	1 (0.2)	0	0	0	0
Cholecystitis Acute	0	0	0	0	0	0	0	1 (2.0)	0
Cholelithiasis	0	1 (0.2)	0	0	0	0	0	0	0
Cholestasis	0	2 (0.4)	0	0	0	0	0	0	0
Drug-Induced Liver Injury	0	0	0	0	1 (0.2)	0	0	0	0
Hepatic Failure	0	6 (1.1)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Hepatic Function Abnormal	0	2 (0.4)	0	0	2 (0.4)	1 (1.6)	0	0	0
Hepatic Necrosis	0	1 (0.2)	0	0	0	0	0	0	0
Hepatitis	0	0	0	0	2 (0.4)	0	0	0	0
Hepatitis Acute	0	1 (0.2)	0	0	0	0	0	0	0

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Age Group
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Hepatocellular Injury	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Hepatotoxicity	0	3 (0.6)	0	0	0	0	0	0	0
Hyperbilirubinaemia	0	12 (2.3)	4 (6.3)	0	11 (2.4)	2 (3.2)	0	4 (8.2)	0
Hypertransaminasaemia	0	1 (0.2)	0	0	0	0	0	0	0
Jaundice	0	6 (1.1)	0	0	3 (0.7)	2 (3.2)	0	0	0
Liver Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Liver Injury	0	1 (0.2)	0	0	0	0	0	0	0
Ocular Icterus	0	1 (0.2)	0	0	0	0	0	0	0
Immune System Disorders	**0**	**49 (9.2)**	**1 (1.6)**	**1 (6.3)**	**52 (11.3)**	**0**	**0**	**2 (4.1)**	**0**
Acute Graft Versus Host Disease In Liver	0	0	0	0	1 (0.2)	0	0	0	0
Anaphylactic Reaction	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Chronic Graft Versus Host Disease	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Drug Hypersensitivity	0	0	1 (1.6)	0	1 (0.2)	0	0	2 (4.1)	0
Graft Versus Host Disease	0	31 (5.8)	0	1 (6.3)	27 (5.9)	0	0	0	0
Graft Versus Host Disease In Gastrointestinal Tract	0	15 (2.8)	0	0	12 (2.6)	0	0	0	0
Graft Versus Host Disease In Liver	0	10 (1.9)	0	0	5 (1.1)	0	0	0	0
Graft Versus Host Disease In Lung	0	0	0	0	3 (0.7)	0	0	0	0
Graft Versus Host Disease In Skin	0	9 (1.7)	0	0	6 (1.3)	0	0	0	0
Hypogammaglobulinaemia	0	1 (0.2)	0	0	0	0	0	0	0
Immune System Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Transplant Rejection	0	2 (0.4)	0	0	0	0	0	0	0

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Infections And Infestations	**3 (25.0)**	**166 (31.3)**	**22 (34.9)**	**6 (37.5)**	**138 (30.0)**	**22 (34.9)**	**0**	**20 (40.8)**	**4 (44.4)**
Abscess Fungal	0	0	0	0	1 (0.2)	0	0	0	0
Abscess Limb	0	0	0	0	1 (0.2)	0	0	0	0
Acid Fast Bacilli Infection	0	1 (0.2)	0	0	0	0	0	0	0
Acinetobacter Infection	0	0	0	1 (6.3)	0	0	0	0	0
Acute Sinusitis	0	1 (0.2)	0	0	0	0	0	0	0
Anal Abscess	0	0	1 (1.6)	0	0	0	0	0	0
Anorectal Infection	0	1 (0.2)	0	0	0	0	0	0	0
Aspergilloma	0	0	0	0	1 (0.2)	0	0	0	0
Aspergillus Infection	0	2 (0.4)	1 (1.6)	0	7 (1.5)	3 (4.8)	0	1 (2.0)	0
Atypical Pneumonia	0	1 (0.2)	0	0	0	0	0	0	0
Bacteraemia	0	30 (5.7)	6 (9.5)	0	14 (3.0)	5 (7.9)	0	6 (12.2)	0
Bacterial Infection	0	5 (0.9)	0	0	1 (0.2)	2 (3.2)	0	1 (2.0)	0
Bacterial Sepsis	0	4 (0.8)	0	0	3 (0.7)	0	0	0	0
Bk Virus Infection	0	0	1 (1.6)	0	0	0	0	0	0
Bronchitis	0	2 (0.4)	0	1 (6.3)	2 (0.4)	0	0	0	0
Bronchopulmonary Aspergillosis	0	3 (0.6)	0	0	8 (1.7)	1 (1.6)	0	2 (4.1)	0
Candida Infection	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Candida Sepsis	0	0	1 (1.6)	0	0	0	0	0	0
Catheter Site Cellulitis	0	0	0	0	1 (0.2)	0	0	0	0
Catheter Site Infection	0	0	1 (1.6)	0	3 (0.7)	0	0	0	0
Cavernous Sinus Thrombosis	0	0	0	0	1 (0.2)	0	0	0	0

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Cellulitis	0	4 (0.8)	0	0	3 (0.7)	1 (1.6)	0	0	0
Cerebral Toxoplasmosis	0	0	0	0	2 (0.4)	0	0	0	0
Chronic Sinusitis	0	1 (0.2)	0	0	0	0	0	0	0
Clostridial Infection	0	2 (0.4)	0	0	0	0	0	0	0
Clostridium Bacteraemia	0	0	0	0	0	1 (1.6)	0	0	0
Clostridium Difficile Colitis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Clostridium Difficile Infection	0	1 (0.2)	0	0	0	0	0	0	0
Conjunctivitis	0	1 (0.2)	0	1 (6.3)	0	0	0	0	0
Corynebacterium Infection	0	0	0	0	1 (0.2)	0	0	0	0
Corynebacterium Sepsis	0	1 (0.2)	0	0	0	0	0	0	0
Cystitis	0	2 (0.4)	0	0	0	0	0	0	0
Cystitis Klebsiella	0	0	1 (1.6)	0	0	0	0	0	0
Cytomegalovirus Colitis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Gastritis	0	0	0	0	1 (0.2)	0	0	0	0
Cytomegalovirus Gastroenteritis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Infection	0	11 (2.1)	0	0	10 (2.2)	1 (1.6)	0	0	0
Cytomegalovirus Viraemia	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Device Related Infection	0	9 (1.7)	2 (3.2)	0	9 (2.0)	1 (1.6)	0	2 (4.1)	0
Device Related Sepsis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	1 (11 1)
Ear Infection	0	0	1 (1.6)	0	0	0	0	0	0
Emphysematous Cystitis	0	1 (0.2)	0	0	0	0	0	0	0
Encephalitis	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Encephalitis Viral	0	0	0	0	1 (0.2)	0	0	0	0

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Enterobacter Bacteraemia	0	1 (0.2)	0	0	0	0	0	0	0
Enterobacter Infection	0	0	1 (1.6)	0	0	0	0	0	0
Enterobacter Sepsis	0	1 (0.2)	0	0	0	0	0	0	0
Enterococcal Bacteraemia	0	2 (0.4)	0	0	0	0	0	2 (4.1)	1 (11 1)
Enterococcal Infection	0	1 (0.2)	0	0	3 (0.7)	1 (1.6)	0	0	0
Enterococcal Sepsis	0	0	0	0	1 (0.2)	0	0	0	0
Epstein-Barr Virus Infection	0	0	0	0	4 (0.9)	0	0	0	0
Erysipelas	0	0	0	0	1 (0.2)	0	0	0	1 (11 1)
Escherichia Bacteraemia	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Escherichia Infection	0	0	0	0	0	1 (1.6)	0	0	0
Escherichia Sepsis	0	1 (0.2)	0	1 (6.3)	1 (0.2)	0	0	0	0
Escherichia Urinary Tract Infection	0	0	0	0	0	1 (1.6)	0	0	0
Fungaemia	0	0	0	0	0	1 (1.6)	0	0	0
Fungal Infection	0	3 (0.6)	1 (1.6)	0	5 (1.1)	0	0	0	0
Fungal Rhinitis	0	0	0	0	1 (0.2)	0	0	0	0
Fungal Sepsis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Fusobacterium Infection	0	0	0	0	1 (0.2)	0	0	0	0
Gangrene	0	0	0	0	1 (0.2)	0	0	0	0
Gastroenteritis	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Gastroenteritis Rotavirus	0	0	0	0	1 (0.2)	0	0	0	0
Gastrointestinal Infection	0	1 (0.2)	0	0	0	0	0	0	0
Herpes Dermatitis	0	0	0	0	1 (0.2)	0	0	0	0
Herpes Pharyngitis	0	0	0	0	1 (0.2)	0	0	0	0

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Herpes Simplex	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Herpes Virus Infection	0	0	0	0	0	1 (1.6)	0	0	0
Herpes Zoster	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Human Herpesvirus 6 Infection	0	0	0	0	1 (0.2)	0	0	0	0
Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Influenza	0	0	0	0	1 (0.2)	0	0	0	0
Infusion Site Infection	0	0	0	0	1 (0.2)	0	0	0	0
Klebsiella Bacteraemia	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	1 (2.0)	0
Klebsiella Infection	0	0	0	0	2 (0.4)	0	0	0	0
Klebsiella Sepsis	0	1 (0.2)	0	0	0	0	0	0	0
Leptotrichia Infection	0	0	0	0	1 (0.2)	0	0	0	0
Liver Abscess	0	0	0	0	1 (0.2)	0	0	0	0
Localised Infection	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Lower Respiratory Tract Infection	0	2 (0.4)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0
Lung Abscess	0	1 (0.2)	0	0	0	0	0	0	0
Mastoiditis	0	1 (0.2)	0	0	0	0	0	0	0
Meningitis Listeria	0	0	0	0	1 (0.2)	0	0	0	0
Meningococcal Infection	0	0	0	0	1 (0.2)	0	0	0	0
Micrococcus Infection	0	1 (0.2)	0	0	0	0	0	0	0
Mycobacterial Infection	0	0	0	0	1 (0.2)	0	0	0	0
Mycobacterium Avium Complex Infection	0	0	0	0	0	1 (1.6)	0	0	0
Neutropenic Sepsis	1 (8.3)	1 (0.2)	0	0	1 (0.2)	0	0	2 (4.1)	1 (11.1)
Nocardiosis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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Oesophageal Candidiasis	0	0	0	0	2 (0.4)	0	0	0	0
Oral Candidiasis	0	0	0	0	0	0	0	1 (2.0)	0
Oral Herpes	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Oropharyngeal Candidiasis	0	0	0	0	0	0	0	1 (2.0)	0
Peritonitis	0	0	0	0	1 (0.2)	0	0	0	0
Peritonitis Bacterial	0	0	0	0	1 (0.2)	0	0	0	0
Pharyngitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pneumocystis Jirovecii Pneumonia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pneumonia	0	24 (4.5)	2 (3.2)	1 (6.3)	20 (4.3)	3 (4.8)	0	3 (6.1)	0
Pneumonia Bacterial	0	3 (0.6)	0	0	0	0	0	0	0
Pneumonia Cytomegaloviral	0	3 (0.6)	0	0	0	0	0	0	0
Pneumonia Fungal	0	3 (0.6)	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	1 (11 1)
Pneumonia Klebsiella	0	2 (0.4)	0	0	4 (0.9)	0	0	0	0
Pneumonia Necrotising	0	0	0	0	1 (0.2)	0	0	0	0
Pneumonia Pseudomonal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Pneumonia Staphylococcal	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Pneumonia Streptococcal	0	0	0	0	1 (0.2)	0	0	0	0
Pneumonia Viral	0	1 (0.2)	0	0	0	0	0	0	0
Pseudomembranous Colitis	0	2 (0.4)	0	0	0	0	0	0	0
Pseudomonal Bacteraemia	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Pseudomonal Sepsis	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Pseudomonas Infection	0	1 (0.2)	1 (1.6)	0	2 (0.4)	2 (3.2)	0	0	0
Pulmonary Mycosis	0	2 (0.4)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	0	0

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Relapsing Fever	0	0	0	0	1 (0.2)	0	0	0	0
Respiratory Syncytial Virus Infection	0	0	0	0	1 (0.2)	0	0	0	0
Rhinovirus Infection	0	0	0	0	0	0	0	1 (2.0)	0
Scedosporium Infection	0	0	0	0	1 (0.2)	0	0	0	0
Sepsis	0	12 (2.3)	2 (3.2)	1 (6.3)	14 (3.0)	0	0	2 (4.1)	1 (11 1)
Sepsis Syndrome	0	0	1 (1.6)	0	0	0	0	0	0
Septic Embolus	0	1 (0.2)	0	0	0	0	0	0	0
Septic Shock	0	14 (2.6)	2 (3.2)	2 (12.5)	11 (2.4)	1 (1.6)	0	4 (8.2)	2 (22.2)
Sinusitis	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Sinusitis Bacterial	0	1 (0.2)	0	0	0	0	0	0	0
Sinusitis Fungal	0	0	0	0	0	0	0	0	1 (11.1)
Staphylococcal Bacteraemia	0	7 (1.3)	0	0	5 (1.1)	0	0	1 (2.0)	0
Staphylococcal Infection	0	2 (0.4)	0	0	0	1 (1.6)	0	0	0
Staphylococcal Sepsis	0	1 (0.2)	1 (1.6)	1 (6.3)	1 (0.2)	1 (1.6)	0	0	0
Streptococcal Bacteraemia	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Streptococcal Infection	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Streptococcal Sepsis	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Superinfection	0	1 (0.2)	0	0	0	0	0	0	0
Systemic Candida	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Systemic Mycosis	1 (8.3)	0	0	0	3 (0.7)	0	0	0	0
Tracheobronchitis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Upper Respiratory Tract Infection	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Urinary Tract Infection	1 (8.3)	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	0	0

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Urinary Tract Infection Pseudomonal	0	0	1 (1.6)	0	0	0	0	0	0
Urinary Tract Infection Viral	0	0	0	0	1 (0.2)	0	0	0	0
Varicella Zoster Pneumonia	0	1 (0.2)	0	0	0	0	0	0	0
Varicella Zoster Virus Infection	0	2 (0.4)	0	0	0	0	0	0	0
Viral Haemorrhagic Cystitis	0	1 (0.2)	0	0	0	0	0	0	0
Viral Infection	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Injury, Poisoning And Procedural Complications	**0**	**17 (3.2)**	**0**	**0**	**19 (4.1)**	**3 (4.8)**	**0**	**1 (2.0)**	**0**
Accidental Overdose	0	0	0	0	1 (0.2)	0	0	0	0
Back Injury	0	1 (0.2)	0	0	0	0	0	0	0
Brain Herniation	0	0	0	0	0	0	0	1 (2.0)	0
Complications Of Transplant Surgery	0	1 (0.2)	0	0	0	0	0	0	0
Compression Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Contusion	0	0	0	0	1 (0.2)	0	0	0	0
Fall	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Femoral Neck Fracture	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Head Injury	0	0	0	0	1 (0.2)	0	0	0	0
Hip Fracture	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Lumbar Vertebral Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Overdose	0	0	0	0	1 (0.2)	0	0	0	0
Post Procedural Haemorrhage	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Postoperative Fever	0	0	0	0	1 (0.2)	0	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Age Group
Number (%) of Subjects

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	13-<18 yr n = 12	18-<65 yr n = 530	>=65 yr n = 63	13-<18 yr n = 16	18-<65 yr n = 460	>=65 yr n = 63	13-<18 yr n = 0	18-<65 yr n = 49	>=65 yr n = 9
Sedation Complication	0	1 (0.2)	0	0	0	0	0	0	0
Spinal Fracture	0	1 (0.2)	0	0	0	0	0	0	0
Subarachnoid Haemorrhage	0	2 (0.4)	0	0	0	0	0	0	0
Subdural Haematoma	0	1 (0.2)	0	0	2 (0.4)	1 (1.6)	0	0	0
Toxicity To Various Agents	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Transfusion Reaction	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Transplant Failure	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Investigations	**1 (8.3)**	**89 (16.8)**	**9 (14.3)**	**2 (12.5)**	**82 (17.8)**	**5 (7.9)**	**0**	**4 (8.2)**	**1 (11 1)**
Activated Partial Thromboplastin Time Prolonged	0	0	0	0	1 (0.2)	0	0	0	0
Alanine Aminotransferase Abnormal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Alanine Aminotransferase Increased	1 (8.3)	10 (1.9)	1 (1.6)	0	13 (2.8)	1 (1.6)	0	0	1 (11 1)
Ammonia Increased	0	1 (0.2)	0	0	0	0	0	0	0
Aspartate Aminotransferase Increased	0	3 (0.6)	0	0	7 (1.5)	1 (1.6)	0	0	0
Bacterial Test Positive	0	3 (0.6)	1 (1.6)	0	6 (1.3)	0	0	0	0
Basophil Count Increased	0	1 (0.2)	0	0	0	0	0	0	0
Bilirubin Conjugated Increased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Blast Cells Present	0	1 (0.2)	0	0	0	0	0	0	0
Bleeding Time Prolonged	0	2 (0.4)	0	0	0	0	0	0	0
Blood Albumin Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Blood Alkaline Phosphatase Increased	0	4 (0.8)	1 (1.6)	0	0	0	0	0	0
Blood Bicarbonate Decreased	0	1 (0.2)	0	0	0	1 (1.6)	0	0	0

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Blood Bilirubin Increased	0	7 (1.3)	0	1 (6.3)	11 (2.4)	2 (3.2)	0	2 (4.1)	0
Blood Calcium Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Cholesterol Increased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Creatinine Increased	0	2 (0.4)	0	0	3 (0.7)	1 (1.6)	0	0	0
Blood Culture Positive	0	1 (0.2)	0	1 (6.3)	3 (0.7)	0	0	0	0
Blood Glucose Increased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Lactate Dehydrogenase	0	0	0	0	1 (0.2)	0	0	0	0
Blood Lactate Dehydrogenase Increased	0	2 (0.4)	0	0	8 (1.7)	0	0	0	0
Blood Magnesium Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Potassium Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Blood Pressure Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Blood Pressure Increased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Blood Urea Increased	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Blood Uric Acid Increased	0	2 (0.4)	0	0	0	0	0	0	0
Body Temperature	0	1 (0.2)	0	0	0	0	0	0	0
Breath Sounds Abnormal	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Bronchoscopy	0	0	0	0	1 (0.2)	0	0	0	0
C-Reactive Protein Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
C-Reactive Protein Increased	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Central Venous Pressure Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Chest X-Ray Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Clostridium Test Positive	0	1 (0.2)	0	0	0	0	0	0	0
Coagulation Test Abnormal	0	0	0	0	1 (0.2)	0	0	0	0

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Computerised Tomogram Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Cytomegalovirus Test	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Cytomegalovirus Test Positive	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Drug Level Changed	0	1 (0.2)	0	0	0	0	0	0	0
Drug Level Increased	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Ejection Fraction Decreased	0	0	1 (1.6)	0	0	0	0	0	0
Electrocardiogram Abnormal	0	0	1 (1.6)	0	0	0	0	0	0
Electrocardiogram Qt Prolonged	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Electrocardiogram T Wave Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Electroencephalogram Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Gamma-Glutamyltransferase Increased	1 (8.3)	16 (3.0)	3 (4.8)	0	22 (4.8)	0	0	0	0
Haematocrit Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Haemoglobin Decreased	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	1 (2.0)	0
Heart Sounds Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Hepatic Enzyme Abnormal	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hepatic Enzyme Increased	1 (8.3)	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Liver Function Test Abnormal	0	0	1 (1.6)	0	2 (0.4)	0	0	0	0
Liver Function Test Increased	0	6 (1.1)	0	0	6 (1.3)	0	0	0	0
Lymphocyte Count Decreased	0	0	0	0	1 (0.2)	0	0	0	0
Lymphocyte Count Increased	0	0	0	0	1 (0.2)	0	0	0	0
Neutrophil Count Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Neutrophil Count Decreased	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0

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Nutritional Condition Abnormal	0	0	0	0	1 (0.2)	0	0	0	0
Occult Blood Positive	0	1 (0.2)	0	0	0	0	0	0	0
Oxygen Saturation Decreased	0	4 (0.8)	1 (1.6)	0	2 (0.4)	0	0	0	0
Platelet Count Decreased	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0
Protein Total Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Prothrombin Time Prolonged	0	0	0	0	1 (0.2)	0	0	0	0
Pulse Absent	0	0	0	0	1 (0.2)	0	0	0	0
Red Blood Cell Count Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Respiratory Rate Increased	0	1 (0.2)	0	0	0	0	0	0	0
Salmonella Test Positive	0	1 (0.2)	0	0	0	0	0	0	0
Serum Ferritin Increased	0	1 (0.2)	0	0	0	0	0	0	0
Transaminases Increased	0	9 (1.7)	0	0	4 (0.9)	1 (1.6)	0	0	0
Troponin I Increased	0	0	0	0	1 (0.2)	0	0	0	0
Troponin Increased	0	0	1 (1.6)	0	0	0	0	0	0
Urine Output Decreased	0	1 (0.2)	0	0	0	0	0	0	0
Weight Decreased	0	7 (1.3)	0	0	4 (0.9)	1 (1.6)	0	0	0
Weight Increased	0	0	0	0	1 (0.2)	0	0	0	0
White Blood Cell Count Abnormal	0	1 (0.2)	0	0	0	0	0	0	0
Metabolism And Nutrition Disorders	**0**	**80 (15.1)**	**12 (19.0)**	**1 (6.3)**	**62 (13.5)**	**6 (9.5)**	**0**	**9 (18.4)**	**1 (11 1)**
Acidosis	0	6 (1.1)	0	0	1 (0.2)	0	0	2 (4.1)	0
Cachexia	0	1 (0.2)	0	0	0	0	0	0	0
Decreased Appetite	0	7 (1.3)	0	0	10 (2.2)	1 (1.6)	0	0	0

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Dehydration	0	6 (1.1)	1 (1.6)	0	3 (0.7)	1 (1.6)	0	0	0
Diabetes Mellitus	0	4 (0.8)	0	0	2 (0.4)	0	0	0	0
Electrolyte Depletion	0	1 (0.2)	0	0	0	0	0	0	0
Electrolyte Imbalance	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Failure To Thrive	0	1 (0.2)	0	0	0	0	0	0	0
Feeding Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Fluid Overload	0	0	0	0	3 (0.7)	2 (3.2)	0	1 (2.0)	0
Fluid Retention	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Gout	0	0	1 (1.6)	0	0	0	0	0	0
Hypercholesterolaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperglycaemia	0	17 (3.2)	0	0	16 (3.5)	1 (1.6)	0	0	0
Hyperinsulinaemic Hypoglycaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hyperkalaemia	0	3 (0.6)	1 (1.6)	0	5 (1.1)	0	0	0	0
Hypermagnesaemia	0	0	2 (3.2)	0	0	0	0	0	0
Hypernatraemia	0	1 (0.2)	0	0	0	0	0	1 (2.0)	0
Hyperphosphataemia	0	0	0	0	0	1 (1.6)	0	0	0
Hypertriglyceridaemia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Hyperuricaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hypoalbuminaemia	0	4 (0.8)	1 (1.6)	0	2 (0.4)	0	0	1 (2.0)	0
Hypocalcaemia	0	6 (1.1)	2 (3.2)	0	2 (0.4)	0	0	1 (2.0)	0
Hypoglycaemia	0	4 (0.8)	0	0	0	0	0	0	0
Hypokalaemia	0	23 (4.3)	4 (6.3)	1 (6.3)	14 (3.0)	3 (4.8)	0	5 (10.2)	0
Hypomagnesaemia	0	6 (1.1)	2 (3.2)	0	2 (0.4)	1 (1.6)	0	0	0

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Hyponatraemia	0	3 (0.6)	1 (1.6)	0	4 (0.9)	0	0	1 (2.0)	0
Hypophagia	0	1 (0.2)	2 (3.2)	0	0	0	0	0	0
Hypophosphataemia	0	3 (0.6)	4 (6.3)	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Hypoproteinaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hypovolaemia	0	0	0	0	2 (0.4)	0	0	0	0
Malnutrition	0	4 (0.8)	0	0	4 (0.9)	0	0	0	0
Metabolic Acidosis	0	5 (0.9)	0	0	4 (0.9)	0	0	1 (2.0)	1 (11 1)
Metabolic Alkalosis	0	0	0	0	1 (0.2)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders	**0**	**32 (6.0)**	**1 (1.6)**	**0**	**20 (4.3)**	**2 (3.2)**	**0**	**2 (4.1)**	**0**
Arthralgia	0	5 (0.9)	0	0	4 (0.9)	0	0	0	0
Back Pain	0	7 (1.3)	1 (1.6)	0	4 (0.9)	0	0	1 (2.0)	0
Bone Pain	0	6 (1.1)	0	0	2 (0.4)	0	0	0	0
Flank Pain	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Intervertebral Disc Degeneration	0	0	0	0	1 (0.2)	0	0	0	0
Intervertebral Disc Protrusion	0	0	0	0	1 (0.2)	0	0	0	0
Muscle Contracture	0	1 (0.2)	0	0	0	0	0	0	0
Muscle Spasms	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Muscular Weakness	0	5 (0.9)	0	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Musculoskeletal Pain	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Musculoskeletal Stiffness	0	0	0	0	1 (0.2)	0	0	0	0
Myalgia	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0

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Myopathy	0	8 (1.5)	0	0	1 (0.2)	0	0	0	0
Neck Pain	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Osteonecrosis	0	0	0	0	1 (0.2)	0	0	0	0
Pain In Extremity	0	3 (0.6)	0	0	2 (0.4)	0	0	1 (2.0)	0
Pathological Fracture	0	0	0	0	1 (0.2)	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**2 (16.7)**	**35 (6.6)**	**7 (11.1)**	**1 (6.3)**	**33 (7.2)**	**5 (7.9)**	**0**	**0**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	0	1 (6.3)	4 (0.9)	0	0	0	0
Acute Myeloid Leukaemia	2 (16.7)	6 (1.1)	5 (7.9)	0	6 (1.3)	3 (4.8)	0	0	0
Acute Myeloid Leukaemia Recurrent	0	11 (2.1)	1 (1.6)	0	6 (1.3)	0	0	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	0	0	1 (0.2)	0	0	0	0
B-Cell Lymphoma	0	0	0	0	1 (0.2)	0	0	0	0
Chronic Myeloid Leukaemia	0	1 (0.2)	0	0	0	0	0	0	0
Hodgkin's Disease	0	0	0	0	1 (0.2)	0	0	0	0
Hodgkin's Disease Recurrent	0	0	0	0	1 (0.2)	0	0	0	0
Leukaemia	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	0	0
Leukaemia Recurrent	0	4 (0.8)	1 (1.6)	0	3 (0.7)	0	0	0	0
Lymphoma	0	5 (0.9)	0	0	2 (0.4)	0	0	0	0
Meningioma	0	1 (0.2)	0	0	0	0	0	0	0
Metastases To Kidney	0	0	0	0	1 (0.2)	0	0	0	0
Metastases To Liver	0	0	0	0	1 (0.2)	0	0	0	0
Metastatic Neoplasm	0	1 (0.2)	0	0	0	0	0	0	0

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Myelodysplastic Syndrome	0	1 (0.2)	0	0	0	0	0	0	0
Neoplasm Malignant	0	1 (0.2)	0	0	2 (0.4)	1 (1.6)	0	0	0
Non-Hodgkin's Lymphoma	0	1 (0.2)	0	0	3 (0.7)	0	0	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	0	0	2 (0.4)	0	0	0	0
Plasma Cell Myeloma	0	0	0	0	1 (0.2)	0	0	0	0
Post Transplant Lymphoproliferative Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Renal Cancer	0	1 (0.2)	0	0	0	0	0	0	0
Squamous Cell Carcinoma	0	0	0	0	1 (0.2)	0	0	0	0
Tumour Pain	0	1 (0.2)	0	0	0	0	0	0	0
Uterine Leiomyoma	0	1 (0.2)	0	0	0	0	0	0	0
Nervous System Disorders	**2 (16.7)**	**57 (10.8)**	**5 (7.9)**	**0**	**52 (11.3)**	**3 (4.8)**	**0**	**3 (6.1)**	**1 (11 1)**
Amnesia	0	1 (0.2)	0	0	0	0	0	0	0
Ataxia	0	1 (0.2)	0	0	0	0	0	0	0
Balance Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Brain Compression	0	0	0	0	0	0	0	1 (2.0)	0
Brain Oedema	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Central Nervous System Lesion	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Cerebellar Haemorrhage	0	2 (0.4)	0	0	0	0	0	1 (2.0)	0
Cerebral Haemorrhage	0	4 (0.8)	1 (1.6)	0	4 (0.9)	1 (1.6)	0	0	0
Cerebral Hypoperfusion	0	0	0	0	1 (0.2)	0	0	0	0
Cerebral Infarction	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0

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