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
Cerebrovascular Accident	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Cognitive Disorder	0	2 (0.4)	0	0	0	0	0	0	0
Coma	0	3 (0.6)	0	0	5 (1.1)	0	0	0	0
Demyelination	0	1 (0.2)	0	0	0	0	0	0	0
Depressed Level Of Consciousness	0	2 (0.4)	1 (1.6)	0	2 (0.4)	0	0	0	0
Dizziness	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Encephalopathy	0	3 (0.6)	1 (1.6)	0	2 (0.4)	0	0	0	0
Facial Paresis	0	0	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	5 (1.1)	0	0	0	0
Haemorrhagic Stroke	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Headache	1 (8.3)	14 (2.6)	0	0	12 (2.6)	0	0	1 (2.0)	1 (11 1)
Hemiparesis	0	0	0	0	4 (0.9)	0	0	0	0
Hemiplegia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Hydrocephalus	0	0	0	0	0	0	0	1 (2.0)	0
Hypoglycaemic Coma	0	1 (0.2)	0	0	0	0	0	0	0
Hypokinesia	0	0	0	0	1 (0.2)	0	0	0	0
Hyporeflexia	0	1 (0.2)	0	0	0	0	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	0	0	0	1 (2.0)	0
Lethargy	0	3 (0.6)	0	0	0	0	0	1 (2.0)	0
Leukoencephalopathy	0	1 (0.2)	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

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All Randomized Subjects
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Meningism	0	1 (0.2)	0	0	0	0	0	0	0
Metabolic Encephalopathy	0	1 (0.2)	0	0	0	0	0	0	0
Migraine	0	1 (0.2)	0	0	0	0	0	0	0
Myoclonus	0	0	1 (1.6)	0	0	0	0	0	0
Nervous System Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Neuropathy Peripheral	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Neurotoxicity	0	0	0	0	1 (0.2)	0	0	0	0
Nystagmus	0	0	0	0	0	0	0	1 (2.0)	0
Paralysis	0	1 (0.2)	0	0	0	0	0	0	0
Paresis	0	0	0	0	1 (0.2)	0	0	0	0
Peroneal Nerve Palsy	0	1 (0.2)	0	0	0	0	0	0	0
Post Herpetic Neuralgia	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Psychomotor Hyperactivity	0	0	1 (1.6)	0	0	0	0	0	0
Seizure	0	7 (1.3)	2 (3.2)	0	5 (1.1)	0	0	0	0
Sensory Loss	0	1 (0.2)	0	0	0	0	0	0	0
Somnolence	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Stupor	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Syncope	0	9 (1.7)	0	0	1 (0.2)	1 (1.6)	0	1 (2.0)	0
Tonic Convulsion	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	0	0	0	2 (0.4)	0	0	0	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

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All Randomized Subjects
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Visual Field Defect	0	0	0	0	1 (0.2)	0	0	0	0
Product Issues	**0**	**0**	**0**	**1 (6.3)**	**0**	**0**	**0**	**0**	**0**
Device Breakage	0	0	0	1 (6.3)	0	0	0	0	0
Psychiatric Disorders	**0**	**19 (3.6)**	**5 (7.9)**	**0**	**18 (3.9)**	**2 (3.2)**	**0**	**1 (2.0)**	**0**
Abnormal Behaviour	0	0	0	0	1 (0.2)	0	0	0	0
Agitation	0	1 (0.2)	0	0	1 (0.2)	1 (1.6)	0	0	0
Anxiety	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Confusional State	0	4 (0.8)	2 (3.2)	0	3 (0.7)	1 (1.6)	0	1 (2.0)	0
Delirium	0	1 (0.2)	0	0	0	0	0	0	0
Depression	0	4 (0.8)	1 (1.6)	0	5 (1.1)	0	0	0	0
Depression Suicidal	0	0	0	0	1 (0.2)	0	0	0	0
Disorientation	0	0	0	0	0	1 (1.6)	0	0	0
Eating Disorder	0	0	0	0	1 (0.2)	0	0	0	0
Fear	0	0	0	0	1 (0.2)	0	0	0	0
Flat Affect	0	1 (0.2)	0	0	0	0	0	0	0
Hallucination	0	0	1 (1.6)	0	2 (0.4)	0	0	0	0
Hallucination, Visual	0	1 (0.2)	0	0	0	0	0	0	0
Hypomania	0	1 (0.2)	0	0	0	0	0	0	0
Insomnia	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Mental Status Changes	0	4 (0.8)	1 (1.6)	0	5 (1.1)	0	0	0	0
Mood Altered	0	0	0	0	1 (0.2)	0	0	0	0

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Stress	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Suicidal Ideation	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Renal And Urinary Disorders	**1 (8.3)**	**35 (6.6)**	**7 (11.1)**	**0**	**37 (8.0)**	**6 (9.5)**	**0**	**1 (2.0)**	**0**
Acute Kidney Injury	0	8 (1.5)	1 (1.6)	0	8 (1.7)	0	0	1 (2.0)	0
Anuria	0	3 (0.6)	0	0	0	0	0	0	0
Azotaemia	0	0	0	0	1 (0.2)	0	0	0	0
Bladder Spasm	0	2 (0.4)	0	0	0	0	0	0	0
Choluria	0	0	1 (1.6)	0	0	0	0	0	0
Cystitis Haemorrhagic	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Dysuria	0	2 (0.4)	0	0	3 (0.7)	0	0	0	0
Haematuria	0	8 (1.5)	0	0	6 (1.3)	1 (1.6)	0	0	0
Hydronephrosis	0	2 (0.4)	0	0	0	0	0	0	0
Obstructive Nephropathy	0	0	0	0	1 (0.2)	0	0	0	0
Oliguria	0	4 (0.8)	1 (1.6)	0	1 (0.2)	0	0	0	0
Polyuria	0	1 (0.2)	0	0	0	0	0	0	0
Renal Failure	1 (8.3)	13 (2.5)	3 (4.8)	0	18 (3.9)	4 (6.3)	0	0	0
Renal Haematoma	0	1 (0.2)	0	0	0	0	0	0	0
Renal Impairment	0	2 (0.4)	1 (1.6)	0	3 (0.7)	0	0	0	0
Renal Tubular Necrosis	0	0	0	0	1 (0.2)	1 (1.6)	0	0	0
Tubulointerstitial Nephritis	0	0	0	0	1 (0.2)	0	0	0	0
Urethral Discharge	0	0	0	0	1 (0.2)	0	0	0	0
Urinary Incontinence	0	0	1 (1.6)	0	1 (0.2)	1 (1.6)	0	0	0

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Urinary Retention	0	0	1 (1.6)	0	0	0	0	0	0
Reproductive System And Breast Disorders	**0**	**10 (1.9)**	**2 (3.2)**	**0**	**8 (1.7)**	**0**	**0**	**0**	**0**
Erectile Dysfunction	0	1 (0.2)	0	0	0	0	0	0	0
Menorrhagia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Menstrual Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Penile Pain	0	0	0	0	1 (0.2)	0	0	0	0
Prostatitis	0	1 (0.2)	0	0	0	0	0	0	0
Scrotal Oedema	0	1 (0.2)	0	0	0	0	0	0	0
Testicular Pain	0	0	0	0	1 (0.2)	0	0	0	0
Uterine Haemorrhage	0	0	0	0	1 (0.2)	0	0	0	0
Vaginal Haemorrhage	0	5 (0.9)	1 (1.6)	0	3 (0.7)	0	0	0	0
Vulval Oedema	0	0	1 (1.6)	0	0	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**1 (8.3)**	**90 (17.0)**	**10 (15.9)**	**2 (12.5)**	**95 (20.7)**	**11 (17.5)**	**0**	**13 (26.5)**	**1 (11.1)**
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	0	0	0	1 (0.2)	0	0	0	0
Atelectasis	0	2 (0.4)	0	0	2 (0.4)	0	0	0	0
Bronchial Hyperreactivity	0	0	0	0	1 (0.2)	0	0	0	0

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Bronchial Obstruction	0	0	0	1 (6.3)	1 (0.2)	0	0	0	0
Bronchopneumopathy	0	1 (0.2)	0	0	0	0	0	0	0
Bronchospasm	0	0	0	0	2 (0.4)	0	0	0	0
Chronic Obstructive Pulmonary Disease	0	0	0	0	1 (0.2)	0	0	0	0
Cough	0	3 (0.6)	0	0	3 (0.7)	0	0	0	0
Diffuse Alveolar Damage	0	0	0	0	1 (0.2)	0	0	0	0
Dyspnoea	0	25 (4.7)	6 (9.5)	0	23 (5.0)	6 (9.5)	0	4 (8.2)	0
Emphysema	0	1 (0.2)	0	0	0	0	0	0	0
Epiglottis Ulcer	0	1 (0.2)	0	0	0	0	0	0	0
Epistaxis	0	9 (1.7)	0	1 (6.3)	4 (0.9)	0	0	0	0
Haemoptysis	0	4 (0.8)	0	0	2 (0.4)	1 (1.6)	0	0	0
Haemothorax	0	0	0	0	2 (0.4)	0	0	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
Hypoxia	0	8 (1.5)	1 (1.6)	0	16 (3.5)	4 (6.3)	0	7 (14.3)	0
Interstitial Lung Disease	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Laryngeal Oedema	0	0	0	0	0	0	0	1 (2.0)	0
Lung Consolidation	0	0	0	0	1 (0.2)	0	0	1 (2.0)	0
Lung Disorder	0	1 (0.2)	1 (1.6)	0	1 (0.2)	0	0	0	0
Lung Infiltration	0	4 (0.8)	0	0	7 (1.5)	0	0	0	0
Nasal Congestion	0	1 (0.2)	0	0	0	0	0	0	0
Nasal Necrosis	0	0	0	0	1 (0.2)	0	0	0	0
Obliterative Bronchiolitis	0	0	0	0	1 (0.2)	0	0	0	0

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Organising Pneumonia	0	2 (0.4)	0	0	0	0	0	0	0
Oropharyngeal Pain	0	0	0	0	4 (0.9)	0	0	0	0
Pleural Effusion	0	6 (1.1)	0	0	6 (1.3)	0	0	0	0
Pleurisy	0	0	0	0	1 (0.2)	0	0	0	0
Pleuritic Pain	0	1 (0.2)	1 (1.6)	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	0	4 (0.8)	0	0	1 (0.2)	0	0	0	0
Pneumothorax	0	3 (0.6)	0	0	2 (0.4)	0	0	0	0
Productive Cough	0	1 (0.2)	0	0	4 (0.9)	0	0	0	0
Pulmonary Alveolar Haemorrhage	0	3 (0.6)	0	0	0	1 (1.6)	0	1 (2.0)	0
Pulmonary Congestion	0	0	1 (1.6)	0	0	0	0	0	0
Pulmonary Embolism	0	3 (0.6)	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	6 (1.1)	0	0	4 (0.9)	0	0	0	0
Pulmonary Haemosiderosis	0	0	0	0	1 (0.2)	0	0	0	0
Pulmonary Hypertension	0	2 (0.4)	0	0	0	0	0	0	0
Pulmonary Mass	0	3 (0.6)	0	0	4 (0.9)	0	0	0	0
Pulmonary Oedema	0	6 (1.1)	2 (3.2)	0	7 (1.5)	2 (3.2)	0	1 (2.0)	0
Rales	0	0	1 (1.6)	0	0	0	0	0	0
Respiratory Acidosis	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Respiratory Arrest	0	1 (0.2)	0	0	0	0	0	0	0
Respiratory Disorder	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (2.0)	0
Respiratory Distress	0	9 (1.7)	0	0	4 (0.9)	1 (1.6)	0	2 (4.1)	0

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Respiratory Failure	0	24 (4.5)	0	0	34 (7.4)	3 (4.8)	0	1 (2.0)	1 (11 1)
Respiratory Tract Haemorrhage	0	1 (0.2)	0	0	0	0	0	0	0
Restrictive Pulmonary Disease	0	1 (0.2)	0	0	0	0	0	0	0
Rhinalgia	0	0	0	0	1 (0.2)	0	0	0	0
Sinus Congestion	0	0	0	0	1 (0.2)	0	0	0	0
Sinus Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Tachypnoea	0	5 (0.9)	2 (3.2)	0	5 (1.1)	0	0	0	0
Tonsillar Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Wheezing	0	0	0	0	1 (0.2)	0	0	0	0
Skin And Subcutaneous Tissue Disorders	**0**	**21 (4.0)**	**5 (7.9)**	**1 (6.3)**	**14 (3.0)**	**2 (3.2)**	**0**	**3 (6.1)**	**0**
Alopecia	0	1 (0.2)	0	0	2 (0.4)	0	0	0	0
Alopecia Totalis	0	1 (0.2)	0	0	0	0	0	0	0
Blister	0	1 (0.2)	1 (1.6)	0	0	1 (1.6)	0	0	0
Cold Sweat	0	1 (0.2)	0	0	0	0	0	0	0
Decubitus Ulcer	0	0	0	0	1 (0.2)	0	0	0	0
Dry Skin	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Erythema	0	2 (0.4)	0	0	0	0	0	0	0
Exfoliative Rash	0	0	0	0	1 (0.2)	0	0	0	0
Hypersensitivity Vasculitis	0	1 (0.2)	0	0	0	0	0	0	0
Night Sweats	0	1 (0.2)	1 (1.6)	0	0	0	0	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome	0	1 (0.2)	0	0	0	0	0	0	0

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Petechiae	0	1 (0.2)	1 (1.6)	0	2 (0.4)	0	0	0	0
Pruritus	0	2 (0.4)	0	0	1 (0.2)	1 (1.6)	0	0	0
Rash	0	4 (0.8)	1 (1.6)	0	2 (0.4)	1 (1.6)	0	1 (2.0)	0
Rash Erythematous	0	1 (0.2)	0	0	0	0	0	0	0
Rash Generalised	0	0	0	0	0	0	0	2 (4.1)	0
Rash Maculo-Papular	0	2 (0.4)	1 (1.6)	0	0	0	0	0	0
Rash Pruritic	0	0	0	1 (6.3)	2 (0.4)	0	0	0	0
Skin Disorder	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Skin Exfoliation	0	0	0	0	1 (0.2)	0	0	0	0
Skin Hypopigmentation	0	1 (0.2)	0	0	0	0	0	0	0
Skin Lesion	0	0	0	0	2 (0.4)	0	0	0	0
Skin Oedema	0	1 (0.2)	0	0	0	0	0	0	0
Skin Ulcer	0	0	0	0	1 (0.2)	0	0	0	0
Subcutaneous Emphysema	0	1 (0.2)	0	0	0	0	0	0	0
Social Circumstances	**0**	**1 (0.2)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Social Problem	0	1 (0.2)	0	0	0	0	0	0	0
Surgical And Medical Procedures	**0**	**3 (0.6)**	**0**	**0**	**1 (0.2)**	**0**	**0**	**1 (2.0)**	**0**
Bone Marrow Transplant	0	2 (0.4)	0	0	0	0	0	0	0
Chemotherapy	0	0	0	0	1 (0.2)	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

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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
Vascular Disorders	**0**	**51 (9.6)**	**8 (12.7)**	**2 (12.5)**	**56 (12.2)**	**11 (17.5)**	**0**	**6 (12.2)**	**1 (11 1)**
Circulatory Collapse	0	1 (0.2)	0	0	3 (0.7)	1 (1.6)	0	0	0
Deep Vein Thrombosis	0	2 (0.4)	0	0	2 (0.4)	0	0	1 (2.0)	0
Embolism Arterial	0	0	0	0	1 (0.2)	0	0	0	0
Haemodynamic Instability	0	2 (0.4)	0	0	1 (0.2)	0	0	0	0
Haemorrhage	0	1 (0.2)	1 (1.6)	0	3 (0.7)	0	0	0	0
Haemorrhagic Infarction	0	0	0	0	1 (0.2)	0	0	0	0
Hypertension	0	8 (1.5)	3 (4.8)	0	15 (3.3)	1 (1.6)	0	2 (4.1)	0
Hypertensive Crisis	0	0	1 (1.6)	0	0	1 (1.6)	0	0	0
Hypotension	0	34 (6.4)	4 (6.3)	2 (12.5)	29 (6.3)	9 (14.3)	0	4 (8.2)	1 (11.1)
Hypovolaemic Shock	0	2 (0.4)	0	0	2 (0.4)	1 (1.6)	0	0	0
Ischaemia	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	2 (0.4)	0	0	0	0	0	0	0
Pallor	0	1 (0.2)	0	0	0	0	0	0	0
Peripheral Circulatory Failure	0	0	1 (1.6)	0	0	0	0	0	0
Peripheral Vascular Disorder	0	1 (0.2)	0	0	0	0	0	0	0
Shock	0	0	0	1 (6.3)	3 (0.7)	0	0	0	0
Subclavian Vein Thrombosis	0	1 (0.2)	0	0	0	0	0	0	0
Vasodilatation	0	0	0	0	1 (0.2)	0	0	0	0
Vena Cava Embolism	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

	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
Venous Thrombosis	0	0	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 2.7.4-162　　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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Subjects Reporting Any Adverse Event	**5 (100.0)**	**113 (97.4)**	**3 (100.0)**	**11 (100.0)**	**240 (96.8)**	**40 (88.9)**	**16 (100.0)**	**353 (97.0)**	**43 (89.6)**
Blood And Lymphatic System Disorders	**4 (80.0)**	**49 (42.2)**	**2 (66.7)**	**4 (36.4)**	**90 (36.3)**	**14 (31.1)**	**8 (50.0)**	**139 (38.2)**	**16 (33.3)**
Anaemia	2 (40.0)	18 (15.5)	1 (33.3)	2 (18.2)	47 (19.0)	11 (24.4)	4 (25.0)	65 (17.9)	12 (25.0)
Anaemia Megaloblastic	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aplastic Anaemia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Autoimmune Haemolytic Anaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bandaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Coagulopathy	0	3 (2.6)	0	0	4 (1.6)	0	0	7 (1.9)	0
Disseminated Intravascular Coagulation	0	1 (0.9)	0	0	4 (1.6)	0	0	5 (1.4)	0
Eosinophilia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Febrile Neutropenia	0	4 (3.4)	1 (33.3)	0	15 (6.0)	2 (4.4)	0	19 (5.2)	3 (6.3)
Haemolysis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Haemolytic Anaemia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Haemolytic Uraemic Syndrome	0	4 (3.4)	0	0	0	0	0	4 (1.1)	0
Hypercoagulation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Leukocytosis	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Leukopenia	1 (20.0)	3 (2.6)	0	1 (9.1)	6 (2.4)	0	2 (12.5)	9 (2.5)	0
Lymphadenopathy	0	2 (1.7)	0	1 (9.1)	6 (2.4)	0	1 (6.3)	8 (2.2)	0
Neutropenia	2 (40.0)	10 (8.6)	0	2 (18.2)	23 (9.3)	2 (4.4)	4 (25.0)	33 (9.1)	2 (4.2)
Pancytopenia	0	6 (5.2)	0	0	12 (4.8)	1 (2.2)	0	18 (4.9)	1 (2.1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Polycythaemia	0	0	1 (33.3)	0	1 (0.4)	0	0	1 (0.3)	1 (2.1)
Retroperitoneal Lymphadenopathy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Splenic Infarction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Splenic Lesion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Splenomegaly	1 (20.0)	4 (3.4)	0	0	4 (1.6)	0	1 (6.3)	8 (2.2)	0
Thrombocytopenia	2 (40.0)	20 (17.2)	0	2 (18.2)	36 (14.5)	5 (11.1)	4 (25.0)	56 (15.4)	5 (10.4)
Thrombocytosis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Thrombotic Thrombocytopenic Purpura	0	5 (4.3)	0	0	0	1 (2.2)	0	5 (1.4)	1 (2 1)
Cardiac Disorders	**3 (60.0)**	**53 (45.7)**	**0**	**4 (36.4)**	**56 (22.6)**	**19 (42.2)**	**7 (43.8)**	**109 (29.9)**	**19 (39.6)**
Angina Pectoris	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Aortic Valve Incompetence	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aortic Valve Sclerosis	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Arrhythmia	0	0	0	0	0	2 (4.4)	0	0	2 (4.2)
Arrhythmia Supraventricular	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Arteriosclerosis Coronary Artery	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Atrial Fibrillation	0	7 (6.0)	0	0	7 (2.8)	4 (8.9)	0	14 (3.8)	4 (8.3)
Atrial Flutter	0	4 (3.4)	0	0	3 (1.2)	0	0	7 (1.9)	0
Atrioventricular Block	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Atrioventricular Block First Degree	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Bradycardia	0	2 (1.7)	0	0	4 (1.6)	4 (8.9)	0	6 (1.6)	4 (8.3)
Bundle Branch Block	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Bundle Branch Block Left	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Bundle Branch Block Right	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Cardiac Arrest	0	2 (1.7)	0	0	5 (2.0)	1 (2.2)	0	7 (1.9)	1 (2.1)
Cardiac Failure	1 (20.0)	3 (2.6)	0	1 (9.1)	1 (0.4)	0	2 (12.5)	4 (1.1)	0
Cardiac Failure Congestive	0	2 (1.7)	0	0	6 (2.4)	5 (11.1)	0	8 (2.2)	5 (10.4)
Cardiac Valve Disease	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Cardio-Respiratory Arrest	1 (20.0)	7 (6.0)	0	0	6 (2.4)	3 (6.7)	1 (6.3)	13 (3.6)	3 (6.3)
Cardiogenic Shock	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cardiomegaly	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Cardiomyopathy	0	4 (3.4)	0	0	1 (0.4)	0	0	5 (1.4)	0
Cardiopulmonary Failure	1 (20.0)	0	0	0	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Coronary Artery Occlusion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cyanosis	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Defect Conduction Intraventricular	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Dilatation Atrial	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Extrasystoles	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Left Atrial Enlargement	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Left Ventricular Dysfunction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Left Ventricular Hypertrophy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mitral Valve Calcification	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Mitral Valve Incompetence	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Mitral Valve Stenosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Myocardial Infarction	0	0	0	0	1 (0.4)	2 (4.4)	0	1 (0.3)	2 (4.2)
Palpitations	0	3 (2.6)	0	0	2 (0.8)	1 (2.2)	0	5 (1.4)	1 (2.1)
Pericardial Effusion	0	9 (7.8)	0	1 (9.1)	4 (1.6)	0	1 (6.3)	13 (3.6)	0
Pericardial Rub	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Pericarditis	0	2 (1.7)	0	0	0	1 (2.2)	0	2 (0.5)	1 (2.1)
Pulseless Electrical Activity	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Sinus Bradycardia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Sinus Tachycardia	0	5 (4.3)	0	0	4 (1.6)	0	0	9 (2.5)	0
Supraventricular Tachycardia	0	6 (5.2)	0	0	6 (2.4)	2 (4.4)	0	12 (3.3)	2 (4.2)
Tachycardia	2 (40.0)	23 (19.8)	0	2 (18.2)	18 (7.3)	3 (6.7)	4 (25.0)	41 (11.3)	3 (6 3)
Tricuspid Valve Incompetence	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Ventricular Extrasystoles	0	1 (0.9)	0	0	2 (0.8)	3 (6.7)	0	3 (0.8)	3 (6 3)
Ventricular Fibrillation	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Ventricular Hypertrophy	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Ventricular Tachycardia	0	2 (1.7)	0	0	2 (0.8)	2 (4.4)	0	4 (1.1)	2 (4.2)
Congenital, Familial And Genetic Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**1 (2.2)**	**0**	**1 (0.3)**	**1 (2.1)**
Aplasia	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Fanconi Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Ear And Labyrinth Disorders	**1 (20.0)**	**11 (9.5)**	**1 (33.3)**	**0**	**19 (7.7)**	**1 (2.2)**	**1 (6.3)**	**30 (8.2)**	**2 (4.2)**
Cerumen Impaction	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Conductive Deafness	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Deafness	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Ear Discomfort	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Ear Pain	1 (20.0)	4 (3.4)	1 (33.3)	0	5 (2.0)	1 (2.2)	1 (6.3)	9 (2.5)	2 (4 2)
Ear Pruritus	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Excessive Cerumen Production	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
External Ear Inflammation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypoacusis	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Middle Ear Effusion	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Tinnitus	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Vertigo	0	1 (0.9)	0	0	5 (2.0)	0	0	6 (1.6)	0
Vertigo Labyrinthine	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Endocrine Disorders	**2 (40.0)**	**7 (6.0)**	**0**	**0**	**7 (2.8)**	**1 (2.2)**	**2 (12.5)**	**14 (3.8)**	**1 (2.1)**
Adrenal Insufficiency	1 (20.0)	2 (1.7)	0	0	3 (1.2)	1 (2.2)	1 (6.3)	5 (1.4)	1 (2 1)
Adrenocortical Insufficiency Acute	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cushingoid	1 (20.0)	1 (0.9)	0	0	3 (1.2)	0	1 (6.3)	4 (1.1)	0
Hyperthyroidism	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hypogonadism	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hypothyroidism	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0
Eye Disorders	**2 (40.0)**	**33 (28.4)**	**0**	**2 (18.2)**	**46 (18.5)**	**7 (15.6)**	**4 (25.0)**	**79 (21.7)**	**7 (14.6)**

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Blepharitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blindness	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Cataract	0	2 (1.7)	0	0	1 (0.4)	1 (2.2)	0	3 (0.8)	1 (2.1)
Conjunctival Haemorrhage	0	1 (0.9)	0	1 (9.1)	0	2 (4.4)	1 (6.3)	1 (0.3)	2 (4.2)
Conjunctival Hyperaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Conjunctival Irritation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Conjunctival Oedema	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0
Conjunctivitis Allergic	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Corneal Epithelium Defect	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Corneal Erosion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Corneal Perforation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dacryostenosis Acquired	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Diplopia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Dry Eye	1 (20.0)	5 (4.3)	0	0	2 (0.8)	0	1 (6.3)	7 (1.9)	0
Erythema Of Eyelid	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Exophthalmos	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eye Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eye Irritation	0	2 (1.7)	0	0	6 (2.4)	1 (2.2)	0	8 (2.2)	1 (2.1)
Eye Movement Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Oedema	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Eye Pain	0	3 (2.6)	0	0	5 (2.0)	0	0	8 (2.2)	0
Eye Pruritus	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Eye Swelling	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Eyelid Cyst	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eyelid Oedema	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eyelid Ptosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypoaesthesia Eye	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Iridocyclitis	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Keratopathy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Lacrimation Increased	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Mydriasis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Myopia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Ocular Hyperaemia	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Optic Atrophy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Papilloedema	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Periorbital Oedema	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Photophobia	1 (20.0)	2 (1.7)	0	0	1 (0.4)	0	1 (6.3)	3 (0.8)	0
Photopsia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pinguecula	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pupillary Reflex Impaired	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pupils Unequal	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Retinal Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Retinal Exudates	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Scleral Discolouration	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Scleral Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Scleral Oedema	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Uveitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Vision Blurred	0	11 (9.5)	0	0	14 (5.6)	2 (4.4)	0	25 (6.9)	2 (4.2)
Visual Impairment	0	2 (1.7)	0	0	5 (2.0)	0	0	7 (1.9)	0
Gastrointestinal Disorders	**3 (60.0)**	**82 (70.7)**	**3 (100.0)**	**7 (63.6)**	**172 (69.4)**	**27 (60.0)**	**10 (62.5)**	**254 (69.8)**	**30 (62.5)**
Abdominal Discomfort	0	2 (1.7)	0	0	2 (0.8)	1 (2.2)	0	4 (1.1)	1 (2 1)
Abdominal Distension	0	17 (14.7)	0	0	14 (5.6)	2 (4.4)	0	31 (8.5)	2 (4.2)
Abdominal Hernia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Abdominal Pain	3 (60.0)	23 (19.8)	1 (33.3)	2 (18.2)	27 (10.9)	5 (11.1)	5 (31.3)	50 (13.7)	6 (12.5)
Abdominal Pain Lower	0	2 (1.7)	0	0	0	2 (4.4)	0	2 (0.5)	2 (4.2)
Abdominal Pain Upper	0	13 (11.2)	1 (33.3)	0	26 (10.5)	3 (6.7)	0	39 (10.7)	4 (8.3)
Abdominal Rigidity	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Abdominal Tenderness	0	2 (1.7)	0	2 (18.2)	2 (0.8)	0	2 (12.5)	4 (1.1)	0
Abdominal Wall Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Abnormal Faeces	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Anal Incontinence	0	1 (0.9)	0	0	0	2 (4.4)	0	1 (0.3)	2 (4.2)
Anorectal Discomfort	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Ascites	0	8 (6.9)	0	0	5 (2.0)	1 (2.2)	0	13 (3.6)	1 (2.1)
Barrett's Oesophagus	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cheilitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Colitis	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Constipation	1 (20.0)	17 (14.7)	0	1 (9.1)	31 (12.5)	7 (15.6)	2 (12.5)	48 (13.2)	7 (14.6)
Dental Caries	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dental Discomfort	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Diarrhoea	2 (40.0)	41 (35.3)	0	2 (18.2)	67 (27.0)	8 (17.8)	4 (25.0)	108 (29.7)	8 (16.7)
Diarrhoea Haemorrhagic	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Dry Mouth	0	4 (3.4)	0	0	5 (2.0)	0	0	9 (2.5)	0
Duodenal Ulcer	1 (20.0)	2 (1.7)	0	0	0	0	1 (6.3)	2 (0.5)	0
Duodenitis	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Dyspepsia	0	6 (5.2)	1 (33.3)	0	10 (4.0)	3 (6.7)	0	16 (4.4)	4 (8.3)
Dysphagia	0	3 (2.6)	1 (33.3)	0	9 (3.6)	3 (6.7)	0	12 (3.3)	4 (8 3)
Enteritis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eructation	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Faecaloma	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Faeces Discoloured	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Faeces Soft	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Flatulence	1 (20.0)	3 (2.6)	0	0	13 (5.2)	1 (2.2)	1 (6.3)	16 (4.4)	1 (2 1)
Food Poisoning	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Gastric Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Gastric Haemorrhage	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gastric Perforation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Gastric Polyps	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Gastric Ulcer	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Gastritis	0	4 (3.4)	0	0	3 (1.2)	0	0	7 (1.9)	0
Gastrointestinal Haemorrhage	1 (20.0)	5 (4.3)	0	0	3 (1.2)	1 (2.2)	1 (6.3)	8 (2.2)	1 (2 1)
Gastrointestinal Hypermotility	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Gastrointestinal Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gastrointestinal Sounds Abnormal	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Gastrooesophageal Reflux Disease	0	1 (0.9)	0	1 (9.1)	2 (0.8)	1 (2.2)	1 (6.3)	3 (0.8)	1 (2 1)
Gingival Bleeding	0	2 (1.7)	0	0	5 (2.0)	0	0	7 (1.9)	0
Gingival Hypertrophy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gingival Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gingival Swelling	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Glossitis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Glossodynia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Haematemesis	0	4 (3.4)	0	0	2 (0.8)	1 (2.2)	0	6 (1.6)	1 (2.1)
Haematochezia	0	2 (1.7)	0	1 (9.1)	4 (1.6)	0	1 (6.3)	6 (1.6)	0
Haemorrhoidal Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haemorrhoids	0	2 (1.7)	0	0	5 (2.0)	3 (6.7)	0	7 (1.9)	3 (6 3)
Hiatus Hernia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Hypoaesthesia Oral	0	4 (3.4)	0	0	2 (0.8)	0	0	6 (1.6)	0
Ileus	0	1 (0.9)	0	0	5 (2.0)	0	0	6 (1.6)	0
Ileus Paralytic	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Intestinal Dilatation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Intestinal Infarction	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Intestinal Ischaemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Intestinal Obstruction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Intestinal Ulcer	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Irritable Bowel Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Leukoplakia Oral	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lip Dry	0	1 (0.9)	0	0	7 (2.8)	0	0	8 (2.2)	0
Lip Swelling	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Mallory-Weiss Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Melaena	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Mouth Haemorrhage	0	1 (0.9)	0	1 (9.1)	2 (0.8)	0	1 (6.3)	3 (0.8)	0
Mouth Ulceration	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Nausea	1 (20.0)	35 (30.2)	0	2 (18.2)	77 (31.0)	12 (26.7)	3 (18.8)	112 (30.8)	12 (25.0)
Neutropenic Colitis	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Obstruction Gastric	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Odynophagia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Oesophageal Pain	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Oesophageal Perforation	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Oesophageal Stenosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Oesophageal Ulcer	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Oesophagitis	0	2 (1.7)	0	0	3 (1.2)	1 (2.2)	0	5 (1.4)	1 (2.1)
Oesophagitis Ulcerative	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Oral Discomfort	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Oral Disorder	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Oral Mucosal Blistering	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Oral Mucosal Erythema	0	0	1 (33.3)	0	0	0	0	0	1 (2.1)
Oral Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Palatal Swelling	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pancreatic Atrophy	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Pancreatic Failure	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pancreatitis	0	1 (0.9)	0	2 (18.2)	1 (0.4)	1 (2.2)	2 (12.5)	2 (0.5)	1 (2 1)
Pancreatitis Acute	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Pancreatitis Haemorrhagic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pneumatosis Intestinalis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Proctalgia	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Rectal Haemorrhage	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Rectal Lesion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Retching	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Salivary Hypersecretion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Stomatitis	0	1 (0.9)	0	0	4 (1.6)	0	0	5 (1.4)	0
Submaxillary Gland Enlargement	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Tongue Coated	0	3 (2.6)	0	0	0	1 (2.2)	0	3 (0.8)	1 (2.1)
Tongue Oedema	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Tongue Ulceration	0	4 (3.4)	0	0	0	0	0	4 (1.1)	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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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Tooth Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Toothache	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Umbilical Hernia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Upper Gastrointestinal Haemorrhage	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Vomiting	0	34 (29.3)	1 (33.3)	3 (27.3)	68 (27.4)	6 (13.3)	3 (18.8)	102 (28.0)	7 (14.6)
General Disorders And Administration Site Conditions	**3 (60.0)**	**87 (75.0)**	**2 (66.7)**	**8 (72.7)**	**168 (67.7)**	**25 (55.6)**	**11 (68.8)**	**255 (70.1)**	**27 (56.3)**
Asthenia	0	20 (17.2)	0	0	38 (15.3)	11 (24.4)	0	58 (15.9)	11 (22.9)
Brain Death	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Catheter Site Discharge	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Catheter Site Erythema	0	1 (0.9)	0	0	6 (2.4)	0	0	7 (1.9)	0
Catheter Site Haematoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Catheter Site Haemorrhage	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Catheter Site Pain	0	2 (1.7)	0	0	5 (2.0)	0	0	7 (1.9)	0
Catheter Site Related Reaction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Catheter Site Swelling	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Chest Discomfort	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Chest Pain	1 (20.0)	15 (12.9)	1 (33.3)	2 (18.2)	33 (13.3)	8 (17.8)	3 (18.8)	48 (13.2)	9 (18.8)
Chills	1 (20.0)	13 (11.2)	1 (33.3)	1 (9.1)	25 (10.1)	2 (4.4)	2 (12.5)	38 (10.4)	3 (6 3)
Crepitations	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Crying	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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Cyst	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Death	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Discomfort	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Disease Progression	1 (20.0)	13 (11.2)	0	1 (9.1)	11 (4.4)	3 (6.7)	2 (12.5)	24 (6.6)	3 (6 3)
Drug Interaction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Drug Intolerance	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Early Satiety	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Face Oedema	0	4 (3.4)	0	0	2 (0.8)	0	0	6 (1.6)	0
Facial Pain	1 (20.0)	3 (2.6)	0	0	2 (0.8)	0	1 (6.3)	5 (1.4)	0
Fatigue	0	19 (16.4)	1 (33.3)	1 (9.1)	23 (9.3)	8 (17.8)	1 (6.3)	42 (11.5)	9 (18.8)
Feeling Cold	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Feeling Jittery	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Gait Disturbance	0	2 (1.7)	0	0	6 (2.4)	3 (6.7)	0	8 (2.2)	3 (6.3)
Gait Inability	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
General Physical Health Deterioration	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Generalised Oedema	0	9 (7.8)	0	0	5 (2.0)	1 (2.2)	0	14 (3.8)	1 (2.1)
Granuloma	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hyperthermia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypothermia	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Inflammation	0	1 (0.9)	0	1 (9.1)	1 (0.4)	0	1 (6.3)	2 (0.5)	0
Influenza Like Illness	0	0	0	0	5 (2.0)	0	0	5 (1.4)	0
Infusion Site Erythema	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Infusion Site Inflammation	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Infusion Site Phlebitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Injection Site Pain	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Localised Oedema	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Malaise	0	4 (3.4)	0	0	10 (4.0)	1 (2.2)	0	14 (3.8)	1 (2.1)
Mass	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mucosal Dryness	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Mucosal Inflammation	0	5 (4.3)	1 (33.3)	1 (9.1)	20 (8.1)	3 (6.7)	1 (6.3)	25 (6.9)	4 (8 3)
Multi-Organ Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Multiple Organ Dysfunction Syndrome	1 (20.0)	8 (6.9)	0	1 (9.1)	4 (1.6)	1 (2.2)	2 (12.5)	12 (3.3)	1 (2 1)
Nodule	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Oedema	1 (20.0)	4 (3.4)	0	0	13 (5.2)	1 (2.2)	1 (6.3)	17 (4.7)	1 (2.1)
Oedema Peripheral	0	24 (20.7)	0	1 (9.1)	28 (11.3)	9 (20.0)	1 (6.3)	52 (14.3)	9 (18.8)
Pain	0	5 (4.3)	0	0	14 (5.6)	0	0	19 (5.2)	0
Peripheral Swelling	0	6 (5.2)	0	0	13 (5.2)	0	0	19 (5.2)	0
Pseudocyst	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Puncture Site Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pyrexia	3 (60.0)	40 (34.5)	0	4 (36.4)	88 (35.5)	8 (17.8)	7 (43.8)	128 (35.2)	8 (16.7)
Secretion Discharge	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Sluggishness	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Suprapubic Pain	1 (20.0)	0	0	0	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Swelling	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Vessel Puncture Site Haematoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vessel Puncture Site Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatobiliary Disorders	**1 (20.0)**	**17 (14.7)**	**1 (33.3)**	**2 (18.2)**	**25 (10.1)**	**5 (11.1)**	**3 (18.8)**	**42 (11.5)**	**6 (12 5)**
Cholecystitis	1 (20.0)	1 (0.9)	0	0	1 (0.4)	0	1 (6.3)	2 (0.5)	0
Cholelithiasis	0	4 (3.4)	0	0	2 (0.8)	1 (2.2)	0	6 (1.6)	1 (2.1)
Cholestasis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Deficiency Of Bile Secretion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gallbladder Enlargement	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Gallbladder Polyp	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatic Cyst	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hepatic Failure	0	1 (0.9)	0	0	4 (1.6)	1 (2.2)	0	5 (1.4)	1 (2.1)
Hepatic Function Abnormal	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Hepatic Lesion	0	0	1 (33.3)	0	1 (0.4)	0	0	1 (0.3)	1 (2.1)
Hepatic Necrosis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hepatic Steatosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatitis Acute	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatocellular Injury	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hepatomegaly	0	2 (1.7)	0	0	5 (2.0)	0	0	7 (1.9)	0
Hepatosplenomegaly	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Hepatotoxicity	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Hyperbilirubinaemia	0	4 (3.4)	0	0	5 (2.0)	0	0	9 (2.5)	0

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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, Age
Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Jaundice	0	4 (3.4)	0	1 (9.1)	5 (2.0)	1 (2.2)	1 (6.3)	9 (2.5)	1 (2.1)
Liver Disorder	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Ocular Icterus	0	3 (2.6)	0	1 (9.1)	3 (1.2)	1 (2.2)	1 (6.3)	6 (1.6)	1 (2.1)
Immune System Disorders	**2 (40.0)**	**38 (32.8)**	**1 (33.3)**	**1 (9.1)**	**17 (6.9)**	**2 (4.4)**	**3 (18.8)**	**55 (15.1)**	**3 (6.3)**
Acute Graft Versus Host Disease In Intestine	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Acute Graft Versus Host Disease In Liver	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Chronic Graft Versus Host Disease	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Drug Hypersensitivity	0	3 (2.6)	0	1 (9.1)	1 (0.4)	1 (2.2)	1 (6.3)	4 (1.1)	1 (2 1)
Graft Versus Host Disease	0	16 (13.8)	0	0	3 (1.2)	0	0	19 (5.2)	0
Graft Versus Host Disease In Gastrointestinal Tract	1 (20.0)	6 (5.2)	0	0	1 (0.4)	0	1 (6.3)	7 (1.9)	0
Graft Versus Host Disease In Liver	1 (20.0)	5 (4.3)	0	0	0	0	1 (6.3)	5 (1.4)	0
Graft Versus Host Disease In Lung	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Graft Versus Host Disease In Skin	1 (20.0)	18 (15.5)	1 (33.3)	0	3 (1.2)	0	1 (6.3)	21 (5.8)	1 (2 1)
Hypersensitivity	0	1 (0.9)	0	0	5 (2.0)	1 (2.2)	0	6 (1.6)	1 (2.1)
Hypogammaglobulinaemia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Iodine Allergy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Kidney Transplant Rejection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Seasonal Allergy	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Transplant Rejection	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0

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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, Age
Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Infections And Infestations	**5 (100.0)**	**86 (74.1)**	**2 (66.7)**	**9 (81.8)**	**158 (63.7)**	**20 (44.4)**	**14 (87.5)**	**244 (67.0)**	**22 (45.8)**
Abdominal Abscess	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Abdominal Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Abscess	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Abscess Limb	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Abscess Neck	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Abscess Of Eyelid	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Abscess Oral	0	0	1 (33.3)	0	0	0	0	0	1 (2.1)
Acarodermatitis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Acid Fast Bacilli Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Acinetobacter Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Acquired Immunodeficiency Syndrome	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Actinomycosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Adenovirus Infection	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Aids Related Complication	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Alpha Haemolytic Streptococcal Infection	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Anal Abscess	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Arthritis Bacterial	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Arthritis Infective	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aspergilloma	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Aspergillus Infection	0	4 (3.4)	0	0	2 (0.8)	1 (2.2)	0	6 (1.6)	1 (2 1)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Atypical Pneumonia	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Bacteraemia	1 (20.0)	9 (7.8)	0	2 (18.2)	7 (2.8)	2 (4.4)	3 (18.8)	16 (4.4)	2 (4 2)
Bacterial Disease Carrier	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bacterial Infection	1 (20.0)	5 (4.3)	0	0	11 (4.4)	0	1 (6.3)	16 (4.4)	0
Brain Abscess	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Bronchiolitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bronchitis	0	4 (3.4)	0	0	11 (4.4)	0	0	15 (4.1)	0
Bronchitis Bacterial	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bronchitis Viral	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Bronchopulmonary Aspergillosis	0	1 (0.9)	0	0	5 (2.0)	0	0	6 (1.6)	0
Candida Infection	0	4 (3.4)	0	0	1 (0.4)	0	0	5 (1.4)	0
Catheter Site Cellulitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Catheter Site Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Cellulitis	0	3 (2.6)	0	1 (9.1)	10 (4.0)	0	1 (6.3)	13 (3.6)	0
Cellulitis Of Male External Genital Organ	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cellulitis Orbital	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Cerebral Aspergillosis	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Cerebral Toxoplasmosis	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Chronic Sinusitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Clostridium Difficile Colitis	0	3 (2.6)	0	0	3 (1.2)	1 (2.2)	0	6 (1.6)	1 (2.1)
Clostridium Difficile Infection	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Conjunctivitis	0	4 (3.4)	0	2 (18.2)	7 (2.8)	1 (2.2)	2 (12.5)	11 (3.0)	1 (2.1)

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Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Corynebacterium Infection	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Corynebacterium Sepsis	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Cystitis Bacterial	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Cytomegalovirus Chorioretinitis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Cytomegalovirus Colitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cytomegalovirus Duodenitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Cytomegalovirus Infection	0	10 (8.6)	0	0	3 (1.2)	0	0	13 (3.6)	0
Dacryocystitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Device Related Infection	0	4 (3.4)	0	1 (9.1)	5 (2.0)	1 (2.2)	1 (6.3)	9 (2.5)	1 (2 1)
Disseminated Tuberculosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Diverticulitis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Ear Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Empyema	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Encephalitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
End Stage Aids	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Endocarditis Bacterial	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Endophthalmitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Enterobacter Infection	0	0	1 (33.3)	0	0	0	0	0	1 (2.1)
Enterococcal Bacteraemia	0	0	0	0	4 (1.6)	1 (2.2)	0	4 (1.1)	1 (2.1)
Enterococcal Infection	1 (20.0)	13 (11.2)	0	0	6 (2.4)	2 (4.4)	1 (6.3)	19 (5.2)	2 (4.2)
Enterococcal Sepsis	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Escherichia Bacteraemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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Escherichia Infection	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Escherichia Sepsis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Escherichia Urinary Tract Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eye Infection Staphylococcal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eyelid Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Folliculitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Fungaemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Fungal Infection	0	1 (0.9)	0	0	4 (1.6)	0	0	5 (1.4)	0
Fungal Rhinitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Fungal Sepsis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Fungal Skin Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Furuncle	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Fusarium Infection	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Gastroenteritis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gastroenteritis Viral	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Genital Herpes	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Gingival Abscess	0	0	1 (33.3)	0	0	0	0	0	1 (2.1)
Gingivitis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Helicobacter Gastritis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hepatic Candidiasis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Hepatosplenic Candidiasis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Herpes Simplex	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0

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Herpes Simplex Pneumonia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Herpes Zoster	0	3 (2.6)	0	1 (9.1)	5 (2.0)	0	1 (6.3)	8 (2.2)	0
Hiv Wasting Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hordeolum	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Human Polyomavirus Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Infection Parasitic	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Influenza	0	0	0	0	5 (2.0)	1 (2.2)	0	5 (1.4)	1 (2.1)
Infusion Site Cellulitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Intervertebral Discitis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Klebsiella Bacteraemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Klebsiella Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Klebsiella Sepsis	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Localised Infection	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Lower Respiratory Tract Infection	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Lung Abscess	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Lung Infection	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Lung Infection Pseudomonal	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Mastoiditis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Meningitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Meningitis Cryptococcal	0	0	0	0	8 (3.2)	0	0	8 (2.2)	0
Meningitis Tuberculous	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Molluscum Contagiosum	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Mucormycosis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Mycobacterial Infection	0	0	0	0	5 (2.0)	0	0	5 (1.4)	0
Mycobacterium Avium Complex Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mycobacterium Kansasii Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Mycoplasma Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nasopharyngitis	0	0	0	0	6 (2.4)	1 (2.2)	0	6 (1.6)	1 (2.1)
Neurosyphilis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nocardiosis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Oesophageal Candidiasis	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Onychomycosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Oral Candidiasis	0	8 (6.9)	0	0	2 (0.8)	1 (2.2)	0	10 (2.7)	1 (2.1)
Oral Fungal Infection	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Oral Hairy Leukoplakia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Oral Herpes	0	4 (3.4)	0	1 (9.1)	7 (2.8)	0	1 (6.3)	11 (3.0)	0
Orchitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Osteomyelitis	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Otitis Media	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Parainfluenzae Virus Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Paronychia	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Pelvic Abscess	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Periorbital Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Peritonitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Pharyngitis	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Pharyngotonsillitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Plague	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pleural Infection Bacterial	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pneumococcal Sepsis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pneumocystis Jirovecii Pneumonia	0	0	0	1 (9.1)	4 (1.6)	1 (2.2)	1 (6.3)	4 (1.1)	1 (2.1)
Pneumonia	1 (20.0)	15 (12.9)	1 (33.3)	2 (18.2)	26 (10.5)	4 (8.9)	3 (18.8)	41 (11.3)	5 (10.4)
Pneumonia Bacterial	1 (20.0)	3 (2.6)	0	0	1 (0.4)	0	1 (6.3)	4 (1.1)	0
Pneumonia Cytomegaloviral	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pneumonia Escherichia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pneumonia Fungal	0	7 (6.0)	0	0	6 (2.4)	1 (2.2)	0	13 (3.6)	1 (2.1)
Pneumonia Klebsiella	1 (20.0)	0	0	0	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Pneumonia Pseudomonal	1 (20.0)	0	0	0	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Pneumonia Staphylococcal	0	2 (1.7)	0	1 (9.1)	0	0	1 (6.3)	2 (0.5)	0
Postoperative Wound Infection	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Proctitis Herpes	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pseudallescheria Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pseudomembranous Colitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pseudomonas Infection	1 (20.0)	2 (1.7)	0	0	2 (0.8)	0	1 (6.3)	4 (1.1)	0
Pulmonary Mycosis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Pulmonary Tuberculosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Purulent Discharge	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Pyelonephritis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Respiratory Syncytial Virus Infection	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Respiratory Tract Infection	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Retinitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rhinitis	1 (20.0)	0	0	0	3 (1.2)	0	1 (6.3)	3 (0.8)	0
Salmonella Sepsis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Sepsis	0	9 (7.8)	0	0	10 (4.0)	2 (4.4)	0	19 (5.2)	2 (4.2)
Septic Embolus	0	4 (3.4)	0	0	0	0	0	4 (1.1)	0
Septic Shock	0	6 (5.2)	0	0	2 (0.8)	0	0	8 (2.2)	0
Serratia Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Sinusitis	0	10 (8.6)	0	1 (9.1)	13 (5.2)	1 (2.2)	1 (6.3)	23 (6.3)	1 (2.1)
Sinusitis Aspergillus	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Sinusitis Bacterial	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Sinusitis Fungal	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Skin Bacterial Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Skin Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Staphylococcal Bacteraemia	0	10 (8.6)	0	0	7 (2.8)	1 (2.2)	0	17 (4.7)	1 (2.1)
Staphylococcal Infection	1 (20.0)	6 (5.2)	0	0	11 (4.4)	2 (4.4)	1 (6.3)	17 (4.7)	2 (4 2)
Staphylococcal Sepsis	0	2 (1.7)	0	3 (27.3)	3 (1.2)	0	3 (18.8)	5 (1.4)	0
Staphylococcal Skin Infection	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Stenotrophomonas Infection	0	2 (1.7)	1 (33.3)	0	0	0	0	2 (0.5)	1 (2.1)
Stenotrophomonas Sepsis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Subcutaneous Abscess	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Superinfection Fungal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Syphilis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Systemic Candida	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Tooth Abscess	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Tooth Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Torulopsis Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Tracheitis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Trichosporon Infection	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Tuberculosis	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Upper Respiratory Tract Infection	0	7 (6.0)	1 (33.3)	0	11 (4.4)	0	0	18 (4.9)	1 (2.1)
Urinary Tract Infection	1 (20.0)	4 (3.4)	0	0	9 (3.6)	5 (11.1)	1 (6.3)	13 (3.6)	5 (10.4)
Urinary Tract Infection Staphylococcal	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Varicella	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Varicella Zoster Virus Infection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Viral Infection	0	3 (2.6)	0	1 (9.1)	2 (0.8)	0	1 (6.3)	5 (1.4)	0
Viral Sinusitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Wound Infection	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Wound Infection Fungal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Injury, Poisoning And Procedural Complications	**2 (40.0)**	**26 (22.4)**	**2 (66.7)**	**6 (54.5)**	**39 (15.7)**	**8 (17.8)**	**8 (50.0)**	**65 (17.9)**	**10 (20.8)**

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Arthropod Bite	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Barotitis Media	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Contusion	0	5 (4.3)	1 (33.3)	2 (18.2)	1 (0.4)	0	2 (12.5)	6 (1.6)	1 (2 1)
Corneal Abrasion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eschar	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Excoriation	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Eye Burns	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Eye Contusion	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Fall	1 (20.0)	7 (6.0)	0	0	5 (2.0)	3 (6.7)	1 (6.3)	12 (3.3)	3 (6.3)
Femur Fracture	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Foot Fracture	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Graft Complication	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haemolytic Transfusion Reaction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Head Injury	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hip Fracture	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Hyphaema	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Incision Site Haematoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Incision Site Pain	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Infusion Related Reaction	0	1 (0.9)	1 (33.3)	0	4 (1.6)	0	0	5 (1.4)	1 (2.1)
Injury	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Joint Injury	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Laceration	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Limb Injury	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Muscle Strain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Overdose	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Post Lumbar Puncture Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Post Procedural Haemorrhage	0	3 (2.6)	0	1 (9.1)	1 (0.4)	0	1 (6.3)	4 (1.1)	0
Procedural Complication	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Procedural Pain	0	4 (3.4)	0	1 (9.1)	6 (2.4)	0	1 (6.3)	10 (2.7)	0
Procedural Site Reaction	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Scratch	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Skin Abrasion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Spinal Compression Fracture	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Spinal Cord Injury	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Stress Fracture	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Subarachnoid Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Sunburn	0	0	0	2 (18.2)	0	0	2 (12.5)	0	0
Toxicity To Various Agents	0	1 (0.9)	0	0	3 (1.2)	2 (4.4)	0	4 (1.1)	2 (4.2)
Tracheal Haemorrhage	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Transfusion Reaction	0	1 (0.9)	0	2 (18.2)	4 (1.6)	1 (2.2)	2 (12.5)	5 (1.4)	1 (2 1)
Wound	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Wound Complication	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Wound Decomposition	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Wound Necrosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Investigations	**3 (60.0)**	**69 (59.5)**	**1 (33.3)**	**8 (72.7)**	**109 (44.0)**	**23 (51.1)**	**11 (68.8)**	**178 (48.9)**	**24 (50.0)**
Activated Partial Thromboplastin Time Prolonged	0	1 (0.9)	0	1 (9.1)	1 (0.4)	0	1 (6.3)	2 (0.5)	0
Alanine Aminotransferase	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Alanine Aminotransferase Increased	0	10 (8.6)	0	1 (9.1)	13 (5.2)	2 (4.4)	1 (6.3)	23 (6.3)	2 (4 2)
Ammonia Increased	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Amylase	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Amylase Increased	0	1 (0.9)	0	1 (9.1)	1 (0.4)	1 (2.2)	1 (6.3)	2 (0.5)	1 (2 1)
Anticoagulation Drug Level Above Therapeutic	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aspartate Aminotransferase Increased	0	3 (2.6)	0	1 (9.1)	16 (6.5)	0	1 (6.3)	19 (5.2)	0
Aspiration Pleural Cavity	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Atrial Pressure Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bacterial Test Positive	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2 1)
Bilirubin Conjugated Increased	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Biopsy Brain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Biopsy Skin	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Biopsy Skin Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blast Cell Count Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Albumin Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Alkaline Phosphatase Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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Blood Alkaline Phosphatase Increased	0	9 (7.8)	0	1 (9.1)	14 (5.6)	0	1 (6.3)	23 (6.3)	0
Blood Bilirubin Increased	0	8 (6.9)	0	1 (9.1)	5 (2.0)	2 (4.4)	1 (6.3)	13 (3.6)	2 (4 2)
Blood Cholesterol Increased	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Blood Creatinine Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Creatinine Increased	0	13 (11.2)	0	0	10 (4.0)	3 (6.7)	0	23 (6.3)	3 (6 3)
Blood Culture Positive	0	1 (0.9)	0	0	5 (2.0)	2 (4.4)	0	6 (1.6)	2 (4 2)
Blood Electrolytes Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Fibrinogen Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Gases Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Glucose Decreased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Blood Glucose Increased	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2 1)
Blood Immunoglobulin G Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Lactate Dehydrogenase Increased	0	4 (3.4)	0	0	4 (1.6)	2 (4.4)	0	8 (2.2)	2 (4 2)
Blood Lactic Acid Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Magnesium Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Phosphorus Increased	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Blood Potassium Decreased	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Blood Potassium Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Pressure Decreased	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Blood Pressure Increased	0	3 (2.6)	0	0	4 (1.6)	1 (2.2)	0	7 (1.9)	1 (2.1)
Blood Pressure Orthostatic	0	2 (1.7)	0	0	0	1 (2.2)	0	2 (0.5)	1 (2.1)
Blood Pressure Systolic Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Blood Sodium Decreased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Blood Sodium Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Triglycerides Increased	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Blood Urea Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Urea Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Urea Increased	0	7 (6.0)	0	0	2 (0.8)	1 (2.2)	0	9 (2.5)	1 (2.1)
Blood Uric Acid	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Blood Uric Acid Increased	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Blood Urine Present	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Body Temperature	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Body Temperature Increased	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Breath Sounds Abnormal	0	2 (1.7)	1 (33.3)	2 (18.2)	2 (0.8)	0	2 (12.5)	4 (1.1)	1 (2 1)
Carbon Dioxide Increased	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Cardiac Murmur	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Cardioactive Drug Level Decreased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Cardioactive Drug Level Increased	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Chest X-Ray Abnormal	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2.1)
Clostridium Test	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Clostridium Test Positive	0	3 (2.6)	0	0	4 (1.6)	2 (4.4)	0	7 (1.9)	2 (4 2)
Computerised Tomogram Abnormal	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Csf Protein Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Culture Urine Positive	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Cytomegalovirus Test	0	1 (0.9)	0	1 (9.1)	3 (1.2)	0	1 (6.3)	4 (1.1)	0
Cytomegalovirus Test Positive	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Drug Level Changed	2 (40.0)	1 (0.9)	0	0	1 (0.4)	0	2 (12.5)	2 (0.5)	0
Drug Level Increased	0	5 (4.3)	0	0	3 (1.2)	0	0	8 (2.2)	0
Ejection Fraction Decreased	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Electrocardiogram Abnormal	0	2 (1.7)	0	0	0	2 (4.4)	0	2 (0.5)	2 (4.2)
Electrocardiogram Change	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram Qrs Complex Prolonged	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram Qt Interval Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram Qt Prolonged	0	0	0	1 (9.1)	10 (4.0)	0	1 (6.3)	10 (2.7)	0
Electrocardiogram St Segment Abnormal	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Electrocardiogram St Segment Elevation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Electrocardiogram T Wave Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram T Wave Inversion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram T Wave Peaked	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Electroencephalogram Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Eosinophil Count Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Fundoscopy Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Fungal Test Positive	1 (20.0)	1 (0.9)	0	1 (9.1)	3 (1.2)	0	2 (12.5)	4 (1.1)	0
Gamma-Glutamyltransferase Increased	0	0	0	1 (9.1)	2 (0.8)	0	1 (6.3)	2 (0.5)	0
General Physical Condition Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Glucocorticoids Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Haemoglobin Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haemoglobin Decreased	0	3 (2.6)	0	0	1 (0.4)	2 (4.4)	0	4 (1.1)	2 (4 2)
Heart Rate Irregular	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Hepatic Enzyme Increased	0	5 (4.3)	0	0	4 (1.6)	0	0	9 (2.5)	0
Hepatitis A Antibody Positive	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hepatitis C Virus Test Positive	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Herpes Simplex Test Positive	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
International Normalised Ratio Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
International Normalised Ratio Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Laboratory Test Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lipase	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lipase Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lipase Increased	0	1 (0.9)	0	1 (9.1)	0	1 (2.2)	1 (6.3)	1 (0.3)	1 (2.1)
Liver Function Test Abnormal	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Liver Function Test Increased	0	10 (8.6)	0	1 (9.1)	6 (2.4)	1 (2.2)	1 (6.3)	16 (4.4)	1 (2.1)
Medical Observation Normal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Myocardial Necrosis Marker Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Neutrophil Count Decreased	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nutritional Condition Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Occult Blood Positive	0	2 (1.7)	0	0	1 (0.4)	2 (4.4)	0	3 (0.8)	2 (4.2)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Oxygen Saturation Decreased	0	7 (6.0)	0	0	1 (0.4)	0	0	8 (2.2)	0
Pancreatic Enzymes Increased	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Platelet Count Decreased	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Platelet Count Increased	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Prostatic Specific Antigen Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Prothrombin Level Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Prothrombin Time Prolonged	0	2 (1.7)	0	0	3 (1.2)	1 (2.2)	0	5 (1.4)	1 (2.1)
Prothrombin Time Shortened	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Pulmonary Function Test Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pupillary Light Reflex Tests Abnormal	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Qrs Axis Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Renal Scan	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Respiratory Rate Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Right Ventricular Systolic Pressure Increased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Serum Ferritin Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Spleen Palpable	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Sputum Culture Positive	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Transaminases Increased	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Troponin Increased	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Urine Output Decreased	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Viral Load Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Weight Decreased	0	6 (5.2)	1 (33.3)	2 (18.2)	17 (6.9)	0	2 (12.5)	23 (6.3)	1 (2.1)

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Weight Increased	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
White Blood Cell Count Decreased	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
White Blood Cell Count Increased	0	2 (1.7)	0	0	5 (2.0)	1 (2.2)	0	7 (1.9)	1 (2 1)
White Blood Cells Urine Positive	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
X-Ray Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Metabolism And Nutrition Disorders	**3 (60.0)**	**75 (64.7)**	**3 (100.0)**	**4 (36.4)**	**103 (41.5)**	**19 (42.2)**	**7 (43.8)**	**178 (48.9)**	**22 (45.8)**
Acidosis	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Cachexia	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Decreased Appetite	0	21 (18.1)	2 (66.7)	1 (9.1)	36 (14.5)	6 (13.3)	1 (6.3)	57 (15.7)	8 (16.7)
Dehydration	0	11 (9.5)	0	0	16 (6.5)	3 (6.7)	0	27 (7.4)	3 (6.3)
Diabetes Mellitus	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Diabetes Mellitus Inadequate Control	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Electrolyte Imbalance	0	2 (1.7)	0	1 (9.1)	3 (1.2)	0	1 (6.3)	5 (1.4)	0
Failure To Thrive	0	4 (3.4)	0	0	2 (0.8)	1 (2.2)	0	6 (1.6)	1 (2 1)
Fluid Overload	0	7 (6.0)	0	2 (18.2)	4 (1.6)	2 (4.4)	2 (12.5)	11 (3.0)	2 (4.2)
Fluid Retention	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Hypercalcaemia	0	7 (6.0)	0	0	3 (1.2)	0	0	10 (2.7)	0
Hypercholesterolaemia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Hypercreatininaemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hyperglycaemia	1 (20.0)	19 (16.4)	1 (33.3)	0	11 (4.4)	3 (6.7)	1 (6.3)	30 (8.2)	4 (8.3)
Hyperkalaemia	1 (20.0)	11 (9.5)	1 (33.3)	0	13 (5.2)	2 (4.4)	1 (6.3)	24 (6.6)	3 (6.3)

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All Randomized Subjects
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Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Hyperlipidaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypernatraemia	0	4 (3.4)	0	1 (9.1)	0	0	1 (6.3)	4 (1.1)	0
Hyperphosphataemia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Hypertriglyceridaemia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hyperuricaemia	0	4 (3.4)	0	0	3 (1.2)	0	0	7 (1.9)	0
Hypervolaemia	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Hypoalbuminaemia	0	3 (2.6)	0	0	1 (0.4)	1 (2.2)	0	4 (1.1)	1 (2.1)
Hypocalcaemia	0	14 (12.1)	0	3 (27.3)	10 (4.0)	1 (2.2)	3 (18.8)	24 (6.6)	1 (2.1)
Hypoglycaemia	0	1 (0.9)	0	0	4 (1.6)	2 (4.4)	0	5 (1.4)	2 (4 2)
Hypokalaemia	1 (20.0)	16 (13.8)	1 (33.3)	2 (18.2)	29 (11.7)	7 (15.6)	3 (18.8)	45 (12.4)	8 (16.7)
Hypomagnesaemia	1 (20.0)	10 (8.6)	0	2 (18.2)	13 (5.2)	3 (6.7)	3 (18.8)	23 (6.3)	3 (6.3)
Hyponatraemia	0	6 (5.2)	0	0	6 (2.4)	2 (4.4)	0	12 (3.3)	2 (4.2)
Hypophagia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hypophosphataemia	0	4 (3.4)	0	0	6 (2.4)	0	0	10 (2.7)	0
Hypoproteinaemia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Hypovolaemia	0	0	0	0	5 (2.0)	2 (4.4)	0	5 (1.4)	2 (4.2)
Iron Overload	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Lactic Acidosis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Malnutrition	0	3 (2.6)	0	1 (9.1)	5 (2.0)	2 (4.4)	1 (6.3)	8 (2.2)	2 (4 2)
Metabolic Acidosis	0	11 (9.5)	0	2 (18.2)	7 (2.8)	0	2 (12.5)	18 (4.9)	0
Metabolic Alkalosis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Metabolic Disorder	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0

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Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Polydipsia	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Tumour Lysis Syndrome	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Vitamin K Deficiency	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Musculoskeletal And Connective Tissue Disorders	**2 (40.0)**	**50 (43.1)**	**3 (100.0)**	**4 (36.4)**	**100 (40.3)**	**14 (31.1)**	**6 (37.5)**	**150 (41.2)**	**17 (35.4)**
Amyotrophy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Arthralgia	1 (20.0)	11 (9.5)	0	0	17 (6.9)	2 (4.4)	1 (6.3)	28 (7.7)	2 (4 2)
Arthritis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Back Pain	1 (20.0)	16 (13.8)	1 (33.3)	1 (9.1)	19 (7.7)	2 (4.4)	2 (12.5)	35 (9.6)	3 (6 3)
Bone Lesion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Bone Pain	0	4 (3.4)	0	0	8 (3.2)	0	0	12 (3.3)	0
Bursitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Chest Wall Mass	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Compartment Syndrome	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Dactylitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Fistula	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Fistula Discharge	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Flank Pain	0	3 (2.6)	0	0	7 (2.8)	0	0	10 (2.7)	0
Groin Pain	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Haemarthrosis	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Hypercreatinaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Joint Range Of Motion Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Joint Stiffness	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Joint Swelling	0	2 (1.7)	0	0	4 (1.6)	0	0	6 (1.6)	0
Mobility Decreased	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Muscle Atrophy	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Muscle Contracture	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Muscle Rigidity	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Muscle Spasms	0	2 (1.7)	0	0	12 (4.8)	1 (2.2)	0	14 (3.8)	1 (2.1)
Muscle Twitching	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Muscular Weakness	0	10 (8.6)	0	1 (9.1)	10 (4.0)	3 (6.7)	1 (6.3)	20 (5.5)	3 (6 3)
Musculoskeletal Chest Pain	0	2 (1.7)	1 (33.3)	0	4 (1.6)	1 (2.2)	0	6 (1.6)	2 (4 2)
Musculoskeletal Discomfort	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Musculoskeletal Pain	1 (20.0)	5 (4.3)	1 (33.3)	0	16 (6.5)	2 (4.4)	1 (6.3)	21 (5.8)	3 (6 3)
Musculoskeletal Stiffness	0	3 (2.6)	0	0	3 (1.2)	0	0	6 (1.6)	0
Myalgia	0	2 (1.7)	1 (33.3)	0	13 (5.2)	0	0	15 (4.1)	1 (2.1)
Myopathy	0	5 (4.3)	0	0	0	1 (2.2)	0	5 (1.4)	1 (2.1)
Myositis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Neck Pain	0	2 (1.7)	0	0	7 (2.8)	2 (4.4)	0	9 (2.5)	2 (4 2)
Nuchal Rigidity	0	0	0	0	7 (2.8)	0	0	7 (1.9)	0
Osteoarthritis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Osteonecrosis	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Pain In Extremity	0	23 (19.8)	0	3 (27.3)	22 (8.9)	5 (11.1)	3 (18.8)	45 (12.4)	5 (10.4)

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Pain In Jaw	0	0	1 (33.3)	0	2 (0.8)	0	0	2 (0.5)	1 (2.1)
Pathological Fracture	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Psoriatic Arthropathy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rhabdomyolysis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Rheumatoid Arthritis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rotator Cuff Syndrome	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Soft Tissue Mass	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Spinal Osteoarthritis	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Synovitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Systemic Lupus Erythematosus	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Tendon Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vertebral Lesion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**0**	**28 (24.1)**	**0**	**1 (9.1)**	**41 (16.5)**	**7 (15.6)**	**1 (6.3)**	**69 (19.0)**	**7 (14.6)**
Acute Lymphocytic Leukaemia Recurrent	0	0	0	1 (9.1)	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Acute Myeloid Leukaemia	0	10 (8.6)	0	0	17 (6.9)	4 (8.9)	0	27 (7.4)	4 (8.3)
Acute Myeloid Leukaemia Recurrent	0	2 (1.7)	0	0	9 (3.6)	0	0	11 (3.0)	0
Anogenital Warts	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Blast Cell Crisis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blast Crisis In Myelogenous Leukaemia	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Central Nervous System Lymphoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Chloroma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Chronic Lymphocytic Leukaemia	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Chronic Lymphocytic Leukaemia Recurrent	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Chronic Myeloid Leukaemia	0	4 (3.4)	0	0	4 (1.6)	0	0	8 (2.2)	0
Fibroadenoma Of Breast	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatic Cancer	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatic Neoplasm	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Kaposi's Sarcoma	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Leukaemia	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Leukaemia Cutis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Leukaemic Retinopathy	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Lipoma Of Breast	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Lung Neoplasm	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Lymphocytic Leukaemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Lymphoma	0	1 (0.9)	0	0	1 (0.4)	2 (4.4)	0	2 (0.5)	2 (4 2)
Metastases To Bone	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Metastases To Meninges	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Myelodysplastic Syndrome	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Neoplasm	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Neoplasm Malignant	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Non-Hodgkin's Lymphoma	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Plasma Cell Myeloma	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Respiratory Tract Neoplasm	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
T-Cell Lymphoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nervous System Disorders	**4 (80.0)**	**68 (58.6)**	**2 (66.7)**	**3 (27.3)**	**137 (55.2)**	**23 (51.1)**	**7 (43.8)**	**205 (56.3)**	**25 (52.1)**
Ageusia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Amnesia	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2.1)
Aphasia	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Arachnoiditis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Asterixis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Ataxia	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Balance Disorder	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Brain Oedema	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Brain Stem Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cauda Equina Syndrome	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Central Nervous System Inflammation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Central Nervous System Lesion	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Cerebral Atrophy	1 (20.0)	1 (0.9)	0	0	1 (0.4)	0	1 (6.3)	2 (0.5)	0
Cerebral Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Cerebral Haematoma	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cerebral Haemorrhage	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Cerebral Infarction	0	2 (1.7)	0	0	0	2 (4.4)	0	2 (0.5)	2 (4.2)
Cerebrovascular Accident	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Age
Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Choreoathetosis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Cognitive Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Coma	1 (20.0)	6 (5.2)	0	0	0	1 (2.2)	1 (6.3)	6 (1.6)	1 (2.1)
Coordination Abnormal	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2.1)
Cranial Nerve Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Demyelination	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Depressed Level Of Consciousness	0	3 (2.6)	0	0	0	2 (4.4)	0	3 (0.8)	2 (4.2)
Dizziness	0	17 (14.7)	1 (33.3)	0	26 (10.5)	4 (8.9)	0	43 (11.8)	5 (10.4)
Dizziness Postural	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dysarthria	0	2 (1.7)	0	1 (9.1)	4 (1.6)	0	1 (6.3)	6 (1.6)	0
Dysgeusia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Dyskinesia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dystonia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Embolic Stroke	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Encephalomalacia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Encephalopathy	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Facial Paralysis	0	0	0	0	1 (0.4)	2 (4.4)	0	1 (0.3)	2 (4.2)
Facial Paresis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haemorrhage Intracranial	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Haemorrhagic Cerebral Infarction	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Head Titubation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Headache	2 (40.0)	21 (18.1)	1 (33.3)	1 (9.1)	79 (31.9)	8 (17.8)	3 (18.8)	100 (27.5)	9 (18.8)

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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, Age
Number (%) of Subjects

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Hemianopia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hemianopia Homonymous	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hemiparesis	0	4 (3.4)	0	0	3 (1.2)	0	0	7 (1.9)	0
Hemiplegia	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Hyperreflexia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Hypoaesthesia	0	7 (6.0)	0	0	9 (3.6)	1 (2.2)	0	16 (4.4)	1 (2.1)
Hypokinesia	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Hyporeflexia	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2.1)
Hypotonia	0	0	0	0	2 (0.8)	2 (4.4)	0	2 (0.5)	2 (4.2)
IIIrd Nerve Paralysis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Intellectual Disability	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Intention Tremor	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Intracranial Pressure Increased	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Intraventricular Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Ischaemic Stroke	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Lethargy	0	12 (10.3)	0	1 (9.1)	6 (2.4)	0	1 (6.3)	18 (4.9)	0
Loss Of Consciousness	0	3 (2.6)	0	0	1 (0.4)	1 (2.2)	0	4 (1.1)	1 (2 1)
Memory Impairment	0	2 (1.7)	0	0	4 (1.6)	1 (2.2)	0	6 (1.6)	1 (2.1)
Mental Impairment	0	0	0	0	2 (0.8)	2 (4.4)	0	2 (0.5)	2 (4.2)
Metabolic Encephalopathy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Migraine	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Mononeuropathy Multiplex	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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All Randomized Subjects
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Number (%) of Subjects

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Motor Dysfunction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Myoclonus	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Nervous System Disorder	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2 1)
Neurological Decompensation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Neuropathy Peripheral	0	1 (0.9)	0	0	4 (1.6)	0	0	5 (1.4)	0
Nystagmus	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Occipital Neuralgia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Paraesthesia	0	6 (5.2)	0	0	12 (4.8)	1 (2.2)	0	18 (4.9)	1 (2.1)
Parkinsonism	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Peroneal Nerve Palsy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Post Herpetic Neuralgia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Postural Tremor	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Presyncope	0	0	0	0	1 (0.4)	2 (4.4)	0	1 (0.3)	2 (4.2)
Psychomotor Skills Impaired	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Restless Legs Syndrome	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Sciatica	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Sedation	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Seizure	2 (40.0)	5 (4.3)	0	1 (9.1)	9 (3.6)	0	3 (18.8)	14 (3.8)	0
Sensory Loss	0	1 (0.9)	0	1 (9.1)	3 (1.2)	1 (2.2)	1 (6.3)	4 (1.1)	1 (2 1)
Sinus Headache	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Slow Response To Stimuli	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Somnolence	0	9 (7.8)	0	0	10 (4.0)	2 (4.4)	0	19 (5.2)	2 (4.2)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Speech Disorder	0	2 (1.7)	0	0	3 (1.2)	2 (4.4)	0	5 (1.4)	2 (4 2)
Syncope	0	0	0	0	2 (0.8)	2 (4.4)	0	2 (0.5)	2 (4.2)
Tension Headache	0	0	0	0	4 (1.6)	0	0	4 (1.1)	0
Toxic Encephalopathy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Tremor	0	11 (9.5)	0	0	16 (6.5)	4 (8.9)	0	27 (7.4)	4 (8.3)
Unresponsive To Stimuli	1 (20.0)	9 (7.8)	0	1 (9.1)	2 (0.8)	2 (4.4)	2 (12.5)	11 (3.0)	2 (4.2)
Visual Field Defect	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vocal Cord Paralysis	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Product Issues	**0**	**0**	**0**	**0**	**2 (0.8)**	**0**	**0**	**2 (0.5)**	**0**
Device Occlusion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Thrombosis In Device	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Psychiatric Disorders	**1 (20.0)**	**64 (55.2)**	**1 (33.3)**	**1 (9.1)**	**75 (30.2)**	**18 (40.0)**	**2 (12.5)**	**139 (38.2)**	**19 (39.6)**
Adjustment Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aggression	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Agitation	1 (20.0)	6 (5.2)	0	0	7 (2.8)	3 (6.7)	1 (6.3)	13 (3.6)	3 (6.3)
Anxiety	1 (20.0)	16 (13.8)	0	0	24 (9.7)	8 (17.8)	1 (6.3)	40 (11.0)	8 (16.7)
Belligerence	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blunted Affect	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Confusional State	0	18 (15.5)	0	0	14 (5.6)	3 (6.7)	0	32 (8.8)	3 (6.3)
Delirium	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2.1)

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Delusion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Depressed Mood	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Depression	0	23 (19.8)	0	1 (9.1)	21 (8.5)	5 (11.1)	1 (6.3)	44 (12.1)	5 (10.4)
Disorientation	0	2 (1.7)	0	0	2 (0.8)	1 (2.2)	0	4 (1.1)	1 (2.1)
Eating Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Echolalia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Flat Affect	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Hallucination	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Hallucination, Auditory	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hallucination, Visual	0	2 (1.7)	0	0	0	1 (2.2)	0	2 (0.5)	1 (2.1)
Insomnia	0	22 (19.0)	0	0	27 (10.9)	4 (8.9)	0	49 (13.5)	4 (8.3)
Irritability	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Libido Decreased	0	0	1 (33.3)	0	1 (0.4)	0	0	1 (0.3)	1 (2.1)
Mental Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Mental Status Changes	1 (20.0)	14 (12.1)	0	1 (9.1)	11 (4.4)	5 (11.1)	2 (12.5)	25 (6.9)	5 (10.4)
Mood Altered	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Mood Swings	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Nervousness	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nightmare	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Organic Brain Syndrome	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Paranoia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Perseveration	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Posturing	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Psychomotor Retardation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Psychotic Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Restlessness	0	6 (5.2)	0	0	2 (0.8)	0	0	8 (2.2)	0
Sleep Disorder	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Staring	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Substance-Induced Psychotic Disorder	1 (20.0)	0	0	0	0	0	1 (6.3)	0	0
Tearfulness	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Renal And Urinary Disorders	**1 (20.0)**	**61 (52.6)**	**1 (33.3)**	**4 (36.4)**	**42 (16.9)**	**14 (31.1)**	**5 (31.3)**	**103 (28.3)**	**15 (31.3)**
Acute Kidney Injury	0	9 (7.8)	0	0	5 (2.0)	0	0	14 (3.8)	0
Anuria	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Azotaemia	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Bladder Pain	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Bladder Spasm	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2 1)
Choluria	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Chronic Kidney Disease	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Cystitis Haemorrhagic	1 (20.0)	2 (1.7)	0	0	2 (0.8)	1 (2.2)	1 (6.3)	4 (1.1)	1 (2 1)
Dysuria	1 (20.0)	9 (7.8)	0	0	5 (2.0)	0	1 (6.3)	14 (3.8)	0
End Stage Renal Disease	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haematuria	1 (20.0)	3 (2.6)	0	0	5 (2.0)	1 (2.2)	1 (6.3)	8 (2.2)	1 (2 1)
Hydronephrosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Incontinence	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0
Micturition Urgency	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Nephritis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nephrolithiasis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Nephropathy Toxic	0	2 (1.7)	0	1 (9.1)	2 (0.8)	0	1 (6.3)	4 (1.1)	0
Nocturia	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Oliguria	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Pollakiuria	0	4 (3.4)	1 (33.3)	0	3 (1.2)	0	0	7 (1.9)	1 (2.1)
Polyuria	0	0	0	1 (9.1)	2 (0.8)	1 (2.2)	1 (6.3)	2 (0.5)	1 (2.1)
Renal Colic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Renal Cyst	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Renal Disorder	0	1 (0.9)	0	1 (9.1)	3 (1.2)	0	1 (6.3)	4 (1.1)	0
Renal Failure	1 (20.0)	33 (28.4)	0	4 (36.4)	13 (5.2)	4 (8.9)	5 (31.3)	46 (12.6)	4 (8 3)
Renal Impairment	0	5 (4.3)	0	0	2 (0.8)	1 (2.2)	0	7 (1.9)	1 (2.1)
Renal Mass	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Renal Tubular Acidosis	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Renal Tubular Necrosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Urinary Hesitation	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Urinary Incontinence	0	3 (2.6)	0	0	0	5 (11.1)	0	3 (0.8)	5 (10.4)
Urinary Retention	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Urine Flow Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Reproductive System And Breast Disorders	**0**	**11 (9.5)**	**0**	**1 (9.1)**	**19 (7.7)**	**3 (6.7)**	**1 (6.3)**	**30 (8.2)**	**3 (6.3)**
Amenorrhoea	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Benign Prostatic Hyperplasia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Breast Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Breast Swelling	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Breast Tenderness	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Dysmenorrhoea	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Erectile Dysfunction	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Hypomenorrhoea	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Menstruation Delayed	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nipple Exudate Bloody	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Ovarian Cyst	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pelvic Fluid Collection	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Premature Menopause	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Prostatitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pruritus Genital	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Scrotal Mass	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Scrotal Oedema	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Scrotal Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Scrotal Ulcer	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Testicular Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Uterine Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Vaginal Discharge	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vaginal Haemorrhage	0	5 (4.3)	0	0	5 (2.0)	1 (2.2)	0	10 (2.7)	1 (2.1)
Vulvovaginal Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vulvovaginal Pruritus	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Respiratory, Thoracic And Mediastinal Disorders	**3 (60.0)**	**88 (75.9)**	**2 (66.7)**	**5 (45.5)**	**131 (52.8)**	**28 (62.2)**	**8 (50.0)**	**219 (60.2)**	**30 (62.5)**
Acute Respiratory Distress Syndrome	0	6 (5.2)	0	0	1 (0.4)	0	0	7 (1.9)	0
Acute Respiratory Failure	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Allergic Sinusitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Apnoea	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Asthma	0	1 (0.9)	0	0	2 (0.8)	1 (2.2)	0	3 (0.8)	1 (2 1)
Atelectasis	1 (20.0)	3 (2.6)	0	1 (9.1)	1 (0.4)	0	2 (12.5)	4 (1.1)	0
Bronchial Obstruction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bronchial Wall Thickening	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Bronchiectasis	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Bronchospasm	0	2 (1.7)	1 (33.3)	0	2 (0.8)	0	0	4 (1.1)	1 (2.1)
Cheyne-Stokes Respiration	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Chronic Obstructive Pulmonary Disease	0	0	0	0	3 (1.2)	3 (6.7)	0	3 (0.8)	3 (6.3)
Cough	0	26 (22.4)	1 (33.3)	3 (27.3)	49 (19.8)	6 (13.3)	3 (18.8)	75 (20.6)	7 (14.6)
Dysphonia	0	1 (0.9)	0	0	3 (1.2)	1 (2.2)	0	4 (1.1)	1 (2 1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Dyspnoea	1 (20.0)	30 (25.9)	2 (66.7)	2 (18.2)	54 (21.8)	10 (22.2)	3 (18.8)	84 (23.1)	12 (25.0)
Dyspnoea Exertional	0	5 (4.3)	0	0	3 (1.2)	1 (2.2)	0	8 (2.2)	1 (2 1)
Emphysema	0	1 (0.9)	0	1 (9.1)	0	0	1 (6.3)	1 (0.3)	0
Epistaxis	1 (20.0)	23 (19.8)	0	1 (9.1)	19 (7.7)	4 (8.9)	2 (12.5)	42 (11.5)	4 (8 3)
Haemoptysis	0	20 (17.2)	1 (33.3)	0	17 (6.9)	1 (2.2)	0	37 (10.2)	2 (4 2)
Haemothorax	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0
Hiccups	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Hypercapnia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypopnoea	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Hypoxia	0	11 (9.5)	0	1 (9.1)	9 (3.6)	0	1 (6.3)	20 (5.5)	0
Interstitial Lung Disease	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Lower Respiratory Tract Congestion	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lung Consolidation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lung Disorder	0	2 (1.7)	0	0	1 (0.4)	1 (2.2)	0	3 (0.8)	1 (2.1)
Lung Infiltration	0	9 (7.8)	0	0	12 (4.8)	0	0	21 (5.8)	0
Mediastinal Haematoma	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nasal Congestion	0	7 (6.0)	0	0	6 (2.4)	3 (6.7)	0	13 (3.6)	3 (6.3)
Nasal Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nasal Dryness	0	1 (0.9)	0	0	3 (1.2)	1 (2.2)	0	4 (1.1)	1 (2.1)
Nasal Obstruction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nasal Oedema	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nasal Septum Perforation	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Nasal Ulcer	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Obliterative Bronchiolitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Obstructive Airways Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Organising Pneumonia	0	3 (2.6)	0	0	0	0	0	3 (0.8)	0
Oropharyngeal Pain	0	10 (8.6)	0	2 (18.2)	16 (6.5)	4 (8.9)	2 (12.5)	26 (7.1)	4 (8.3)
Oropharyngeal Plaque	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Orthopnoea	0	1 (0.9)	0	1 (9.1)	1 (0.4)	0	1 (6.3)	2 (0.5)	0
Painful Respiration	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Paranasal Sinus Hypersecretion	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Pharyngeal Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pharyngeal Erythema	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Pharyngeal Ulceration	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pleural Effusion	0	17 (14.7)	0	1 (9.1)	17 (6.9)	2 (4.4)	1 (6.3)	34 (9.3)	2 (4.2)
Pleural Fibrosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pleuritic Pain	0	7 (6.0)	0	0	8 (3.2)	1 (2.2)	0	15 (4.1)	1 (2 1)
Pneumomediastinum	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pneumonia Aspiration	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Pneumonitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pneumothorax	1 (20.0)	2 (1.7)	0	0	3 (1.2)	0	1 (6.3)	5 (1.4)	0
Productive Cough	0	5 (4.3)	0	0	7 (2.8)	2 (4.4)	0	12 (3.3)	2 (4.2)
Pulmonary Alveolar Haemorrhage	0	2 (1.7)	0	0	1 (0.4)	0	0	3 (0.8)	0
Pulmonary Congestion	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2 1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Pulmonary Fibrosis	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Pulmonary Haemorrhage	0	4 (3.4)	0	0	3 (1.2)	0	0	7 (1.9)	0
Pulmonary Hypertension	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Pulmonary Infarction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pulmonary Mass	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Pulmonary Oedema	0	5 (4.3)	0	2 (18.2)	6 (2.4)	2 (4.4)	2 (12.5)	11 (3.0)	2 (4 2)
Rales	0	4 (3.4)	1 (33.3)	3 (27.3)	3 (1.2)	2 (4.4)	3 (18.8)	7 (1.9)	3 (6.3)
Respiratory Acidosis	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Respiratory Alkalosis	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Respiratory Arrest	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2.1)
Respiratory Disorder	0	1 (0.9)	0	1 (9.1)	0	1 (2.2)	1 (6.3)	1 (0.3)	1 (2.1)
Respiratory Distress	1 (20.0)	8 (6.9)	0	1 (9.1)	9 (3.6)	2 (4.4)	2 (12.5)	17 (4.7)	2 (4 2)
Respiratory Failure	1 (20.0)	22 (19.0)	0	2 (18.2)	18 (7.3)	1 (2.2)	3 (18.8)	40 (11.0)	1 (2 1)
Respiratory Tract Congestion	0	2 (1.7)	0	0	3 (1.2)	1 (2.2)	0	5 (1.4)	1 (2.1)
Rhinitis Allergic	0	1 (0.9)	0	0	5 (2.0)	1 (2.2)	0	6 (1.6)	1 (2.1)
Rhinorrhoea	1 (20.0)	8 (6.9)	1 (33.3)	0	8 (3.2)	1 (2.2)	1 (6.3)	16 (4.4)	2 (4.2)
Rhonchi	0	1 (0.9)	0	1 (9.1)	4 (1.6)	0	1 (6.3)	5 (1.4)	0
Sinus Congestion	0	7 (6.0)	0	0	5 (2.0)	0	0	12 (3.3)	0
Sinus Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Sneezing	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Sputum Increased	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Tachypnoea	1 (20.0)	5 (4.3)	0	2 (18.2)	9 (3.6)	1 (2.2)	3 (18.8)	14 (3.8)	1 (2 1)

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Throat Irritation	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Throat Tightness	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Upper-Airway Cough Syndrome	1 (20.0)	3 (2.6)	0	0	1 (0.4)	1 (2.2)	1 (6.3)	4 (1.1)	1 (2 1)
Vocal Cord Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Wheezing	0	5 (4.3)	1 (33.3)	2 (18.2)	8 (3.2)	3 (6.7)	2 (12.5)	13 (3.6)	4 (8.3)
Skin And Subcutaneous Tissue Disorders	**3 (60.0)**	**56 (48.3)**	**0**	**4 (36.4)**	**104 (41.9)**	**17 (37.8)**	**7 (43.8)**	**160 (44.0)**	**17 (35.4)**
Acne	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Alopecia	0	1 (0.9)	0	0	12 (4.8)	2 (4.4)	0	13 (3.6)	2 (4.2)
Blister	1 (20.0)	1 (0.9)	0	0	1 (0.4)	1 (2.2)	1 (6.3)	2 (0.5)	1 (2.1)
Blood Blister	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Cold Sweat	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cutaneous Lupus Erythematosus	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Decubitus Ulcer	0	3 (2.6)	0	0	4 (1.6)	2 (4.4)	0	7 (1.9)	2 (4 2)
Dermal Cyst	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dermatitis Allergic	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Dermatitis Atopic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Dermatosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Drug Eruption	0	0	0	1 (9.1)	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Dry Skin	0	4 (3.4)	0	1 (9.1)	6 (2.4)	1 (2.2)	1 (6.3)	10 (2.7)	1 (2 1)
Ecchymosis	0	7 (6.0)	0	0	2 (0.8)	4 (8.9)	0	9 (2.5)	4 (8.3)
Erythema	1 (20.0)	7 (6.0)	0	1 (9.1)	7 (2.8)	1 (2.2)	2 (12.5)	14 (3.8)	1 (2.1)

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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Hyperhidrosis	0	2 (1.7)	0	0	7 (2.8)	1 (2.2)	0	9 (2.5)	1 (2 1)
Ingrowing Nail	0	1 (0.9)	0	1 (9.1)	3 (1.2)	0	1 (6.3)	4 (1.1)	0
Lipodystrophy Acquired	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Livedo Reticularis	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Macule	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Miliaria	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Neutrophilic Dermatosis	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Night Sweats	0	3 (2.6)	0	0	10 (4.0)	0	0	13 (3.6)	0
Onychoclasis	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Palmar Erythema	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Petechiae	0	6 (5.2)	0	0	8 (3.2)	0	0	14 (3.8)	0
Photosensitivity Reaction	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pigmentation Disorder	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Prurigo	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pruritus	1 (20.0)	14 (12.1)	0	0	13 (5.2)	1 (2.2)	1 (6.3)	27 (7.4)	1 (2 1)
Pruritus Allergic	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pruritus Generalised	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Psoriasis	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Purpura	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rash	0	17 (14.7)	0	0	27 (10.9)	2 (4.4)	0	44 (12.1)	2 (4 2)
Rash Erythematous	0	3 (2.6)	0	0	3 (1.2)	0	0	6 (1.6)	0
Rash Generalised	0	2 (1.7)	0	0	5 (2.0)	1 (2.2)	0	7 (1.9)	1 (2 1)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Rash Macular	0	3 (2.6)	0	0	2 (0.8)	0	0	5 (1.4)	0
Rash Maculo-Papular	0	2 (1.7)	0	1 (9.1)	4 (1.6)	1 (2.2)	1 (6.3)	6 (1.6)	1 (2 1)
Rash Papular	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Rash Pruritic	0	0	0	1 (9.1)	7 (2.8)	0	1 (6.3)	7 (1.9)	0
Rash Vesicular	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Scab	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Skin Burning Sensation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Skin Discolouration	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Skin Disorder	0	3 (2.6)	0	0	1 (0.4)	0	0	4 (1.1)	0
Skin Exfoliation	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Skin Haemorrhage	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Skin Hyperpigmentation	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Skin Irritation	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Skin Lesion	1 (20.0)	7 (6.0)	0	0	10 (4.0)	1 (2.2)	1 (6.3)	17 (4.7)	1 (2.1)
Skin Mass	0	5 (4.3)	0	0	2 (0.8)	1 (2.2)	0	7 (1.9)	1 (2 1)
Skin Ulcer	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Skin Ulcer Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Stevens-Johnson Syndrome	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Subcutaneous Emphysema	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Swelling Face	0	3 (2.6)	0	0	3 (1.2)	0	0	6 (1.6)	0
Urticaria	0	2 (1.7)	0	0	7 (2.8)	0	0	9 (2.5)	0
Urticaria Papular	0	0	0	0	4 (1.6)	0	0	4 (1.1)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Social Circumstances	**0**	**0**	**0**	**0**	**0**	**1 (2.2)**	**0**	**0**	**1 (2.1)**
Treatment Noncompliance	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Surgical And Medical Procedures	**0**	**19 (16.4)**	**0**	**2 (18.2)**	**36 (14.5)**	**3 (6.7)**	**2 (12.5)**	**55 (15.1)**	**3 (6.3)**
Abdominal Cavity Drainage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Autologous Bone Marrow Transplantation Therapy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bone Marrow Transplant	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cataract Operation	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Catheter Removal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Central Venous Catheter Removal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Chemotherapy	0	0	0	0	4 (1.6)	1 (2.2)	0	4 (1.1)	1 (2.1)
Choledocholithotomy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Corneal Transplant	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Debridement	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Endotracheal Intubation	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Exploratory Operation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Laser Surgery	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Operation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Gastrostomy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Haemofiltration	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Laparotomy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Lung Lobectomy	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0
Lung Operation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lung Transplant	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Maxillofacial Operation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Medical Device Implantation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Metabolic Abnormality Management	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nail Operation	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Omentectomy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Orthopaedic Procedure	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Photopheresis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Plastic Surgery To The Face	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Pneumonectomy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Polypectomy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pulmonary Resection	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Sinus Operation	0	4 (3.4)	0	0	7 (2.8)	0	0	11 (3.0)	0
Skin Graft	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Splenectomy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Stem Cell Transplant	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Surgery	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Therapeutic Procedure	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Thoracotomy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Tooth Extraction	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Transfusion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Transplant	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Wisdom Teeth Removal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Wound Drainage	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vascular Disorders	**2 (40.0)**	**56 (48.3)**	**2 (66.7)**	**3 (27.3)**	**68 (27.4)**	**15 (33.3)**	**5 (31.3)**	**124 (34.1)**	**17 (35.4)**
Aneurysm	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Angiopathy	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Aortic Aneurysm	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Arterial Insufficiency	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Arteriosclerosis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Circulatory Collapse	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Deep Vein Thrombosis	0	4 (3.4)	0	0	1 (0.4)	1 (2.2)	0	5 (1.4)	1 (2 1)
Flushing	0	5 (4.3)	0	0	3 (1.2)	0	0	8 (2.2)	0
Haematoma	0	4 (3.4)	0	0	6 (2.4)	1 (2.2)	0	10 (2.7)	1 (2.1)
Haemodynamic Instability	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Haemorrhage	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Hot Flush	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypertension	1 (20.0)	21 (18.1)	2 (66.7)	1 (9.1)	22 (8.9)	8 (17.8)	2 (12.5)	43 (11.8)	10 (20.8)
Hypoperfusion	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypotension	1 (20.0)	28 (24.1)	0	3 (27.3)	28 (11.3)	3 (6.7)	4 (25.0)	56 (15.4)	3 (6 3)

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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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Hypovolaemic Shock	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Infarction	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Intermittent Claudication	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Ischaemia	0	2 (1.7)	0	0	1 (0.4)	1 (2.2)	0	3 (0.8)	1 (2.1)
Orthostatic Hypertension	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Orthostatic Hypotension	0	4 (3.4)	0	0	2 (0.8)	1 (2.2)	0	6 (1.6)	1 (2 1)
Pallor	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Peripheral Artery Thrombosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Peripheral Ischaemia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Peripheral Venous Disease	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Phlebitis	0	1 (0.9)	0	0	4 (1.6)	0	0	5 (1.4)	0
Poor Peripheral Circulation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Raynaud's Phenomenon	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Shock Haemorrhagic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Thrombophlebitis	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Thrombophlebitis Superficial	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Thrombosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vasodilatation	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Venous Thrombosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0

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

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付録 2.7.4-163　　年齢別の副作用の発現例数（%）（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, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Subjects Reporting Any Adverse Event	**1 (20.0)**	**36 (31.0)**	**0**	**5 (45.5)**	**103 (41.5)**	**19 (42.2)**	**6 (37.5)**	**139 (38.2)**	**19 (39.6)**
Blood And Lymphatic System Disorders	**0**	**0**	**0**	**0**	**6 (2.4)**	**2 (4.4)**	**0**	**6 (1.6)**	**2 (4.2)**
Anaemia	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Eosinophilia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pancytopenia	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Thrombocytopenia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Cardiac Disorders	**1 (20.0)**	**3 (2.6)**	**0**	**0**	**8 (3.2)**	**2 (4.4)**	**1 (6.3)**	**11 (3.0)**	**2 (4.2)**
Aortic Valve Sclerosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Arteriosclerosis Coronary Artery	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Atrial Fibrillation	0	1 (0.9)	0	0	0	2 (4.4)	0	1 (0.3)	2 (4 2)
Atrial Flutter	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Bundle Branch Block	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cardio-Respiratory Arrest	1 (20.0)	0	0	0	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Extrasystoles	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Left Ventricular Hypertrophy	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mitral Valve Stenosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Myocardial Infarction	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Supraventricular Tachycardia	0	1 (0.9)	0	0	1 (0.4)	1 (2.2)	0	2 (0.5)	1 (2 1)
Tachycardia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	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

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Ventricular Extrasystoles	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Ventricular Hypertrophy	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Ventricular Tachycardia	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Ear And Labyrinth Disorders	**0**	**1 (0.9)**	**0**	**0**	**1 (0.4)**	**0**	**0**	**2 (0.5)**	**0**
Ear Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypoacusis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Tinnitus	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Endocrine Disorders	**0**	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**1 (0.3)**	**0**
Adrenal Insufficiency	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Adrenocortical Insufficiency Acute	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypogonadism	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Disorders	**0**	**1 (0.9)**	**0**	**0**	**6 (2.4)**	**0**	**0**	**7 (1.9)**	**0**
Conjunctival Hyperaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Erythema Of Eyelid	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Irritation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eye Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Vision Blurred	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Gastrointestinal Disorders	**0**	**19 (16.4)**	**0**	**2 (18.2)**	**51 (20.6)**	**9 (20.0)**	**2 (12.5)**	**70 (19.2)**	**9 (18 8)**

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events by Risk Group, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Abdominal Discomfort	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Abdominal Distension	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Abdominal Pain	0	2 (1.7)	0	0	4 (1.6)	1 (2.2)	0	6 (1.6)	1 (2.1)
Abdominal Pain Upper	0	1 (0.9)	0	0	11 (4.4)	0	0	12 (3.3)	0
Abdominal Tenderness	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Abnormal Faeces	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Constipation	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Diarrhoea	0	3 (2.6)	0	0	12 (4.8)	0	0	15 (4.1)	0
Dry Mouth	0	0	0	0	4 (1.6)	0	0	4 (1.1)	0
Dyspepsia	0	0	0	0	1 (0.4)	2 (4.4)	0	1 (0.3)	2 (4.2)
Dysphagia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Eructation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Faeces Soft	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Flatulence	0	0	0	0	3 (1.2)	0	0	3 (0.8)	0
Gastrointestinal Haemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Gastrooesophageal Reflux Disease	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Hypoaesthesia Oral	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Ileus	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lip Dry	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Lip Swelling	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nausea	0	10 (8.6)	0	1 (9.1)	19 (7.7)	5 (11.1)	1 (6.3)	29 (8.0)	5 (10.4)
Oesophageal Ulcer	0	0	0	0	1 (0.4)	0	0	1 (0.3)	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 by Risk Group, Age
Number (%) of Subjects

	BMT			Non-BMT			Overall rIFI Pool		
	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Oral Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pancreatitis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Retching	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Vomiting	0	8 (6.9)	0	2 (18.2)	13 (5.2)	3 (6.7)	2 (12.5)	21 (5.8)	3 (6.3)
General Disorders And Administration Site Conditions	**0**	**4 (3.4)**	**0**	**0**	**13 (5.2)**	**2 (4.4)**	**0**	**17 (4.7)**	**2 (4.2)**
Asthenia	0	1 (0.9)	0	0	3 (1.2)	1 (2.2)	0	4 (1.1)	1 (2 1)
Chest Pain	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Chills	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Death	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Fatigue	0	4 (3.4)	0	0	1 (0.4)	2 (4.4)	0	5 (1.4)	2 (4.2)
Malaise	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mucosal Inflammation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Oedema Peripheral	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Pyrexia	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Hepatobiliary Disorders	**0**	**2 (1.7)**	**0**	**0**	**5 (2.0)**	**0**	**0**	**7 (1.9)**	**0**
Cholestasis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hepatic Failure	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatic Function Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatocellular Injury	0	1 (0.9)	0	0	0	0	0	1 (0.3)	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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Hepatomegaly	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatosplenomegaly	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hyperbilirubinaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Jaundice	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Immune System Disorders	**0**	**0**	**0**	**1 (9.1)**	**0**	**0**	**1 (6.3)**	**0**	**0**
Drug Hypersensitivity	0	0	0	1 (9.1)	0	0	1 (6.3)	0	0
Infections And Infestations	**0**	**0**	**0**	**0**	**3 (1.2)**	**1 (2.2)**	**0**	**3 (0.8)**	**1 (2.1)**
Conjunctivitis	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Meningitis Cryptococcal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Oesophageal Candidiasis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Injury, Poisoning And Procedural Complications	**0**	**1 (0.9)**	**0**	**0**	**2 (0.8)**	**2 (4.4)**	**0**	**3 (0.8)**	**2 (4.2)**
Excoriation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Overdose	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Toxicity To Various Agents	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Transfusion Reaction	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Investigations	**0**	**9 (7.8)**	**0**	**1 (9.1)**	**37 (14.9)**	**5 (11.1)**	**1 (6.3)**	**46 (12.6)**	**5 (10.4)**
Alanine Aminotransferase Increased	0	2 (1.7)	0	0	9 (3.6)	0	0	11 (3.0)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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Amylase	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Aspartate Aminotransferase Increased	0	1 (0.9)	0	0	8 (3.2)	0	0	9 (2.5)	0
Bilirubin Conjugated Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Alkaline Phosphatase Abnormal	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Blood Alkaline Phosphatase Increased	0	0	0	0	5 (2.0)	0	0	5 (1.4)	0
Blood Bilirubin Increased	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2 1)
Blood Creatinine Increased	0	0	0	0	2 (0.8)	3 (6.7)	0	2 (0.5)	3 (6.3)
Blood Gases Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Triglycerides Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Blood Urea Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Cardioactive Drug Level Decreased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Cardioactive Drug Level Increased	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Drug Level Changed	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Drug Level Increased	0	2 (1.7)	0	0	2 (0.8)	0	0	4 (1.1)	0
Electrocardiogram Change	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram Qrs Complex Prolonged	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Electrocardiogram Qt Prolonged	0	0	0	0	6 (2.4)	0	0	6 (1.6)	0
Gamma-Glutamyltransferase Increased	0	0	0	1 (9.1)	1 (0.4)	0	1 (6.3)	1 (0.3)	0
Glucocorticoids Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hepatic Enzyme Increased	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Laboratory Test Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lipase	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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All Randomized Subjects
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Number (%) of Subjects

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Lipase Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Liver Function Test Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Liver Function Test Increased	0	2 (1.7)	0	0	3 (1.2)	0	0	5 (1.4)	0
Pancreatic Enzymes Increased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Platelet Count Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Qrs Axis Abnormal	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Weight Decreased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Weight Increased	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Metabolism And Nutrition Disorders	**0**	**3 (2.6)**	**0**	**0**	**11 (4.4)**	**0**	**0**	**14 (3.8)**	**0**
Decreased Appetite	0	2 (1.7)	0	0	6 (2.4)	0	0	8 (2.2)	0
Electrolyte Imbalance	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hyperkalaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hyperphosphataemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hyperuricaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypokalaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Metabolic Acidosis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Polydipsia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Musculoskeletal And Connective Tissue Disorders	**0**	**4 (3.4)**	**0**	**0**	**8 (3.2)**	**0**	**0**	**12 (3.3)**	**0**
Arthralgia	0	2 (1.7)	0	0	0	0	0	2 (0.5)	0

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Back Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Bone Pain	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Fistula	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Mobility Decreased	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Muscular Weakness	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Musculoskeletal Chest Pain	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Myalgia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nuchal Rigidity	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pain In Extremity	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Pain In Jaw	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Nervous System Disorders	**1 (20.0)**	**6 (5.2)**	**0**	**0**	**25 (10.1)**	**7 (15.6)**	**1 (6.3)**	**31 (8.5)**	**7 (14.6)**
Balance Disorder	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dizziness	0	1 (0.9)	0	0	4 (1.6)	2 (4.4)	0	5 (1.4)	2 (4.2)
Dysgeusia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Headache	0	3 (2.6)	0	0	14 (5.6)	3 (6.7)	0	17 (4.7)	3 (6.3)
Hyperreflexia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Hypoaesthesia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Hypotonia	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Memory Impairment	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Mental Impairment	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Mononeuropathy Multiplex	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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	<18 n = 5	>=18-<65 n = 116	>=65 n = 3	<18 n = 11	>=18-<65 n = 248	>=65 n = 45	<18 n = 16	>=18-<65 n = 364	>=65 n = 48
Neuropathy Peripheral	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Paraesthesia	0	1 (0.9)	0	0	5 (2.0)	0	0	6 (1.6)	0
Seizure	1 (20.0)	1 (0.9)	0	0	0	0	1 (6.3)	1 (0.3)	0
Somnolence	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Speech Disorder	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Tremor	0	0	0	0	1 (0.4)	1 (2.2)	0	1 (0.3)	1 (2.1)
Psychiatric Disorders	**0**	**0**	**0**	**0**	**2 (0.8)**	**4 (8.9)**	**0**	**2 (0.5)**	**4 (8.3)**
Anxiety	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Confusional State	0	0	0	0	2 (0.8)	1 (2.2)	0	2 (0.5)	1 (2.1)
Delirium	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Mental Status Changes	0	0	0	0	0	2 (4.4)	0	0	2 (4.2)
Renal And Urinary Disorders	**0**	**2 (1.7)**	**0**	**2 (18.2)**	**5 (2.0)**	**0**	**2 (12.5)**	**7 (1.9)**	**0**
Acute Kidney Injury	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Choluria	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Chronic Kidney Disease	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nephropathy Toxic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Nocturia	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Renal Failure	0	1 (0.9)	0	2 (18.2)	0	0	2 (12.5)	1 (0.3)	0
Renal Tubular Acidosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Urinary Hesitation	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Reproductive System And Breast Disorders	**0**	**0**	**0**	**0**	**2 (0.8)**	**1 (2.2)**	**0**	**2 (0.5)**	**1 (2.1)**
Breast Swelling	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Breast Tenderness	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Hypomenorrhoea	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Menstruation Delayed	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**0**	**0**	**4 (1.6)**	**0**	**0**	**4 (1.1)**	**0**
Dyspnoea	0	0	0	0	2 (0.8)	0	0	2 (0.5)	0
Epistaxis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Lung Infiltration	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Skin And Subcutaneous Tissue Disorders	**0**	**5 (4.3)**	**0**	**1 (9.1)**	**22 (8.9)**	**1 (2.2)**	**1 (6.3)**	**27 (7.4)**	**1 (2.1)**
Alopecia	0	0	0	0	3 (1.2)	1 (2.2)	0	3 (0.8)	1 (2.1)
Dermatitis Atopic	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Dermatosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Dry Skin	0	1 (0.9)	0	0	2 (0.8)	0	0	3 (0.8)	0
Hyperhidrosis	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Pruritus	0	1 (0.9)	0	0	3 (1.2)	0	0	4 (1.1)	0
Rash	0	2 (1.7)	0	0	5 (2.0)	0	0	7 (1.9)	0
Rash Macular	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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Rash Maculo-Papular	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rash Papular	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Rash Pruritic	0	0	0	1 (9.1)	2 (0.8)	0	1 (6.3)	2 (0.5)	0
Rash Vesicular	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Urticaria	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Urticaria Papular	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0
Surgical And Medical Procedures	**0**	**0**	**0**	**0**	**0**	**1 (2.2)**	**0**	**0**	**1 (2.1)**
Therapeutic Procedure	0	0	0	0	0	1 (2.2)	0	0	1 (2.1)
Vascular Disorders	**0**	**3 (2.6)**	**0**	**0**	**2 (0.8)**	**1 (2.2)**	**0**	**5 (1.4)**	**1 (2.1)**
Haematoma	0	1 (0.9)	0	0	0	0	0	1 (0.3)	0
Hypertension	0	1 (0.9)	0	0	0	1 (2.2)	0	1 (0.3)	1 (2.1)
Hypotension	0	1 (0.9)	0	0	1 (0.4)	0	0	2 (0.5)	0
Ischaemia	0	0	0	0	1 (0.4)	0	0	1 (0.3)	0

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

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付録 2.7.4-164　　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 by Age (Years) (Incidence > 0% in Any Column)
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 events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Blood and lymphatic system disorders	**2**	**(6.7)**	**3**	**(18.8)**	**3**	**(9.7)**	**4**	**(21.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Anaemia	0	(0.0)	0	(0.0)	2	(6.5)	2	(10.5)	0	(0.0)	0	(0.0)
Eosinophilia	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	2	(6.7)	2	(12.5)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Hypochromic anaemia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Iron deficiency anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(6.7)**	**0**	**(0.0)**	**6**	**(19.4)**	**3**	**(15.8)**	**1**	**(14.3)**	**0**	**(0.0)**
Atrioventricular block first degree	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Bundle branch block right	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Cardiac failure	1	(3 3)	0	(0.0)	3	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cor pulmonale	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.3)**	**0**	**(0.0)**	**0**	**(0.0)**

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Eye disorders	**6**	**(20.0)**	**1**	**(6.3)**	**5**	**(16.1)**	**13**	**(68.4)**	**5**	**(71.4)**	**5**	**(41.7)**
Blepharitis	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Colour blindness acquired	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	1	(14.3)	3	(25.0)
Conjunctival hyperaemia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Diplopia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Dyschromatopsia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Ocular hyperaemia	1	(3 3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Ocular hypertension	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Photophobia	4	(13 3)	0	(0.0)	1	(3.2)	7	(36.8)	2	(28.6)	2	(16.7)
Vision blurred	1	(3 3)	0	(0.0)	0	(0.0)	4	(21.1)	0	(0.0)	0	(0.0)
Visual impairment	0	(0.0)	0	(0.0)	0	(0.0)	3	(15.8)	1	(14.3)	1	(8.3)
Gastrointestinal disorders	**12**	**(40.0)**	**7**	**(43.8)**	**11**	**(35.5)**	**8**	**(42.1)**	**3**	**(42.9)**	**6**	**(50.0)**
Abdominal discomfort	1	(3 3)	0	(0.0)	2	(6.5)	0	(0.0)	1	(14.3)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Cheilitis	0	(0.0)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Constipation	5	(16.7)	4	(25.0)	4	(12.9)	1	(5.3)	3	(42.9)	2	(16.7)
Dental caries	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(14.3)	0	(0.0)
Diarrhoea	1	(3 3)	1	(6.3)	4	(12.9)	1	(5.3)	0	(0.0)	3	(25.0)
Enterocolitis	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Faeces hard	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Faeces soft	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**12**	**(40.0)**	**7**	**(43.8)**	**11**	**(35.5)**	**8**	**(42.1)**	**3**	**(42.9)**	**6**	**(50.0)**
Gastrointestinal disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Gastrointestinal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Haemorrhoidal haemorrhage	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Haemorrhoids	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Hypoaesthesia oral	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Lip dry	1	(3.3)	0	(0.0)	1	(3.2)	2	(10.5)	0	(0.0)	0	(0.0)
Melaena	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	4	(13.3)	1	(6.3)	2	(6.5)	0	(0.0)	0	(0.0)	1	(8.3)
Oral discomfort	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Oral dysaesthesia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(6.7)	1	(6.3)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Trichoglossia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(3.3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	2	(16.7)
General disorders and administration site conditions	**13**	**(43.3)**	**6**	**(37.5)**	**19**	**(61.3)**	**3**	**(15.8)**	**3**	**(42.9)**	**3**	**(25.0)**
Catheter site erythema	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Chest discomfort	0	(0.0)	1	(6.3)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Chest pain	1	(3 3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	1	(3 3)	0	(0.0)	1	(3.2)	0	(0.0)	1	(14.3)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Malaise	0	(0.0)	1	(6.3)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**13**	**(43.3)**	**6**	**(37.5)**	**19**	**(61.3)**	**3**	**(15.8)**	**3**	**(42.9)**	**3**	**(25.0)**
Mucosal inflammation	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	1	(3 3)	0	(0.0)	6	(19.4)	0	(0.0)	0	(0.0)	1	(8.3)
Peripheral swelling	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	9	(30.0)	4	(25.0)	12	(38.7)	1	(5.3)	0	(0.0)	1	(8.3)
Thirst	1	(3 3)	1	(6.3)	1	(3.2)	0	(0.0)	1	(14.3)	0	(0.0)
Hepatobiliary disorders	**4**	**(13.3)**	**3**	**(18.8)**	**7**	**(22.6)**	**6**	**(31.6)**	**0**	**(0.0)**	**2**	**(16.7)**
Hepatic function abnormal	4	(13 3)	3	(18.8)	7	(22.6)	4	(21.1)	0	(0.0)	2	(16.7)
Hepatobiliary disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)	0	(0.0)
Immune system disorders	**2**	**(6.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cytokine release syndrome	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Graft versus host disease in gastrointestinal tract	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**20**	**(66.7)**	**8**	**(50.0)**	**16**	**(51.6)**	**7**	**(36.8)**	**0**	**(0.0)**	**5**	**(41.7)**
Angular cheilitis	2	(6.7)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Bacterial sepsis	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blister infected	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Bronchiolitis	0	(0.0)	1	(6.3)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**20**	**(66.7)**	**8**	**(50.0)**	**16**	**(51.6)**	**7**	**(36.8)**	**0**	**(0.0)**	**5**	**(41.7)**
Bronchitis	1	(3 3)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Bronchopulmonary aspergillosis	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Cellulitis	1	(3.3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(3 3)	1	(6.3)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Conjunctivitis bacterial	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis viral	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cytomegalovirus infection	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Device related infection	1	(3.3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Enterocolitis viral	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroenteritis bacterial	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gingivitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Infected dermal cyst	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	3	(10.0)	0	(0.0)	0	(0.0)	3	(15.8)	0	(0.0)	4	(33.3)
Oral herpes	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Osteomyelitis	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Paronychia	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Periodontitis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	2	(6.5)	1	(5.3)	0	(0.0)	0	(0.0)
Pneumonia	5	(16.7)	4	(25.0)	3	(9.7)	1	(5.3)	0	(0.0)	1	(8.3)
Pneumonia bacterial	1	(3.3)	0	(0.0)	5	(16.1)	1	(5.3)	0	(0.0)	0	(0.0)
Pneumonia fungal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)

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Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**20**	**(66.7)**	**8**	**(50.0)**	**16**	**(51.6)**	**7**	**(36.8)**	**0**	**(0.0)**	**5**	**(41.7)**
Pyelonephritis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Sepsis	1	(3.3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcal bacteraemia	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	2	(6.7)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary tract infection	1	(3.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**5**	**(16.7)**	**3**	**(18.8)**	**5**	**(16.1)**	**2**	**(10.5)**	**0**	**(0.0)**	**1**	**(8.3)**
Accidental overdose	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Allergic transfusion reaction	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Arthropod bite	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Complications of bone marrow transplant	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	1	(6.3)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Fall	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Laceration	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ligament sprain	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Limb injury	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Post procedural complication	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Postoperative fever	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin abrasion	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal compression fracture	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	1	(8.3)
Thermal burn	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)

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Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**5**	**(16.7)**	**3**	**(18.8)**	**5**	**(16.1)**	**2**	**(10.5)**	**0**	**(0.0)**	**1**	**(8.3)**
Transplantation complication	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Wound	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**11**	**(36.7)**	**6**	**(37.5)**	**13**	**(41.9)**	**7**	**(36.8)**	**2**	**(28.6)**	**6**	**(50.0)**
Alanine aminotransferase increased	5	(16.7)	0	(0.0)	4	(12.9)	1	(5.3)	0	(0.0)	1	(8.3)
Aspartate aminotransferase increased	5	(16.7)	0	(0.0)	5	(16.1)	2	(10.5)	1	(14.3)	1	(8.3)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	3	(9.7)	1	(5.3)	1	(14.3)	3	(25.0)
Blood creatinine increased	1	(3 3)	0	(0.0)	2	(6.5)	1	(5.3)	1	(14.3)	1	(8.3)
Blood glucose increased	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Blood lactate dehydrogenase increased	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Blood potassium decreased	1	(3.3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Blood pressure increased	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea decreased	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	0	(0.0)	1	(6.3)	4	(12.9)	0	(0.0)	0	(0.0)	0	(0.0)
Cytomegalovirus test positive	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Electrocardiogram QT prolonged	2	(6.7)	1	(6.3)	4	(12.9)	1	(5.3)	0	(0.0)	1	(8.3)
Electrocardiogram ST segment elevation	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Eosinophil count increased	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**11**	**(36.7)**	**6**	**(37.5)**	**13**	**(41.9)**	**7**	**(36.8)**	**2**	**(28.6)**	**6**	**(50.0)**
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(3.2)	3	(15.8)	1	(14.3)	0	(0.0)
Liver function test increased	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	1	(8.3)
Neutrophil count decreased	0	(0.0)	1	(6.3)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Platelet count decreased	2	(6.7)	3	(18.8)	0	(0.0)	1	(5.3)	0	(0.0)	1	(8.3)
Renal function test abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Weight decreased	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	1	(3.3)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Metabolism and nutrition disorders	**10**	**(33.3)**	**5**	**(31.3)**	**16**	**(51.6)**	**2**	**(10.5)**	**1**	**(14.3)**	**2**	**(16.7)**
Decreased appetite	4	(13 3)	1	(6.3)	9	(29.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Hyperkalaemia	1	(3 3)	0	(0.0)	0	(0.0)	1	(5.3)	1	(14.3)	1	(8.3)
Hyperuricaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Hypoalbuminaemia	1	(3 3)	1	(6.3)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycaemia	1	(3 3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	5	(16.7)	4	(25.0)	7	(22.6)	1	(5.3)	0	(0.0)	0	(0.0)
Hyponatraemia	1	(3 3)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**6**	**(20.0)**	**3**	**(18.8)**	**4**	**(12.9)**	**4**	**(21.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Arthralgia	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**6**	**(20.0)**	**3**	**(18.8)**	**4**	**(12.9)**	**4**	**(21.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Back pain	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Chondrocalcinosis pyrophosphate	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cytarabine syndrome	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Joint effusion	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Muscular weakness	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Osteoporosis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pain in extremity	0	(0.0)	1	(6.3)	1	(3.2)	2	(10.5)	0	(0.0)	0	(0.0)
Periarthritis	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(3.3)**	**2**	**(12.5)**	**1**	**(3.2)**	**2**	**(10.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Acute myeloid leukaemia	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cancer pain	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastric cancer	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Lung cancer metastatic	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin papilloma	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Squamous cell carcinoma of lung	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(3.3)**	**2**	**(12.5)**	**1**	**(3.2)**	**2**	**(10.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Tumour associated fever	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tumour inflammation	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**1**	**(3.3)**	**4**	**(25.0)**	**3**	**(9.7)**	**3**	**(15.8)**	**1**	**(14.3)**	**4**	**(33.3)**
Dizziness	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	1	(14.3)	1	(8.3)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Headache	0	(0.0)	2	(12.5)	1	(3.2)	0	(0.0)	0	(0.0)	1	(8.3)
Hypoaesthesia	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypogeusia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Loss of consciousness	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Neuropathy peripheral	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Parosmia	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Psychiatric disorders	**2**	**(6.7)**	**3**	**(18.8)**	**0**	**(0.0)**	**5**	**(26.3)**	**2**	**(28.6)**	**5**	**(41.7)**
Anxiety	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Delirium	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(25.0)
Hallucination	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(28.6)	1	(8.3)
Hallucination, auditory	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**2**	**(6.7)**	**3**	**(18.8)**	**0**	**(0.0)**	**5**	**(26.3)**	**2**	**(28.6)**	**5**	**(41.7)**
Insomnia	0	(0.0)	3	(18.8)	0	(0.0)	5	(26.3)	0	(0.0)	1	(8.3)
Mental disorder	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**1**	**(3.3)**	**1**	**(6.3)**	**4**	**(12.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(25.0)**
Acute kidney injury	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonic bladder	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Neurogenic bladder	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Pollakiuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Renal impairment	1	(3 3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Urethral pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Urinary incontinence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Reproductive system and breast disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(9.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Benign prostatic hyperplasia	0	(0.0)	0	(0.0)	3	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**10**	**(33.3)**	**2**	**(12.5)**	**11**	**(35.5)**	**8**	**(42.1)**	**0**	**(0.0)**	**1**	**(8.3)**
Asthma	1	(3.3)	0	(0.0)	1	(3.2)	2	(10.5)	0	(0.0)	0	(0.0)
Bronchitis chronic	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(6.3)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	3	(10.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**10**	**(33.3)**	**2**	**(12.5)**	**11**	**(35.5)**	**8**	**(42.1)**	**0**	**(0.0)**	**1**	**(8.3)**
Haemoptysis	3	(10.0)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Hypercapnia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(3 3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Laryngeal pain	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Oropharyngeal discomfort	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Oropharyngeal pain	1	(3 3)	0	(0.0)	3	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	2	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Pneumothorax spontaneous	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	1	(8.3)
Skin and subcutaneous tissue disorders	**8**	**(26.7)**	**7**	**(43.8)**	**11**	**(35.5)**	**4**	**(21.1)**	**2**	**(28.6)**	**2**	**(16.7)**
Alopecia	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Decubitus ulcer	1	(3.3)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis contact	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	1	(14.3)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	2	(6.7)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema asteatotic	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**8**	**(26.7)**	**7**	**(43.8)**	**11**	**(35.5)**	**4**	**(21.1)**	**2**	**(28.6)**	**2**	**(16.7)**
Erythema	2	(6.7)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema nodosum	2	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperhidrosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Hyperkeratosis	0	(0.0)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Ingrowing nail	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Perivascular dermatitis	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Petechiae	0	(0.0)	2	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Photosensitivity reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	1	(14.3)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Rash	2	(6.7)	2	(12.5)	2	(6.5)	1	(5.3)	1	(14.3)	0	(0.0)
Rash maculo-papular	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rash pruritic	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Skin exfoliation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Skin irritation	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**6**	**(20.0)**	**2**	**(12.5)**	**7**	**(22.6)**	**1**	**(5.3)**	**0**	**(0.0)**	**1**	**(8.3)**
Hypertension	6	(20.0)	2	(12.5)	6	(19.4)	0	(0.0)	0	(0.0)	1	(8.3)
Orthostatic hypotension	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombophlebitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	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]

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付録 2.7.4-165　　年齢別の副作用の発現例数（%）（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 by Age (Years) (Incidence > 0% in Any Column)
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 drug-related adverse events	19	(63.3)	11	(68.8)	26	(83.9)	18	(94.7)	6	(85.7)	10	(83.3)
with no drug-related adverse events	11	(36.7)	5	(31.3)	5	(16.1)	1	(5.3)	1	(14.3)	2	(16.7)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(6.5)**	**1**	**(5.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Anaemia	0	(0.0)	0	(0.0)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(6.5)**	**2**	**(10.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Bundle branch block right	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Eye disorders	**1**	**(3.3)**	**0**	**(0.0)**	**1**	**(3.2)**	**13**	**(68.4)**	**5**	**(71.4)**	**5**	**(41.7)**
Colour blindness acquired	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	1	(14.3)	3	(25.0)
Diplopia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dyschromatopsia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Photophobia	0	(0.0)	0	(0.0)	0	(0.0)	7	(36.8)	2	(28.6)	2	(16.7)
Vision blurred	1	(3 3)	0	(0.0)	0	(0.0)	4	(21.1)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**1**	**(3.3)**	**0**	**(0.0)**	**1**	**(3.2)**	**13**	**(68.4)**	**5**	**(71.4)**	**5**	**(41.7)**
Visual impairment	0	(0.0)	0	(0.0)	0	(0.0)	3	(15.8)	1	(14.3)	1	(8.3)
Gastrointestinal disorders	**2**	**(6.7)**	**1**	**(6.3)**	**6**	**(19.4)**	**3**	**(15.8)**	**1**	**(14.3)**	**3**	**(25.0)**
Abdominal discomfort	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(14.3)	0	(0.0)
Constipation	0	(0.0)	1	(6.3)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(3 3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Lip dry	0	(0.0)	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)	0	(0.0)
Nausea	2	(6.7)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	1	(8.3)
Oral discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Oral dysaesthesia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
General disorders and administration site conditions	**9**	**(30.0)**	**3**	**(18.8)**	**12**	**(38.7)**	**1**	**(5.3)**	**2**	**(28.6)**	**1**	**(8.3)**
Chest pain	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	1	(3 3)	0	(0.0)	1	(3.2)	0	(0.0)	1	(14.3)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Malaise	0	(0.0)	1	(6.3)	1	(3.2)	1	(5.3)	0	(0.0)	0	(0.0)
Oedema	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	1	(3 3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	6	(20.0)	3	(18.8)	8	(25.8)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**9**	**(30.0)**	**3**	**(18.8)**	**12**	**(38.7)**	**1**	**(5.3)**	**2**	**(28.6)**	**1**	**(8.3)**
Thirst	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**3**	**(10.0)**	**2**	**(12.5)**	**5**	**(16.1)**	**6**	**(31.6)**	**0**	**(0.0)**	**2**	**(16.7)**
Hepatic function abnormal	3	(10.0)	2	(12.5)	5	(16.1)	4	(21.1)	0	(0.0)	2	(16.7)
Hepatobiliary disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(10.5)	0	(0.0)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**2**	**(12.5)**	**2**	**(6.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cellulitis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	2	(12.5)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**6**	**(20.0)**	**2**	**(12.5)**	**7**	**(22.6)**	**4**	**(21.1)**	**2**	**(28.6)**	**4**	**(33.3)**
Alanine aminotransferase increased	4	(13.3)	0	(0.0)	3	(9.7)	1	(5.3)	0	(0.0)	1	(8.3)
Aspartate aminotransferase increased	4	(13.3)	0	(0.0)	3	(9.7)	2	(10.5)	0	(0.0)	1	(8.3)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	2	(6.5)	1	(5.3)	1	(14.3)	2	(16.7)
Blood creatinine increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Blood lactate dehydrogenase increased	1	(3.3)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Blood potassium decreased	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	0	(0.0)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**6**	**(20.0)**	**2**	**(12.5)**	**7**	**(22.6)**	**4**	**(21.1)**	**2**	**(28.6)**	**4**	**(33.3)**
Electrocardiogram QT prolonged	2	(6.7)	1	(6.3)	3	(9.7)	1	(5.3)	0	(0.0)	1	(8.3)
Electrocardiogram ST segment elevation	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	1	(3.2)	3	(15.8)	1	(14.3)	0	(0.0)
Liver function test increased	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Platelet count decreased	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**4**	**(13.3)**	**3**	**(18.8)**	**11**	**(35.5)**	**0**	**(0.0)**	**1**	**(14.3)**	**1**	**(8.3)**
Decreased appetite	2	(6.7)	1	(6.3)	6	(19.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	1	(8.3)
Hypokalaemia	2	(6.7)	3	(18.8)	5	(16.1)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**1**	**(3.3)**	**1**	**(6.3)**	**1**	**(3.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Arthralgia	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**1**	**(5.3)**	**1**	**(14.3)**	**2**	**(16.7)**
Dizziness	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	1	(8.3)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)

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Subjects With Drug-Related Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**1**	**(5.3)**	**1**	**(14.3)**	**2**	**(16.7)**
Hypogeusia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(12.5)**	**0**	**(0.0)**	**2**	**(10.5)**	**2**	**(28.6)**	**5**	**(41.7)**
Delirium	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(16.7)
Hallucination	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(28.6)	1	(8.3)
Hallucination, auditory	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Insomnia	0	(0.0)	2	(12.5)	0	(0.0)	2	(10.5)	0	(0.0)	1	(8.3)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertonic bladder	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(6.7)**	**0**	**(0.0)**	**2**	**(6.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Epistaxis	1	(3 3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**4**	**(13.3)**	**2**	**(12.5)**	**4**	**(12.9)**	**1**	**(5.3)**	**1**	**(14.3)**	**1**	**(8.3)**
Dermatitis acneiform	1	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	1	(3.3)	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	2	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Age (Years) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	< 65		65 to < 70		>= 70		< 65		65 to < 70		>= 70	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**4**	**(13.3)**	**2**	**(12.5)**	**4**	**(12.9)**	**1**	**(5.3)**	**1**	**(14.3)**	**1**	**(8.3)**
Hyperhidrosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)
Photosensitivity reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)
Rash	1	(3.3)	1	(6.3)	2	(6.5)	0	(0.0)	1	(14.3)	0	(0.0)
Rash maculo-papular	0	(0.0)	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**6**	**(20.0)**	**2**	**(12.5)**	**3**	**(9.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**
Hypertension	6	(20.0)	2	(12.5)	3	(9.7)	0	(0.0)	0	(0.0)	1	(8.3)

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]

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付録 2.7.4-166　　性別ごと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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Subjects Reporting Any Adverse Event	**240 (98.4)**	**355 (98.3)**	**222 (99.1)**	**309 (98 1)**	**26 (100.0)**	**32 (100.0)**
Blood And Lymphatic System Disorders	**153 (62.7)**	**227 (62.9)**	**139 (62.1)**	**191 (60.6)**	**18 (69.2)**	**23 (71.9)**
Anaemia	64 (26.2)	97 (26 9)	63 (28.1)	73 (23.2)	9 (34.6)	10 (31.3)
Bone Marrow Disorder	0	0	0	1 (0.3)	0	0
Bone Marrow Failure	2 (0.8)	3 (0.8)	0	0	0	0
Coagulation Factor Deficiency	1 (0.4)	0	0	0	0	0
Coagulopathy	3 (1.2)	9 (2 5)	8 (3.6)	6 (1.9)	1 (3.8)	0
Disseminated Intravascular Coagulation	0	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Eosinophilia	1 (0.4)	0	0	0	0	0
Febrile Neutropenia	52 (21.3)	66 (18 3)	41 (18.3)	44 (14.0)	12 (46.2)	11 (34.4)
Granulocytopenia	0	1 (0 3)	0	3 (1.0)	0	0
Haemolysis	2 (0.8)	3 (0.8)	2 (0.9)	2 (0.6)	0	0
Haemolytic Anaemia	0	0	0	1 (0.3)	0	0
Haemolytic Uraemic Syndrome	1 (0.4)	5 (1.4)	2 (0.9)	1 (0.3)	0	0
Haemorrhagic Diathesis	0	2 (0.6)	1 (0.4)	3 (1.0)	0	0
Haemorrhagic Disorder	0	1 (0 3)	0	0	0	0
Hypercoagulation	0	1 (0 3)	0	0	0	0
Hypofibrinogenaemia	1 (0.4)	0	0	1 (0.3)	0	1 (3.1)
Hypoglobulinaemia	1 (0.4)	0	0	1 (0.3)	0	0
Hypoprothrombinaemia	0	2 (0.6)	0	5 (1.6)	0	0
Increased Tendency To Bruise	0	0	1 (0.4)	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Iron Deficiency Anaemia	0	0	1 (0.4)	0	0	0
Leukocytosis	1 (0.4)	2 (0.6)	3 (1.3)	3 (1.0)	0	0
Leukopenia	10 (4.1)	26 (7.2)	16 (7.1)	25 (7 9)	3 (11.5)	2 (6.3)
Lymph Node Pain	1 (0.4)	2 (0.6)	0	0	1 (3.8)	0
Lymphadenitis	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Lymphadenopathy	2 (0.8)	9 (2 5)	4 (1.8)	5 (1.6)	2 (7.7)	0
Lymphopenia	0	0	0	1 (0.3)	0	1 (3.1)
Macrocytosis	0	1 (0.3)	0	1 (0.3)	0	0
Microangiopathic Haemolytic Anaemia	0	0	1 (0.4)	0	0	0
Monocytosis	0	0	1 (0.4)	0	0	0
Neutropenia	59 (24.2)	86 (23.8)	59 (26.3)	68 (21.6)	8 (30.8)	15 (46.9)
Pancytopenia	4 (1.6)	14 (3.9)	8 (3.6)	13 (4 1)	0	1 (3.1)
Polychromasia	0	0	0	1 (0.3)	0	0
Polycythaemia	0	0	0	1 (0.3)	0	0
Protein Deficiency Anaemia	0	1 (0 3)	0	0	0	0
Red Cell Fragmentation Syndrome	0	1 (0.3)	0	0	0	0
Retroperitoneal Lymphadenopathy	1 (0.4)	0	0	0	0	0
Splenomegaly	3 (1.2)	8 (2 2)	2 (0.9)	5 (1.6)	0	0
Thrombocytopenia	70 (28.7)	119 (33.0)	71 (31.7)	90 (28.6)	10 (38.5)	11 (34.4)
Thrombocytosis	0	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Thrombotic Microangiopathy	0	0	0	1 (0.3)	0	0
Thrombotic Thrombocytopenic Purpura	3 (1.2)	6 (1.7)	3 (1.3)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Cardiac Disorders	**59 (24.2)**	**85 (23 5)**	**57 (25.4)**	**82 (26.0)**	**4 (15.4)**	**10 (31.3)**
Acute Myocardial Infarction	0	3 (0.8)	0	0	0	0
Angina Pectoris	1 (0.4)	3 (0.8)	1 (0.4)	3 (1.0)	0	0
Aortic Valve Incompetence	0	1 (0 3)	1 (0.4)	0	0	0
Arrhythmia	1 (0.4)	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Arrhythmia Supraventricular	0	0	0	1 (0.3)	0	0
Arteriosclerosis Coronary Artery	1 (0.4)	0	0	0	0	0
Atrial Fibrillation	3 (1.2)	8 (2.2)	6 (2.7)	11 (3.5)	1 (3.8)	1 (3.1)
Atrial Flutter	0	3 (0.8)	0	3 (1.0)	0	0
Atrial Hypertrophy	0	1 (0 3)	0	0	0	0
Atrial Tachycardia	0	1 (0 3)	0	0	0	0
Atrioventricular Block	0	0	1 (0.4)	0	0	0
Atrioventricular Block Complete	0	1 (0.3)	0	0	0	0
Atrioventricular Block Second Degree	0	1 (0 3)	0	0	0	0
Bradycardia	2 (0.8)	8 (2 2)	5 (2.2)	3 (1.0)	1 (3.8)	1 (3.1)
Bundle Branch Block	0	0	0	1 (0.3)	0	0
Bundle Branch Block Left	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Bundle Branch Block Right	0	1 (0.3)	0	3 (1.0)	0	0
Cardiac Arrest	2 (0.8)	5 (1.4)	3 (1.3)	3 (1.0)	0	1 (3.1)
Cardiac Disorder	0	1 (0 3)	0	0	0	0
Cardiac Failure	1 (0.4)	3 (0.8)	2 (0.9)	2 (0.6)	0	0
Cardiac Failure Congestive	1 (0.4)	2 (0.6)	2 (0.9)	3 (1.0)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Cardiac Flutter	0	0	0	1 (0.3)	0	0
Cardiac Hypertrophy	1 (0.4)	1 (0 3)	0	0	0	0
Cardiac Tamponade	0	0	1 (0.4)	0	0	0
Cardio-Respiratory Arrest	1 (0.4)	2 (0.6)	3 (1.3)	3 (1.0)	0	0
Cardiomegaly	2 (0.8)	4 (1 1)	0	0	0	1 (3.1)
Cardiomyopathy	0	1 (0 3)	1 (0.4)	0	0	1 (3.1)
Cardiopulmonary Failure	0	1 (0 3)	0	0	0	0
Cardiotoxicity	0	0	0	1 (0.3)	0	0
Cardiovascular Disorder	0	0	1 (0.4)	0	0	0
Cardiovascular Insufficiency	0	3 (0.8)	2 (0.9)	0	0	0
Congestive Cardiomyopathy	0	1 (0 3)	0	0	0	0
Cor Pulmonale	0	0	0	1 (0.3)	0	0
Coronary Artery Stenosis	0	1 (0 3)	0	0	0	0
Cyanosis	0	0	1 (0.4)	0	0	0
Defect Conduction Intraventricular	0	0	0	1 (0.3)	0	0
Endocarditis Noninfective	0	0	0	1 (0.3)	0	0
Extrasystoles	0	1 (0 3)	0	4 (1.3)	0	0
Intracardiac Mass	1 (0.4)	0	0	1 (0.3)	0	0
Left Atrial Dilatation	0	1 (0 3)	0	0	0	0
Left Ventricular Dysfunction	1 (0.4)	3 (0.8)	0	5 (1.6)	0	0
Left Ventricular Hypertrophy	0	2 (0.6)	1 (0.4)	0	0	0
Mitral Valve Disease	0	1 (0 3)	0	0	0	0
Mitral Valve Incompetence	2 (0.8)	2 (0.6)	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Myocardial Infarction	0	3 (0.8)	0	0	0	0
Myocardial Ischaemia	0	2 (0.6)	0	0	0	0
Myocarditis	0	1 (0 3)	0	1 (0.3)	0	0
Palpitations	3 (1.2)	2 (0.6)	3 (1.3)	3 (1.0)	0	1 (3.1)
Pericardial Effusion	3 (1.2)	5 (1.4)	6 (2.7)	11 (3 5)	0	1 (3.1)
Pericardial Mass	0	0	0	1 (0.3)	0	0
Pericardial Rub	0	0	0	1 (0.3)	0	0
Pericarditis	1 (0.4)	1 (0 3)	1 (0.4)	0	0	0
Restrictive Cardiomyopathy	1 (0.4)	0	0	0	0	0
Right Atrial Enlargement	0	0	0	1 (0.3)	0	0
Right Ventricular Enlargement	0	0	0	1 (0.3)	0	0
Right Ventricular Hypertrophy	0	0	0	1 (0.3)	0	0
Sinus Arrhythmia	1 (0.4)	0	0	0	0	0
Sinus Bradycardia	0	1 (0.3)	1 (0.4)	0	1 (3.8)	1 (3.1)
Sinus Tachycardia	2 (0.8)	9 (2.5)	4 (1.8)	6 (1.9)	1 (3.8)	1 (3.1)
Subendocardial Ischaemia	0	0	1 (0.4)	1 (0.3)	0	0
Supraventricular Extrasystoles	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Supraventricular Tachycardia	2 (0.8)	2 (0.6)	0	3 (1.0)	0	1 (3.1)
Tachycardia	35 (14.3)	30 (8.3)	30 (13.4)	39 (12.4)	1 (3.8)	4 (12.5)
Tachycardia Paroxysmal	0	0	1 (0.4)	0	0	0
Torsade De Pointes	1 (0.4)	0	0	1 (0.3)	0	0
Tricuspid Valve Incompetence	1 (0.4)	1 (0.3)	0	0	0	0
Ventricular Dysfunction	0	0	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Ventricular Extrasystoles	3 (1.2)	6 (1.7)	0	1 (0.3)	1 (3.8)	0
Ventricular Hypertrophy	0	0	0	1 (0.3)	0	0
Ventricular Hypokinesia	0	0	1 (0.4)	0	0	0
Ventricular Tachycardia	1 (0.4)	0	1 (0.4)	0	0	0
Congenital, Familial And Genetic Disorders	**3 (1.2)**	**0**	**0**	**1 (0 3)**	**0**	**0**
Antithrombin III Deficiency	0	0	0	1 (0.3)	0	0
Chimerism	1 (0.4)	0	0	0	0	0
Epidermolysis	1 (0.4)	0	0	0	0	0
Factor II Deficiency	1 (0.4)	0	0	0	0	0
Ear And Labyrinth Disorders	**23 (9.4)**	**29 (8.0)**	**11 (4.9)**	**25 (7 9)**	**2 (7.7)**	**2 (6.3)**
Deafness	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Ear Congestion	0	0	1 (0.4)	2 (0.6)	1 (3.8)	0
Ear Discomfort	1 (0.4)	3 (0.8)	0	4 (1.3)	0	0
Ear Disorder	1 (0.4)	1 (0 3)	0	0	0	0
Ear Haemorrhage	1 (0.4)	1 (0 3)	0	1 (0.3)	0	0
Ear Pain	9 (3.7)	8 (2 2)	5 (2.2)	7 (2.2)	0	1 (3.1)
Ear Pruritus	1 (0.4)	0	0	0	1 (3.8)	0
Ear Swelling	1 (0.4)	0	0	1 (0.3)	0	0
Eustachian Tube Obstruction	0	0	0	0	0	1 (3.1)
Excessive Cerumen Production	0	1 (0 3)	0	0	0	0
Hypoacusis	5 (2.0)	3 (0.8)	0	2 (0.6)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Middle Ear Effusion	0	2 (0.6)	0	0	0	0
Otorrhoea	1 (0.4)	1 (0 3)	0	0	0	0
Sudden Hearing Loss	1 (0.4)	0	0	0	0	0
Tinnitus	1 (0.4)	4 (1 1)	1 (0.4)	2 (0.6)	0	0
Vertigo	5 (2.0)	5 (1.4)	3 (1.3)	6 (1.9)	0	0
Endocrine Disorders	**13 (5.3)**	**19 (5.3)**	**14 (6.3)**	**21 (6.7)**	**0**	**1 (3.1)**
Addison's Disease	1 (0.4)	0	0	0	0	0
Adrenal Insufficiency	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	1 (3.1)
Adrenal Mass	1 (0.4)	0	1 (0.4)	0	0	0
Adrenomegaly	0	0	1 (0.4)	0	0	0
Androgen Deficiency	0	1 (0 3)	0	0	0	0
Cushing's Syndrome	0	1 (0 3)	0	0	0	0
Cushingoid	9 (3.7)	15 (4.2)	10 (4.5)	16 (5 1)	0	0
Euthyroid Sick Syndrome	0	0	0	1 (0.3)	0	0
Goitre	1 (0.4)	0	1 (0.4)	0	0	0
Hypogonadism	0	3 (0.8)	1 (0.4)	0	0	0
Hypothyroidism	0	0	1 (0.4)	1 (0.3)	0	0
Inappropriate Antidiuretic Hormone Secretion	0	0	0	2 (0.6)	0	0
Steroid Withdrawal Syndrome	0	0	0	1 (0.3)	0	0
Thyroid Cyst	1 (0.4)	0	0	0	0	0
Eye Disorders	**54 (22.1)**	**71 (19.7)**	**72 (32.1)**	**63 (20.0)**	**4 (15.4)**	**6 (18.8)**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Abnormal Sensation In Eye	0	1 (0 3)	0	0	0	0
Blepharitis	0	0	0	0	1 (3.8)	0
Cataract	2 (0.8)	1 (0 3)	1 (0.4)	3 (1.0)	0	0
Choroiditis	0	0	0	1 (0.3)	0	0
Conjunctival Deposit	0	0	0	0	1 (3.8)	0
Conjunctival Discolouration	0	0	1 (0.4)	0	0	0
Conjunctival Disorder	0	0	0	1 (0.3)	0	0
Conjunctival Haemorrhage	3 (1.2)	5 (1.4)	9 (4.0)	5 (1.6)	1 (3.8)	0
Conjunctival Hyperaemia	2 (0.8)	0	0	0	0	0
Conjunctival Irritation	0	0	0	1 (0.3)	0	0
Conjunctival Oedema	0	1 (0 3)	1 (0.4)	0	0	0
Conjunctivitis Allergic	0	0	1 (0.4)	0	0	0
Corneal Degeneration	0	0	1 (0.4)	0	0	0
Corneal Irritation	0	0	1 (0.4)	0	0	0
Corneal Oedema	0	0	1 (0.4)	0	0	0
Diabetic Retinopathy	0	0	1 (0.4)	0	0	0
Diplopia	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Dry Eye	12 (4.9)	10 (2.8)	13 (5.8)	13 (4 1)	0	1 (3.1)
Episcleritis	0	0	1 (0.4)	0	0	0
Erythema Of Eyelid	0	2 (0.6)	0	0	0	0
Exophthalmos	0	0	1 (0.4)	0	0	0
Eye Discharge	0	1 (0 3)	1 (0.4)	2 (0.6)	0	0
Eye Disorder	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Eye Haemorrhage	1 (0.4)	2 (0.6)	5 (2.2)	2 (0.6)	0	2 (6.3)
Eye Inflammation	0	0	0	1 (0.3)	0	0
Eye Irritation	8 (3.3)	4 (1.1)	3 (1.3)	3 (1.0)	0	1 (3.1)
Eye Movement Disorder	1 (0.4)	0	0	0	0	0
Eye Oedema	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Eye Pain	3 (1.2)	6 (1.7)	6 (2.7)	5 (1.6)	1 (3.8)	0
Eye Pruritus	2 (0.8)	2 (0.6)	1 (0.4)	4 (1.3)	0	0
Eye Swelling	2 (0.8)	2 (0.6)	1 (0.4)	1 (0.3)	0	1 (3.1)
Eyelid Oedema	4 (1.6)	0	1 (0.4)	1 (0.3)	0	0
Eyelid Pain	0	0	0	0	1 (3.8)	0
Foreign Body Sensation In Eyes	1 (0.4)	1 (0.3)	0	0	1 (3.8)	0
Glaucoma	0	1 (0 3)	0	0	0	0
Halo Vision	2 (0.8)	0	0	0	0	0
Iridocyclitis	0	0	0	1 (0.3)	0	0
Iritis	0	1 (0 3)	1 (0.4)	0	0	0
Keratitis	0	1 (0.3)	0	0	0	0
Lacrimation Decreased	0	0	0	1 (0.3)	0	0
Lacrimation Increased	2 (0.8)	4 (1 1)	5 (2.2)	4 (1.3)	1 (3.8)	0
Mydriasis	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Myopia	1 (0.4)	0	0	0	0	0
Ocular Discomfort	2 (0.8)	0	3 (1.3)	0	0	0
Ocular Hyperaemia	2 (0.8)	3 (0.8)	2 (0.9)	1 (0.3)	1 (3.8)	1 (3.1)
Ophthalmoplegia	0	1 (0 3)	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Orbital Oedema	0	0	0	1 (0.3)	0	0
Periorbital Oedema	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
Photophobia	1 (0.4)	5 (1.4)	4 (1.8)	3 (1.0)	0	0
Photopsia	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Punctate Keratitis	0	0	1 (0.4)	0	0	0
Pupils Unequal	1 (0.4)	0	1 (0.4)	0	0	0
Retinal Exudates	0	1 (0 3)	0	0	0	1 (3.1)
Retinal Haemorrhage	3 (1.2)	2 (0.6)	1 (0.4)	2 (0.6)	0	1 (3.1)
Retinal Oedema	0	1 (0 3)	0	0	0	0
Retinopathy Haemorrhagic	0	0	0	1 (0.3)	0	0
Scleral Discolouration	1 (0.4)	0	0	2 (0.6)	0	0
Scleral Haemorrhage	1 (0.4)	0	1 (0.4)	0	0	0
Scleral Oedema	0	0	1 (0.4)	0	0	0
Vision Blurred	7 (2.9)	19 (5.3)	15 (6.7)	16 (5 1)	2 (7.7)	1 (3.1)
Visual Acuity Reduced	1 (0.4)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Visual Impairment	2 (0.8)	7 (1 9)	6 (2.7)	3 (1.0)	2 (7.7)	1 (3.1)
Vitreous Detachment	0	0	1 (0.4)	0	0	0
Vitreous Floaters	2 (0.8)	0	1 (0.4)	0	0	1 (3.1)
Vitreous Haemorrhage	0	1 (0 3)	1 (0.4)	0	0	0
Gastrointestinal Disorders	**205 (84.0)**	**283 (78.4)**	**193 (86.2)**	**236 (74 9)**	**26 (100.0)**	**29 (90.6)**
Abdominal Compartment Syndrome	0	0	1 (0.4)	0	0	0
Abdominal Discomfort	5 (2.0)	21 (5.8)	4 (1.8)	4 (1.3)	1 (3.8)	1 (3.1)

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Abdominal Distension	12 (4.9)	28 (7.8)	16 (7.1)	28 (8 9)	2 (7.7)	2 (6.3)
Abdominal Hernia	0	1 (0 3)	0	0	0	0
Abdominal Mass	0	0	0	1 (0.3)	0	0
Abdominal Pain	52 (21.3)	61 (16 9)	57 (25.4)	55 (17.5)	10 (38.5)	5 (15.6)
Abdominal Pain Lower	7 (2.9)	4 (1 1)	5 (2.2)	2 (0.6)	0	0
Abdominal Pain Upper	21 (8.6)	23 (6.4)	23 (10.3)	20 (6.3)	9 (34.6)	5 (15.6)
Abdominal Rigidity	0	1 (0 3)	0	3 (1.0)	0	0
Abdominal Tenderness	2 (0.8)	8 (2 2)	5 (2.2)	6 (1.9)	2 (7.7)	0
Acute Abdomen	0	1 (0.3)	0	1 (0.3)	0	0
Anal Fissure	5 (2.0)	4 (1 1)	1 (0.4)	1 (0.3)	1 (3.8)	1 (3.1)
Anal Fistula	0	0	0	0	0	1 (3.1)
Anal Haemorrhage	1 (0.4)	0	0	0	1 (3.8)	1 (3.1)
Anal Incontinence	3 (1.2)	3 (0.8)	8 (3.6)	4 (1.3)	0	0
Anal Inflammation	0	0	0	1 (0.3)	0	0
Anal Pruritus	2 (0.8)	0	0	0	0	0
Anal Ulcer	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
Anorectal Discomfort	3 (1.2)	0	1 (0.4)	0	0	0
Aphthous Ulcer	2 (0.8)	3 (0.8)	1 (0.4)	1 (0.3)	2 (7.7)	0
Aptyalism	1 (0.4)	1 (0 3)	0	0	0	0
Ascites	5 (2.0)	18 (5.0)	4 (1.8)	11 (3 5)	0	1 (3.1)
Breath Odour	1 (0.4)	0	0	0	0	0
Change Of Bowel Habit	0	1 (0 3)	0	0	0	0
Chapped Lips	2 (0.8)	1 (0 3)	3 (1.3)	1 (0.3)	1 (3.8)	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Cheilitis	0	2 (0.6)	0	1 (0.3)	0	0
Colitis	8 (3.3)	7 (1 9)	5 (2.2)	6 (1.9)	0	3 (9.4)
Colitis Ulcerative	1 (0.4)	1 (0 3)	0	0	0	0
Constipation	49 (20.1)	76 (21 1)	47 (21.0)	48 (15.2)	3 (11.5)	3 (9.4)
Crohn's Disease	0	1 (0 3)	0	0	0	0
Dental Alveolar Anomaly	0	0	0	1 (0.3)	0	0
Diarrhoea	100 (41.0)	151 (41.8)	99 (44.2)	114 (36 2)	18 (69.2)	18 (56.3)
Diarrhoea Haemorrhagic	2 (0.8)	2 (0.6)	6 (2.7)	2 (0.6)	0	0
Diverticulum	0	1 (0.3)	1 (0.4)	0	0	0
Diverticulum Intestinal	0	1 (0.3)	0	0	0	0
Dry Mouth	13 (5.3)	19 (5.3)	15 (6.7)	12 (3.8)	0	2 (6.3)
Duodenal Perforation	0	1 (0.3)	0	0	0	0
Duodenitis	1 (0.4)	4 (1.1)	1 (0.4)	1 (0.3)	1 (3.8)	0
Duodenitis Haemorrhagic	0	0	0	1 (0.3)	0	0
Dyschezia	3 (1.2)	0	0	0	0	0
Dyspepsia	20 (8.2)	31 (8.6)	25 (11.2)	25 (7.9)	2 (7.7)	3 (9.4)
Dysphagia	3 (1.2)	6 (1.7)	7 (3.1)	13 (4 1)	3 (11.5)	1 (3.1)
Enteritis	2 (0.8)	1 (0 3)	0	1 (0.3)	0	0
Enterocolitis	0	2 (0.6)	1 (0.4)	0	0	0
Epigastric Discomfort	1 (0.4)	3 (0.8)	2 (0.9)	1 (0.3)	0	0
Erosive Oesophagitis	0	1 (0 3)	0	0	0	0
Eructation	1 (0.4)	2 (0.6)	0	0	0	0
Faecal Volume Increased	0	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Faecaloma	0	0	1 (0.4)	0	0	0
Faeces Discoloured	1 (0.4)	0	0	0	0	0
Faeces Hard	0	0	0	0	0	1 (3.1)
Flatulence	5 (2.0)	13 (3.6)	12 (5.4)	16 (5 1)	2 (7.7)	0
Frequent Bowel Movements	1 (0.4)	0	1 (0.4)	0	0	0
Gastric Disorder	1 (0.4)	2 (0.6)	0	1 (0.3)	4 (15.4)	1 (3.1)
Gastric Haemorrhage	0	1 (0 3)	0	0	0	0
Gastric Ulcer	1 (0.4)	1 (0 3)	3 (1.3)	0	0	0
Gastric Ulcer Haemorrhage	0	2 (0.6)	1 (0.4)	0	0	0
Gastric Varices	0	1 (0 3)	0	0	0	0
Gastritis	10 (4.1)	14 (3.9)	8 (3.6)	13 (4 1)	0	1 (3.1)
Gastritis Erosive	0	1 (0.3)	0	1 (0.3)	0	0
Gastritis Haemorrhagic	0	1 (0 3)	0	0	0	0
Gastroenteritis Eosinophilic	0	0	0	1 (0.3)	0	0
Gastrointestinal Disorder	0	1 (0 3)	0	0	0	0
Gastrointestinal Haemorrhage	7 (2.9)	16 (4.4)	8 (3.6)	11 (3 5)	0	0
Gastrointestinal Hypomotility	0	1 (0.3)	0	0	0	0
Gastrointestinal Inflammation	0	0	1 (0.4)	0	1 (3.8)	0
Gastrointestinal Obstruction	0	1 (0.3)	0	0	0	0
Gastrointestinal Pain	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Gastrointestinal Sounds Abnormal	2 (0.8)	2 (0.6)	3 (1.3)	4 (1 3)	0	0
Gastrointestinal Ulcer Haemorrhage	1 (0.4)	1 (0 3)	0	0	0	0
Gastrooesophageal Reflux Disease	6 (2.5)	14 (3.9)	6 (2.7)	7 (2.2)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Gingival Bleeding	13 (5.3)	12 (3.3)	6 (2.7)	5 (1.6)	0	1 (3.1)
Gingival Erosion	0	0	0	0	1 (3.8)	0
Gingival Hypertrophy	1 (0.4)	0	0	1 (0.3)	0	0
Gingival Pain	2 (0.8)	0	3 (1.3)	1 (0.3)	0	0
Gingival Swelling	0	2 (0.6)	1 (0.4)	0	0	0
Gingival Ulceration	0	1 (0 3)	0	0	0	1 (3.1)
Glossitis	0	0	1 (0.4)	0	0	0
Glossodynia	2 (0.8)	2 (0.6)	1 (0.4)	0	0	0
Haematemesis	5 (2.0)	9 (2 5)	7 (3.1)	1 (0.3)	0	0
Haematochezia	6 (2.5)	11 (3.0)	4 (1.8)	5 (1.6)	0	2 (6.3)
Haemorrhoidal Haemorrhage	5 (2.0)	4 (1 1)	2 (0.9)	2 (0.6)	0	0
Haemorrhoids	19 (7.8)	19 (5.3)	16 (7.1)	16 (5 1)	5 (19.2)	6 (18.8)
Haemorrhoids Thrombosed	0	1 (0.3)	0	0	0	0
Hiatus Hernia	0	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Hyperchlorhydria	1 (0.4)	0	0	0	0	0
Hypoaesthesia Oral	3 (1.2)	0	1 (0.4)	0	0	0
Ileus	1 (0.4)	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Ileus Paralytic	0	1 (0.3)	3 (1.3)	0	0	0
Impaired Gastric Emptying	3 (1.2)	0	0	2 (0.6)	0	0
Inguinal Hernia	0	1 (0 3)	0	1 (0.3)	0	0
Intestinal Angioedema	0	0	1 (0.4)	0	0	0
Intestinal Haemorrhage	0	1 (0 3)	2 (0.9)	0	0	0
Intestinal Infarction	0	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Intestinal Ischaemia	0	1 (0 3)	0	0	0	0
Intestinal Mass	0	0	0	1 (0.3)	0	0
Intestinal Obstruction	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Intestinal Ulcer	0	2 (0.6)	0	1 (0.3)	0	0
Intra-Abdominal Fluid Collection	0	1 (0 3)	0	1 (0.3)	0	0
Intra-Abdominal Haematoma	1 (0.4)	0	0	1 (0.3)	0	0
Irritable Bowel Syndrome	0	1 (0 3)	0	0	0	0
Leukoplakia Oral	1 (0.4)	1 (0.3)	2 (0.9)	2 (0.6)	0	0
Lip Blister	0	2 (0.6)	0	0	0	0
Lip Dry	2 (0.8)	1 (0 3)	4 (1.8)	6 (1.9)	0	0
Lip Exfoliation	0	1 (0 3)	0	0	0	0
Lip Haematoma	0	0	0	1 (0.3)	0	0
Lip Haemorrhage	0	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Lip Pain	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Lip Swelling	0	1 (0.3)	0	0	0	0
Lip Ulceration	1 (0.4)	3 (0.8)	0	2 (0.6)	0	0
Loose Tooth	0	0	1 (0.4)	1 (0.3)	0	0
Lower Gastrointestinal Haemorrhage	0	1 (0 3)	0	0	0	0
Malabsorption	0	1 (0 3)	0	0	0	0
Melaena	6 (2.5)	8 (2 2)	5 (2.2)	7 (2.2)	0	1 (3.1)
Mouth Haemorrhage	6 (2.5)	11 (3.0)	1 (0.4)	3 (1.0)	2 (7.7)	0
Mouth Ulceration	5 (2.0)	17 (4.7)	9 (4.0)	7 (2.2)	3 (11.5)	1 (3.1)
Mucous Stools	0	0	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Nausea	101 (41.4)	142 (39.3)	91 (40.6)	112 (35.6)	19 (73.1)	14 (43.8)
Neutropenic Colitis	3 (1.2)	3 (0.8)	1 (0.4)	0	0	2 (6.3)
Odynophagia	2 (0.8)	5 (1.4)	3 (1.3)	0	0	1 (3.1)
Oedema Mouth	0	0	1 (0.4)	0	0	0
Oesophageal Pain	0	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Oesophageal Ulcer	1 (0.4)	1 (0 3)	0	0	0	0
Oesophagitis	1 (0.4)	10 (2.8)	3 (1.3)	3 (1.0)	0	0
Oesophagitis Ulcerative	1 (0.4)	0	0	0	0	0
Oral Discomfort	1 (0.4)	0	0	1 (0.3)	0	0
Oral Disorder	6 (2.5)	6 (1.7)	4 (1.8)	4 (1.3)	1 (3.8)	0
Oral Mucosal Blistering	1 (0.4)	4 (1.1)	0	1 (0.3)	1 (3.8)	1 (3.1)
Oral Mucosal Discolouration	0	0	0	1 (0.3)	0	0
Oral Mucosal Erythema	1 (0.4)	5 (1.4)	3 (1.3)	1 (0.3)	0	0
Oral Mucosal Exfoliation	0	1 (0.3)	1 (0.4)	0	0	0
Oral Mucosal Hypertrophy	0	0	0	1 (0.3)	0	0
Oral Pain	11 (4.5)	15 (4.2)	15 (6.7)	9 (2.9)	2 (7.7)	1 (3.1)
Palatal Disorder	0	0	0	1 (0.3)	0	0
Palatal Swelling	0	1 (0 3)	0	0	0	0
Pancreatitis	0	1 (0 3)	2 (0.9)	0	0	0
Pancreatitis Acute	0	1 (0 3)	0	0	0	0
Paraesthesia Oral	0	1 (0 3)	1 (0.4)	0	0	0
Parotid Gland Enlargement	0	0	0	1 (0.3)	1 (3.8)	0
Perianal Erythema	0	2 (0.6)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Periodontal Disease	0	1 (0 3)	0	0	0	0
Pneumoperitoneum	0	1 (0.3)	0	0	0	0
Proctalgia	6 (2.5)	3 (0.8)	8 (3.6)	9 (2.9)	0	5 (15.6)
Proctitis	1 (0.4)	1 (0.3)	1 (0.4)	0	0	1 (3.1)
Proctitis Ulcerative	0	0	1 (0.4)	0	0	0
Rectal Discharge	0	0	0	1 (0.3)	0	0
Rectal Fissure	0	1 (0 3)	0	0	0	0
Rectal Haemorrhage	4 (1.6)	11 (3.0)	3 (1.3)	4 (1.3)	1 (3.8)	1 (3.1)
Rectal Lesion	0	0	1 (0.4)	0	0	0
Rectal Prolapse	0	0	0	1 (0.3)	0	0
Rectal Tenesmus	1 (0.4)	0	0	0	0	0
Rectal Ulcer	0	0	1 (0.4)	0	0	0
Retching	2 (0.8)	4 (1 1)	3 (1.3)	2 (0.6)	0	0
Retroperitoneal Haemorrhage	1 (0.4)	1 (0 3)	0	0	0	0
Saliva Altered	1 (0.4)	0	0	1 (0.3)	0	0
Salivary Gland Calculus	0	0	0	1 (0.3)	0	0
Salivary Gland Mass	0	1 (0 3)	0	0	0	0
Salivary Gland Pain	0	0	1 (0.4)	0	0	0
Salivary Hypersecretion	1 (0.4)	0	0	2 (0.6)	1 (3.8)	0
Sensitivity Of Teeth	0	1 (0.3)	0	0	0	0
Small Intestinal Obstruction	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Small Intestinal Stenosis	0	0	1 (0.4)	0	0	0
Stomach Mass	0	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Stomatitis	6 (2.5)	12 (3.3)	6 (2.7)	3 (1.0)	3 (11.5)	3 (9.4)
Subileus	0	1 (0.3)	0	0	0	0
Swollen Tongue	0	0	1 (0.4)	0	0	0
Tongue Blistering	0	1 (0.3)	0	0	0	0
Tongue Coated	3 (1.2)	7 (1 9)	3 (1.3)	1 (0.3)	0	0
Tongue Discolouration	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Tongue Discomfort	1 (0.4)	0	0	0	0	0
Tongue Disorder	1 (0.4)	0	0	1 (0.3)	0	0
Tongue Erythema	1 (0.4)	1 (0 3)	0	1 (0.3)	0	0
Tongue Haematoma	2 (0.8)	0	0	0	0	1 (3.1)
Tongue Haemorrhage	1 (0.4)	0	0	0	0	0
Tongue Ulceration	2 (0.8)	2 (0.6)	4 (1.8)	5 (1.6)	1 (3.8)	2 (6.3)
Tooth Discolouration	1 (0.4)	0	0	0	0	0
Tooth Loss	0	0	0	2 (0.6)	0	0
Toothache	4 (1.6)	5 (1.4)	6 (2.7)	7 (2.2)	0	2 (6.3)
Trichoglossia	3 (1.2)	1 (0 3)	2 (0.9)	0	0	0
Umbilical Hernia	1 (0.4)	0	0	0	0	0
Upper Gastrointestinal Haemorrhage	3 (1.2)	1 (0 3)	0	0	0	0
Uvulitis	0	1 (0.3)	0	0	0	0
Vomiting	86 (35.2)	92 (25 5)	84 (37.5)	91 (28.9)	11 (42.3)	13 (40.6)
General Disorders And Administration Site Conditions	**192 (78.7)**	**274 (75.9)**	**182 (81.3)**	**231 (73 3)**	**24 (92.3)**	**31 (96.9)**
Adverse Drug Reaction	0	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Application Site Burn	0	1 (0.3)	0	0	0	0
Application Site Discomfort	0	1 (0 3)	0	0	0	0
Asthenia	20 (8.2)	40 (11 1)	29 (12.9)	31 (9.8)	0	3 (9.4)
Atrophy	0	0	0	1 (0.3)	0	0
Axillary Pain	0	0	0	1 (0.3)	0	0
Catheter Site Bruise	0	1 (0.3)	3 (1.3)	0	0	0
Catheter Site Discharge	0	3 (0.8)	0	0	1 (3.8)	0
Catheter Site Erosion	0	0	0	1 (0.3)	0	0
Catheter Site Erythema	12 (4.9)	27 (7.5)	16 (7.1)	16 (5 1)	6 (23.1)	5 (15.6)
Catheter Site Haematoma	1 (0.4)	2 (0.6)	4 (1.8)	1 (0.3)	0	0
Catheter Site Haemorrhage	7 (2.9)	8 (2.2)	3 (1.3)	3 (1.0)	0	1 (3.1)
Catheter Site Inflammation	4 (1.6)	4 (1.1)	1 (0.4)	2 (0.6)	3 (11.5)	4 (12.5)
Catheter Site Oedema	0	0	0	2 (0.6)	0	0
Catheter Site Pain	21 (8.6)	12 (3.3)	22 (9.8)	11 (3 5)	1 (3.8)	2 (6.3)
Catheter Site Phlebitis	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Catheter Site Pruritus	0	3 (0.8)	0	1 (0.3)	0	1 (3.1)
Catheter Site Rash	1 (0.4)	0	0	0	0	0
Catheter Site Related Reaction	1 (0.4)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Catheter Site Swelling	2 (0.8)	1 (0.3)	1 (0.4)	0	0	0
Chest Discomfort	4 (1.6)	4 (1.1)	4 (1.8)	2 (0.6)	1 (3.8)	2 (6.3)
Chest Pain	20 (8.2)	32 (8.9)	19 (8.5)	16 (5 1)	2 (7.7)	1 (3.1)
Chills	45 (18.4)	72 (19 9)	37 (16.5)	44 (14.0)	8 (30.8)	9 (28.1)
Complication Associated With Device	3 (1.2)	1 (0 3)	3 (1.3)	3 (1.0)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Crepitations	1 (0.4)	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Death	0	0	1 (0.4)	0	0	0
Device Related Thrombosis	1 (0.4)	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Disease Progression	1 (0.4)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Drug Interaction	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Drug Intolerance	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Drug Withdrawal Syndrome	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Early Satiety	0	0	0	3 (1.0)	0	0
Effusion	1 (0.4)	0	0	0	0	0
Exercise Tolerance Decreased	0	2 (0.6)	0	1 (0.3)	0	0
Face Oedema	3 (1.2)	3 (0.8)	6 (2.7)	2 (0.6)	0	0
Facial Pain	2 (0.8)	1 (0 3)	3 (1.3)	2 (0.6)	0	0
Fatigue	38 (15.6)	66 (18 3)	47 (21.0)	56 (17.8)	1 (3.8)	2 (6.3)
Feeling Cold	2 (0.8)	2 (0.6)	4 (1.8)	4 (1.3)	0	0
Feeling Hot	0	1 (0 3)	0	0	0	0
Feeling Jittery	2 (0.8)	2 (0.6)	2 (0.9)	0	0	0
Gait Disturbance	3 (1.2)	6 (1.7)	6 (2.7)	5 (1.6)	0	0
Gait Inability	0	0	0	1 (0.3)	0	0
General Physical Health Deterioration	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
General Symptom	1 (0.4)	0	0	0	0	0
Generalised Oedema	7 (2.9)	8 (2 2)	10 (4.5)	9 (2.9)	0	1 (3.1)
Granuloma	1 (0.4)	2 (0.6)	0	0	0	0
Gravitational Oedema	0	0	0	1 (0.3)	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hyperpyrexia	0	0	0	0	0	1 (3.1)
Hyperthermia	1 (0.4)	3 (0.8)	0	1 (0.3)	2 (7.7)	1 (3.1)
Hypothermia	1 (0.4)	1 (0 3)	1 (0.4)	3 (1.0)	0	0
Impaired Healing	0	1 (0 3)	0	1 (0.3)	0	0
Induration	0	2 (0.6)	0	1 (0.3)	0	0
Inflammation	1 (0.4)	1 (0 3)	0	0	0	0
Influenza Like Illness	1 (0.4)	1 (0.3)	0	2 (0.6)	0	0
Infusion Site Erythema	0	0	1 (0.4)	0	0	0
Infusion Site Extravasation	0	0	2 (0.9)	0	0	0
Infusion Site Haemorrhage	1 (0.4)	0	0	0	0	0
Infusion Site Inflammation	1 (0.4)	0	0	0	0	0
Infusion Site Pain	1 (0.4)	5 (1.4)	0	0	0	0
Infusion Site Swelling	0	0	0	1 (0.3)	0	0
Infusion Site Vesicles	0	1 (0 3)	0	0	0	0
Injection Site Haemorrhage	0	0	0	1 (0.3)	0	0
Injection Site Inflammation	0	0	0	1 (0.3)	0	0
Injection Site Irritation	0	1 (0.3)	2 (0.9)	0	0	0
Injection Site Nodule	0	0	0	1 (0.3)	0	0
Injection Site Pain	0	0	1 (0.4)	0	0	0
Injection Site Reaction	0	0	0	1 (0.3)	0	0
Injection Site Vesicles	0	0	0	0	1 (3.8)	0
Localised Oedema	0	2 (0.6)	2 (0.9)	0	0	1 (3.1)
Malaise	5 (2.0)	10 (2.8)	7 (3.1)	3 (1.0)	0	2 (6.3)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Mass	0	2 (0.6)	0	0	0	0
Mucosa Vesicle	0	1 (0.3)	0	1 (0.3)	0	0
Mucosal Haemorrhage	1 (0.4)	0	0	2 (0.6)	0	0
Mucosal Hyperaemia	0	1 (0.3)	0	0	0	0
Mucosal Inflammation	50 (20.5)	49 (13.6)	30 (13.4)	35 (11.1)	6 (23.1)	8 (25.0)
Mucous Membrane Disorder	0	1 (0 3)	0	0	0	0
Multi-Organ Disorder	1 (0.4)	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	5 (2.0)	10 (2.8)	3 (1.3)	6 (1.9)	2 (7.7)	0
Necrosis	0	3 (0.8)	0	0	0	0
Nodule	1 (0.4)	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Non-Cardiac Chest Pain	0	0	0	0	0	1 (3.1)
Obstruction	0	1 (0.3)	0	0	3 (11.5)	0
Oedema	16 (6.6)	23 (6.4)	23 (10.3)	25 (7.9)	1 (3.8)	3 (9.4)
Oedema Mucosal	0	0	0	1 (0.3)	0	0
Oedema Peripheral	33 (13.5)	63 (17 5)	33 (14.7)	46 (14.6)	4 (15.4)	8 (25.0)
Pain	15 (6.1)	27 (7.5)	16 (7.1)	10 (3 2)	2 (7.7)	3 (9.4)
Paradoxical Drug Reaction	0	0	1 (0.4)	0	0	0
Performance Status Decreased	2 (0.8)	0	0	0	0	0
Peripheral Swelling	6 (2.5)	10 (2.8)	8 (3.6)	4 (1.3)	1 (3.8)	0
Puncture Site Pain	1 (0.4)	2 (0.6)	0	0	0	0
Puncture Site Reaction	1 (0.4)	2 (0.6)	0	0	0	0
Pyrexia	117 (48.0)	149 (41.3)	103 (46.0)	148 (47.0)	13 (50.0)	18 (56.3)
Secretion Discharge	0	1 (0 3)	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Sudden Death	0	0	0	1 (0.3)	0	0
Swelling	0	1 (0 3)	1 (0.4)	0	0	0
Tenderness	0	2 (0.6)	0	0	0	0
Therapeutic Product Ineffective	0	0	1 (0.4)	0	0	0
Therapy Non-Responder	0	4 (1 1)	2 (0.9)	1 (0.3)	0	0
Thirst	1 (0.4)	4 (1 1)	2 (0.9)	2 (0.6)	0	0
Ulcer	1 (0.4)	1 (0 3)	0	0	0	0
Ulcer Haemorrhage	0	0	0	1 (0.3)	0	0
Vessel Puncture Site Inflammation	0	0	0	1 (0.3)	0	0
Vessel Puncture Site Pain	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Xerosis	1 (0.4)	0	0	0	0	0
Hepatobiliary Disorders	**38 (15.6)**	**58 (16 1)**	**34 (15.2)**	**43 (13.7)**	**5 (19.2)**	**7 (21.9)**
Acute Hepatic Failure	0	1 (0.3)	0	0	0	0
Cholecystitis	0	1 (0 3)	1 (0.4)	1 (0.3)	1 (3.8)	0
Cholecystitis Acute	0	0	0	0	0	1 (3.1)
Cholelithiasis	2 (0.8)	5 (1.4)	3 (1.3)	4 (1.3)	2 (7.7)	0
Cholestasis	2 (0.8)	3 (0.8)	0	2 (0.6)	0	0
Drug-Induced Liver Injury	0	0	0	1 (0.3)	0	0
Gallbladder Enlargement	0	0	1 (0.4)	0	0	0
Gallbladder Polyp	0	2 (0.6)	0	0	0	0
Hepatic Cyst	2 (0.8)	0	1 (0.4)	1 (0.3)	0	0
Hepatic Failure	3 (1.2)	5 (1.4)	1 (0.4)	3 (1.0)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hepatic Function Abnormal	1 (0.4)	2 (0.6)	3 (1.3)	5 (1.6)	0	0
Hepatic Lesion	3 (1.2)	1 (0 3)	0	0	0	0
Hepatic Necrosis	0	1 (0 3)	0	0	0	0
Hepatic Steatosis	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Hepatitis	0	1 (0.3)	2 (0.9)	1 (0 3)	0	0
Hepatitis Acute	0	1 (0.3)	0	0	0	0
Hepatocellular Injury	1 (0.4)	2 (0.6)	0	0	0	0
Hepatomegaly	4 (1.6)	6 (1.7)	3 (1.3)	2 (0.6)	0	1 (3.1)
Hepatosplenomegaly	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Hepatotoxicity	3 (1.2)	1 (0 3)	4 (1.8)	0	0	0
Hyperbilirubinaemia	12 (4.9)	16 (4.4)	9 (4.0)	17 (5.4)	3 (11.5)	5 (15.6)
Hypertransaminasaemia	0	1 (0.3)	0	1 (0.3)	0	0
Jaundice	9 (3.7)	18 (5.0)	11 (4.9)	13 (4 1)	0	1 (3.1)
Jaundice Cholestatic	0	1 (0 3)	0	0	0	0
Liver Disorder	0	1 (0.3)	2 (0.9)	0	0	0
Liver Injury	0	2 (0.6)	0	0	0	0
Ocular Icterus	3 (1.2)	8 (2.2)	1 (0.4)	2 (0.6)	0	0
Perihepatic Discomfort	0	1 (0.3)	0	0	0	0
Portal Hypertension	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Portal Vein Thrombosis	1 (0.4)	0	1 (0.4)	0	0	0
Venoocclusive Liver Disease	0	0	1 (0.4)	0	0	0
Immune System Disorders	**33 (13.5)**	**78 (21.6)**	**37 (16.5)**	**74 (23.5)**	**1 (3.8)**	**2 (6.3)**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Acute Graft Versus Host Disease In Liver	0	0	1 (0.4)	0	0	0
Acute Graft Versus Host Disease In Skin	0	0	1 (0.4)	0	0	0
Anaphylactic Reaction	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Chronic Graft Versus Host Disease	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Contrast Media Allergy	0	1 (0 3)	0	0	0	0
Drug Hypersensitivity	5 (2.0)	9 (2 5)	5 (2.2)	2 (0.6)	1 (3.8)	2 (6.3)
Graft Versus Host Disease	17 (7.0)	44 (12 2)	19 (8.5)	36 (11.4)	0	0
Graft Versus Host Disease In Gastrointestinal Tract	6 (2.5)	21 (5.8)	4 (1.8)	17 (5.4)	0	0
Graft Versus Host Disease In Liver	3 (1.2)	11 (3.0)	3 (1.3)	7 (2 2)	0	0
Graft Versus Host Disease In Lung	0	0	1 (0.4)	4 (1.3)	0	0
Graft Versus Host Disease In Skin	7 (2.9)	18 (5.0)	6 (2.7)	21 (6.7)	0	0
Hypersensitivity	1 (0.4)	0	0	5 (1.6)	0	0
Hypogammaglobulinaemia	1 (0.4)	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Immune System Disorder	0	0	1 (0.4)	0	0	0
Sarcoidosis	1 (0.4)	0	0	0	0	0
Seasonal Allergy	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Transplant Rejection	1 (0.4)	2 (0.6)	0	0	0	0
Infections And Infestations	**170 (69.7)**	**267 (74.0)**	**178 (79.5)**	**236 (74 9)**	**23 (88.5)**	**28 (87.5)**
Abscess Fungal	0	0	1 (0.4)	0	0	0
Abscess Jaw	0	0	1 (0.4)	0	0	0
Abscess Limb	0	1 (0 3)	0	3 (1.0)	0	0
Abscess Neck	1 (0.4)	0	0	1 (0.3)	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Acarodermatitis	1 (0.4)	0	1 (0.4)	0	0	0
Acid Fast Bacilli Infection	1 (0.4)	0	0	0	0	0
Acinetobacter Bacteraemia	0	0	1 (0.4)	0	0	0
Acinetobacter Infection	0	0	3 (1.3)	1 (0.3)	0	0
Acute Sinusitis	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Adenovirus Infection	0	0	2 (0.9)	1 (0.3)	0	0
Alpha Haemolytic Streptococcal Infection	0	1 (0 3)	2 (0.9)	3 (1.0)	0	0
Amoebic Dysentery	1 (0.4)	0	0	0	0	0
Anal Abscess	1 (0.4)	4 (1 1)	2 (0.9)	3 (1.0)	0	0
Anal Infection	0	0	1 (0.4)	0	0	0
Angular Cheilitis	0	0	0	1 (0.3)	0	0
Anorectal Cellulitis	0	0	0	1 (0.3)	0	0
Anorectal Infection	0	1 (0 3)	0	0	0	1 (3.1)
Aspergilloma	0	0	0	1 (0.3)	0	0
Aspergillus Infection	3 (1.2)	2 (0.6)	6 (2.7)	8 (2 5)	0	1 (3.1)
Atypical Pneumonia	0	1 (0.3)	0	0	0	0
Bacillus Bacteraemia	0	1 (0 3)	0	0	0	0
Bacillus Infection	0	1 (0.3)	0	0	0	0
Bacteraemia	26 (10.7)	30 (8.3)	17 (7.6)	28 (8 9)	4 (15.4)	4 (12.5)
Bacterial Disease Carrier	1 (0.4)	1 (0.3)	1 (0.4)	0	0	0
Bacterial Infection	7 (2.9)	7 (1.9)	4 (1.8)	8 (2.5)	1 (3.8)	0
Bacterial Sepsis	2 (0.8)	3 (0.8)	2 (0.9)	3 (1.0)	0	1 (3.1)
Bacteriuria	0	0	0	1 (0.3)	0	0

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Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Bartholin's Abscess	1 (0.4)	0	0	0	0	0
Bartholinitis	1 (0.4)	0	0	0	0	0
Bk Virus Infection	0	1 (0.3)	0	0	0	0
Body Tinea	0	0	1 (0.4)	1 (0.3)	0	0
Bronchiolitis	2 (0.8)	2 (0.6)	0	0	0	0
Bronchitis	5 (2.0)	9 (2 5)	3 (1.3)	7 (2.2)	0	0
Bronchopulmonary Aspergillosis	3 (1.2)	0	7 (3.1)	2 (0.6)	2 (7.7)	0
Campylobacter Infection	0	1 (0 3)	0	0	0	0
Candida Infection	5 (2.0)	4 (1 1)	5 (2.2)	4 (1.3)	1 (3.8)	0
Candida Sepsis	0	1 (0 3)	0	0	0	0
Catheter Site Cellulitis	2 (0.8)	2 (0.6)	2 (0.9)	1 (0.3)	1 (3.8)	0
Catheter Site Infection	5 (2.0)	5 (1.4)	2 (0.9)	7 (2.2)	0	1 (3.1)
Cavernous Sinus Thrombosis	0	0	1 (0.4)	0	0	0
Cellulitis	4 (1.6)	11 (3.0)	5 (2.2)	12 (3.8)	1 (3.8)	0
Cellulitis Staphylococcal	0	1 (0.3)	0	0	0	0
Cerebral Fungal Infection	0	0	1 (0.4)	0	0	0
Cerebral Toxoplasmosis	1 (0.4)	0	0	2 (0.6)	0	0
Chlamydial Infection	0	0	1 (0.4)	0	0	0
Chronic Sinusitis	0	1 (0 3)	0	1 (0.3)	0	0
Citrobacter Infection	0	1 (0 3)	0	0	0	0
Clostridial Infection	1 (0.4)	4 (1.1)	0	0	0	0
Clostridium Bacteraemia	0	0	0	1 (0.3)	0	0
Clostridium Colitis	1 (0.4)	0	0	0	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Clostridium Difficile Colitis	2 (0.8)	6 (1.7)	2 (0.9)	8 (2 5)	0	1 (3.1)
Clostridium Difficile Infection	3 (1.2)	6 (1.7)	4 (1.8)	3 (1.0)	0	1 (3.1)
Conjunctivitis	10 (4.1)	13 (3.6)	10 (4.5)	12 (3.8)	0	0
Corynebacterium Bacteraemia	0	1 (0 3)	0	3 (1.0)	0	0
Corynebacterium Infection	0	0	1 (0.4)	2 (0.6)	0	0
Corynebacterium Sepsis	0	2 (0.6)	0	0	0	1 (3.1)
Cystitis	5 (2.0)	5 (1.4)	2 (0.9)	2 (0.6)	0	0
Cystitis Escherichia	0	0	1 (0.4)	0	0	0
Cystitis Klebsiella	0	1 (0.3)	0	0	0	0
Cytomegalovirus Colitis	1 (0.4)	4 (1.1)	0	2 (0.6)	0	0
Cytomegalovirus Enteritis	0	1 (0.3)	0	0	0	0
Cytomegalovirus Enterocolitis	0	0	1 (0.4)	0	0	0
Cytomegalovirus Gastritis	1 (0.4)	0	1 (0.4)	0	0	0
Cytomegalovirus Gastroenteritis	0	1 (0 3)	0	2 (0.6)	0	0
Cytomegalovirus Hepatitis	0	0	0	2 (0.6)	0	0
Cytomegalovirus Infection	17 (7.0)	23 (6.4)	16 (7.1)	13 (4 1)	0	0
Cytomegalovirus Viraemia	3 (1.2)	9 (2 5)	3 (1.3)	4 (1.3)	0	0
Device Related Infection	13 (5.3)	16 (4.4)	12 (5.4)	21 (6.7)	2 (7.7)	1 (3.1)
Device Related Sepsis	2 (0.8)	2 (0.6)	2 (0.9)	1 (0.3)	1 (3.8)	0
Ear Infection	1 (0.4)	3 (0.8)	0	1 (0.3)	0	0
Emphysematous Cystitis	1 (0.4)	0	0	0	0	0
Encephalitis	0	2 (0.6)	0	1 (0.3)	0	0
Encephalitis Viral	0	0	1 (0.4)	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	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Enterobacter Bacteraemia	2 (0.8)	2 (0.6)	1 (0.4)	0	0	0
Enterobacter Infection	3 (1.2)	1 (0.3)	0	3 (1.0)	0	0
Enterobacter Sepsis	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Enterococcal Bacteraemia	3 (1.2)	5 (1.4)	0	3 (1.0)	0	3 (9.4)
Enterococcal Infection	2 (0.8)	1 (0.3)	4 (1.8)	6 (1.9)	0	0
Enterococcal Sepsis	0	0	1 (0.4)	1 (0.3)	0	0
Enterovirus Infection	1 (0.4)	0	1 (0.4)	0	0	0
Epididymitis	0	1 (0 3)	0	1 (0.3)	0	0
Epiglottitis	1 (0.4)	0	0	0	0	0
Epstein-Barr Virus Infection	0	4 (1.1)	0	4 (1.3)	0	0
Erysipelas	0	0	1 (0.4)	0	0	1 (3.1)
Escherichia Bacteraemia	5 (2.0)	6 (1.7)	3 (1.3)	2 (0.6)	0	0
Escherichia Infection	2 (0.8)	0	1 (0.4)	1 (0.3)	0	1 (3.1)
Escherichia Sepsis	1 (0.4)	1 (0.3)	2 (0.9)	0	0	0
Escherichia Urinary Tract Infection	2 (0.8)	1 (0.3)	2 (0.9)	0	0	0
Eye Infection	0	2 (0.6)	0	0	0	1 (3.1)
Eye Infection Staphylococcal	0	0	0	1 (0.3)	0	0
Eyelid Infection	0	0	1 (0.4)	0	0	0
Febrile Infection	0	0	0	1 (0.3)	0	0
Folliculitis	5 (2.0)	6 (1.7)	3 (1.3)	10 (3 2)	1 (3.8)	2 (6.3)
Fungaemia	0	0	1 (0.4)	0	0	0
Fungal Infection	5 (2.0)	8 (2.2)	7 (3.1)	10 (3 2)	1 (3.8)	2 (6.3)
Fungal Oesophagitis	0	1 (0 3)	0	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Fungal Rhinitis	0	0	0	1 (0.3)	0	0
Fungal Sepsis	1 (0.4)	0	0	1 (0.3)	0	0
Fungal Skin Infection	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Furuncle	0	0	0	1 (0.3)	0	0
Fusobacterium Infection	0	1 (0.3)	1 (0.4)	0	0	0
Gangrene	0	0	0	2 (0.6)	0	0
Gastroenteritis	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Gastroenteritis Cryptosporidial	0	1 (0 3)	0	0	0	0
Gastroenteritis Pseudomonas	0	1 (0.3)	0	0	0	0
Gastroenteritis Rotavirus	1 (0.4)	0	0	1 (0.3)	0	0
Gastroenteritis Viral	1 (0.4)	0	0	2 (0.6)	0	0
Gastrointestinal Candidiasis	0	0	1 (0.4)	0	0	0
Gastrointestinal Infection	1 (0.4)	0	0	0	0	0
Genital Herpes	3 (1.2)	2 (0.6)	0	1 (0.3)	0	0
Genital Herpes Simplex	1 (0.4)	0	1 (0.4)	0	0	0
Genital Infection Bacterial	0	1 (0.3)	0	0	0	0
Giardiasis	1 (0.4)	0	0	0	0	0
Gingivitis	2 (0.8)	2 (0.6)	3 (1.3)	3 (1.0)	1 (3.8)	0
Haemophilus Infection	0	2 (0.6)	0	2 (0.6)	0	0
Hepatitis B	0	1 (0.3)	0	0	0	0
Herpes Dermatitis	1 (0.4)	0	1 (0.4)	0	0	0
Herpes Oesophagitis	0	0	1 (0.4)	0	1 (3.8)	0
Herpes Pharyngitis	0	0	1 (0.4)	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Herpes Simplex	6 (2.5)	8 (2 2)	8 (3.6)	8 (2.5)	0	0
Herpes Virus Infection	4 (1.6)	12 (3.3)	4 (1.8)	4 (1.3)	1 (3.8)	2 (6.3)
Herpes Zoster	6 (2.5)	15 (4.2)	2 (0.9)	8 (2.5)	1 (3.8)	0
Herpes Zoster Disseminated	0	1 (0.3)	1 (0.4)	0	0	0
Hookworm Infection	0	0	0	1 (0.3)	0	0
Hordeolum	0	0	1 (0.4)	0	0	0
Human Herpesvirus 6 Infection	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Impetigo	0	0	1 (0.4)	0	0	0
Infected Skin Ulcer	0	1 (0 3)	0	0	0	0
Infection	6 (2.5)	2 (0.6)	2 (0.9)	1 (0.3)	1 (3.8)	0
Infectious Disease Carrier	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Influenza	1 (0.4)	4 (1 1)	1 (0.4)	3 (1.0)	0	0
Infusion Site Infection	0	0	1 (0.4)	0	0	0
Klebsiella Bacteraemia	2 (0.8)	2 (0.6)	4 (1.8)	2 (0.6)	0	1 (3.1)
Klebsiella Infection	1 (0.4)	1 (0.3)	3 (1.3)	3 (1.0)	0	0
Klebsiella Sepsis	0	1 (0.3)	0	0	0	0
Lactobacillus Infection	0	0	1 (0.4)	0	0	0
Laryngitis	2 (0.8)	1 (0 3)	1 (0.4)	0	0	0
Leptotrichia Infection	0	0	0	1 (0.3)	0	0
Lip Infection	0	0	1 (0.4)	0	0	0
Liver Abscess	0	0	0	1 (0.3)	0	0
Localised Infection	1 (0.4)	2 (0.6)	3 (1.3)	1 (0.3)	0	0
Lower Respiratory Tract Infection	1 (0.4)	9 (2.5)	3 (1.3)	4 (1.3)	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Lower Respiratory Tract Infection Fungal	0	0	0	1 (0.3)	0	0
Lung Abscess	1 (0.4)	0	0	0	0	0
Lung Infection	0	0	0	0	0	1 (3.1)
Lymphangitis	1 (0.4)	0	1 (0.4)	0	0	0
Mastitis	1 (0.4)	0	0	0	0	0
Mastoiditis	2 (0.8)	2 (0.6)	1 (0.4)	0	0	0
Meningitis Listeria	0	0	0	1 (0.3)	0	0
Meningococcal Infection	0	0	0	1 (0.3)	0	0
Micrococcus Infection	1 (0.4)	0	1 (0.4)	0	0	0
Mycobacterial Infection	0	0	0	1 (0.3)	0	0
Mycobacterium Avium Complex Infection	0	0	1 (0.4)	0	0	0
Myelitis	0	1 (0 3)	0	0	0	0
Nail Infection	0	1 (0.3)	0	0	0	0
Nasopharyngitis	9 (3.7)	5 (1.4)	11 (4.9)	7 (2.2)	2 (7.7)	1 (3.1)
Neisseria Infection	0	0	1 (0.4)	0	0	0
Neutropenic Sepsis	2 (0.8)	4 (1.1)	1 (0.4)	0	2 (7.7)	3 (9.4)
Nocardia Sepsis	0	0	1 (0.4)	0	0	0
Nocardiosis	0	1 (0 3)	1 (0.4)	0	0	0
Oesophageal Candidiasis	0	0	2 (0.9)	0	0	0
Onychomycosis	0	1 (0 3)	0	0	0	1 (3.1)
Ophthalmic Herpes Simplex	0	0	0	1 (0.3)	0	0
Oral Candidiasis	7 (2.9)	10 (2.8)	8 (3.6)	10 (3 2)	1 (3.8)	1 (3.1)
Oral Fungal Infection	0	0	0	0	0	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Oral Herpes	20 (8.2)	36 (10.0)	14 (6.3)	19 (6.0)	4 (15.4)	4 (12.5)
Oral Infection	0	0	0	1 (0.3)	1 (3.8)	0
Oropharyngeal Candidiasis	0	0	2 (0.9)	1 (0.3)	1 (3.8)	0
Osteomyelitis	0	0	1 (0.4)	0	0	0
Otitis Externa	0	0	0	2 (0.6)	0	0
Otitis Media	1 (0.4)	1 (0 3)	1 (0.4)	3 (1.0)	0	0
Parainfluenzae Virus Infection	1 (0.4)	0	2 (0.9)	2 (0.6)	0	0
Paronychia	0	1 (0 3)	0	1 (0.3)	0	0
Parotitis	1 (0.4)	0	0	1 (0.3)	1 (3.8)	0
Pericoronitis	0	1 (0 3)	0	0	0	0
Perineal Abscess	0	1 (0 3)	0	0	0	0
Periodontitis	2 (0.8)	0	1 (0.4)	0	1 (3.8)	0
Periorbital Cellulitis	0	0	0	0	1 (3.8)	0
Perirectal Abscess	0	2 (0.6)	1 (0.4)	0	0	0
Peritonitis	0	0	1 (0.4)	0	0	0
Peritonitis Bacterial	0	0	0	1 (0.3)	0	0
Pharyngitis	3 (1.2)	7 (1 9)	2 (0.9)	6 (1.9)	0	1 (3.1)
Pharyngitis Bacterial	0	1 (0.3)	0	0	0	0
Pilonidal Cyst	0	1 (0 3)	0	0	0	0
Pneumococcal Bacteraemia	0	1 (0.3)	0	0	1 (3.8)	0
Pneumocystis Jirovecii Infection	1 (0.4)	0	1 (0.4)	0	0	0
Pneumocystis Jirovecii Pneumonia	0	2 (0.6)	2 (0.9)	0	0	1 (3.1)
Pneumonia	27 (11.1)	28 (7.8)	26 (11.6)	27 (8.6)	3 (11.5)	4 (12.5)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Pneumonia Bacterial	1 (0.4)	6 (1.7)	0	0	0	0
Pneumonia Cytomegaloviral	2 (0.8)	4 (1 1)	0	0	0	0
Pneumonia Fungal	1 (0.4)	3 (0.8)	2 (0.9)	4 (1.3)	0	1 (3.1)
Pneumonia Klebsiella	1 (0.4)	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Pneumonia Necrotising	0	0	0	1 (0.3)	0	0
Pneumonia Pseudomonal	0	1 (0.3)	1 (0.4)	1 (0 3)	0	0
Pneumonia Staphylococcal	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Pneumonia Streptococcal	0	0	0	1 (0.3)	0	0
Pneumonia Viral	1 (0.4)	0	0	0	0	0
Polyomavirus-Associated Nephropathy	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Progressive Multifocal Leukoencephalopathy	0	0	1 (0.4)	0	0	0
Pseudomembranous Colitis	0	2 (0.6)	0	0	0	1 (3.1)
Pseudomonal Bacteraemia	0	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Pseudomonal Sepsis	3 (1.2)	0	2 (0.9)	0	0	0
Pseudomonas Infection	4 (1.6)	5 (1.4)	1 (0.4)	5 (1.6)	0	0
Pulmonary Mycosis	1 (0.4)	2 (0.6)	3 (1.3)	2 (0.6)	0	0
Pulmonary Tuberculosis	1 (0.4)	0	0	0	0	0
Purulent Discharge	0	1 (0 3)	0	0	0	0
Pyoderma	0	1 (0 3)	0	0	0	0
Pyuria	0	1 (0 3)	0	0	0	0
Rash Pustular	0	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Relapsing Fever	0	0	0	1 (0.3)	0	0
Respiratory Moniliasis	0	0	0	1 (0.3)	0	0

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Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Respiratory Syncytial Virus Infection	2 (0.8)	4 (1.1)	3 (1.3)	1 (0.3)	0	0
Respiratory Tract Infection	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Rhinitis	4 (1.6)	6 (1.7)	5 (2.2)	5 (1.6)	1 (3.8)	0
Rhinovirus Infection	0	0	0	0	1 (3.8)	0
Rotavirus Infection	2 (0.8)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Salmonellosis	0	1 (0.3)	0	0	0	0
Scedosporium Infection	0	0	1 (0.4)	0	0	0
Sepsis	6 (2.5)	13 (3.6)	13 (5.8)	10 (3 2)	2 (7.7)	1 (3.1)
Sepsis Syndrome	0	1 (0.3)	0	0	0	0
Septic Embolus	0	1 (0 3)	0	0	0	0
Septic Rash	0	1 (0 3)	0	0	0	0
Septic Shock	5 (2.0)	11 (3.0)	5 (2.2)	11 (3 5)	2 (7.7)	4 (12.5)
Serratia Infection	1 (0.4)	2 (0.6)	0	0	0	0
Sialoadenitis	0	1 (0 3)	0	0	0	0
Sinusitis	6 (2.5)	18 (5.0)	15 (6.7)	10 (3 2)	2 (7.7)	0
Sinusitis Bacterial	0	2 (0.6)	0	0	0	0
Sinusitis Fungal	0	0	0	0	0	1 (3.1)
Skin Bacterial Infection	0	1 (0 3)	0	1 (0.3)	0	0
Skin Candida	0	0	1 (0.4)	0	0	0
Skin Infection	0	0	2 (0.9)	2 (0.6)	0	0
Soft Tissue Infection	0	0	0	0	1 (3.8)	0
Sputum Purulent	0	0	0	1 (0.3)	0	0
Staphylococcal Abscess	0	0	0	1 (0.3)	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Staphylococcal Bacteraemia	9 (3.7)	16 (4.4)	9 (4.0)	19 (6.0)	2 (7.7)	1 (3.1)
Staphylococcal Infection	8 (3.3)	18 (5.0)	4 (1.8)	16 (5 1)	0	2 (6.3)
Staphylococcal Sepsis	4 (1.6)	3 (0.8)	2 (0.9)	3 (1.0)	0	1 (3.1)
Staphylococcal Skin Infection	0	1 (0 3)	1 (0.4)	0	0	0
Stenotrophomonas Infection	1 (0.4)	0	0	0	0	0
Streptococcal Bacteraemia	4 (1.6)	2 (0.6)	5 (2.2)	6 (1.9)	1 (3.8)	0
Streptococcal Infection	1 (0.4)	3 (0.8)	0	5 (1.6)	0	0
Streptococcal Sepsis	2 (0.8)	1 (0.3)	0	1 (0.3)	0	0
Strongyloidiasis	0	0	0	1 (0.3)	0	0
Subcutaneous Abscess	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Superinfection	1 (0.4)	0	0	0	0	0
Systemic Candida	3 (1.2)	2 (0.6)	0	2 (0.6)	0	0
Systemic Mycosis	0	1 (0.3)	1 (0.4)	3 (1.0)	0	1 (3.1)
Tinea Infection	0	0	0	1 (0.3)	0	0
Tonsillitis	0	0	2 (0.9)	1 (0.3)	0	2 (6.3)
Tooth Abscess	1 (0.4)	3 (0.8)	0	1 (0.3)	1 (3.8)	0
Tooth Infection	0	2 (0.6)	0	1 (0.3)	0	0
Toxoplasmosis	0	0	0	1 (0.3)	0	0
Tracheobronchitis	1 (0.4)	4 (1 1)	1 (0.4)	3 (1.0)	0	0
Tracheobronchitis Viral	0	0	1 (0.4)	0	0	0
Trichomoniasis	1 (0.4)	0	0	0	0	0
Tuberculosis	0	0	0	1 (0.3)	0	0
Upper Respiratory Tract Infection	10 (4.1)	19 (5.3)	18 (8.0)	17 (5.4)	0	0

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Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Urethritis	0	0	0	1 (0.3)	0	0
Urinary Tract Infection	13 (5.3)	12 (3.3)	19 (8.5)	7 (2.2)	2 (7.7)	2 (6.3)
Urinary Tract Infection Enterococcal	0	0	1 (0.4)	0	0	0
Urinary Tract Infection Fungal	1 (0.4)	0	0	0	0	0
Urinary Tract Infection Pseudomonal	0	1 (0.3)	0	1 (0.3)	0	0
Urinary Tract Infection Staphylococcal	0	1 (0.3)	0	0	0	0
Urinary Tract Infection Viral	0	0	0	1 (0.3)	0	0
Varicella	0	1 (0 3)	0	0	0	0
Varicella Zoster Pneumonia	0	1 (0.3)	0	0	0	0
Varicella Zoster Virus Infection	1 (0.4)	2 (0.6)	0	0	0	0
Viral Haemorrhagic Cystitis	0	1 (0 3)	0	1 (0.3)	0	0
Viral Infection	2 (0.8)	0	3 (1.3)	2 (0.6)	0	0
Vulval Abscess	0	0	1 (0.4)	0	0	0
Vulvitis	1 (0.4)	0	0	0	1 (3.8)	0
Vulvovaginal Candidiasis	0	0	4 (1.8)	0	0	0
Vulvovaginal Mycotic Infection	1 (0.4)	0	0	0	0	0
Vulvovaginitis	1 (0.4)	0	0	0	0	0
Wound Infection	0	0	0	0	0	1 (3.1)
Injury, Poisoning And Procedural Complications	**62 (25.4)**	**76 (21 1)**	**66 (29.5)**	**57 (18.1)**	**12 (46.2)**	**9 (28.1)**
Accidental Overdose	0	0	1 (0.4)	0	0	0
Allergic Transfusion Reaction	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Anal Injury	1 (0.4)	1 (0 3)	0	0	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Animal Bite	0	0	0	0	1 (3.8)	0
Arthropod Bite	1 (0.4)	0	0	0	0	0
Back Injury	0	1 (0 3)	0	0	0	0
Brain Herniation	0	0	0	0	1 (3.8)	0
Chemical Eye Injury	0	0	1 (0.4)	0	0	0
Complications Of Transplant Surgery	0	1 (0.3)	0	0	0	0
Compression Fracture	1 (0.4)	0	0	0	0	0
Contusion	8 (3.3)	8 (2 2)	11 (4.9)	7 (2.2)	0	1 (3.1)
Eschar	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Excoriation	1 (0.4)	2 (0.6)	0	2 (0.6)	0	0
Eye Burns	0	1 (0.3)	1 (0.4)	0	0	0
Eye Injury	0	0	0	1 (0.3)	0	0
Fall	7 (2.9)	13 (3.6)	12 (5.4)	7 (2.2)	3 (11.5)	2 (6.3)
Femoral Neck Fracture	0	1 (0 3)	1 (0.4)	0	0	0
Foreign Body	0	0	0	1 (0.3)	0	0
Gastrointestinal Stoma Complication	0	0	0	1 (0.3)	0	0
Haematuria Traumatic	0	0	0	1 (0.3)	0	0
Haemodilution	0	0	1 (0.4)	0	0	0
Hand Fracture	1 (0.4)	0	0	0	0	0
Head Injury	0	1 (0.3)	0	2 (0.6)	0	0
Hip Fracture	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Incision Site Erythema	0	0	0	0	1 (3.8)	0
Incision Site Haemorrhage	0	1 (0.3)	0	1 (0.3)	0	0

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	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Incision Site Pain	0	2 (0.6)	1 (0.4)	0	0	0
Inflammation Of Wound	0	1 (0.3)	0	1 (0.3)	1 (3.8)	0
Infusion Related Reaction	2 (0.8)	5 (1.4)	6 (2.7)	5 (1.6)	0	0
Injury	0	0	1 (0.4)	0	0	0
Injury Corneal	0	0	0	1 (0.3)	0	0
Joint Injury	0	1 (0 3)	1 (0.4)	0	0	0
Keratorhexis	0	0	1 (0.4)	0	0	0
Laceration	4 (1.6)	5 (1.4)	3 (1.3)	5 (1.6)	0	0
Ligament Sprain	0	1 (0 3)	0	1 (0.3)	0	0
Lip Injury	0	1 (0.3)	0	0	0	0
Lumbar Vertebral Fracture	0	1 (0 3)	0	0	0	0
Mouth Injury	2 (0.8)	0	1 (0.4)	0	0	0
Muscle Rupture	0	0	1 (0.4)	0	0	0
Muscle Strain	1 (0.4)	1 (0.3)	1 (0.4)	0	0	0
Overdose	0	0	0	1 (0.3)	0	0
Periorbital Haematoma	0	0	1 (0.4)	0	0	0
Pneumothorax Traumatic	0	0	0	1 (0.3)	0	0
Post Lumbar Puncture Syndrome	0	2 (0.6)	0	0	0	0
Post Procedural Complication	0	2 (0.6)	0	0	0	1 (3.1)
Post Procedural Discomfort	0	0	0	1 (0.3)	0	0
Post Procedural Haematoma	1 (0.4)	0	3 (1.3)	1 (0.3)	0	0
Post Procedural Haemorrhage	2 (0.8)	1 (0 3)	4 (1.8)	2 (0.6)	0	0
Post Procedural Oedema	0	1 (0 3)	0	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Post-Traumatic Pain	1 (0.4)	0	0	0	0	0
Postoperative Fever	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Procedural Hypertension	1 (0.4)	0	0	0	0	0
Procedural Pain	10 (4.1)	8 (2.2)	14 (6.3)	2 (0.6)	0	0
Rib Fracture	0	1 (0 3)	0	0	0	0
Road Traffic Accident	0	0	1 (0.4)	0	0	0
Scratch	1 (0.4)	0	0	2 (0.6)	0	0
Sedation Complication	0	1 (0 3)	0	0	0	0
Skin Abrasion	1 (0.4)	4 (1 1)	0	4 (1.3)	0	0
Skin Injury	1 (0.4)	1 (0 3)	0	0	0	0
Spinal Fracture	1 (0.4)	0	0	0	0	0
Stoma Site Haemorrhage	0	0	0	1 (0.3)	0	0
Stoma Site Pain	0	0	0	1 (0.3)	0	0
Subarachnoid Haemorrhage	1 (0.4)	1 (0 3)	0	0	1 (3.8)	0
Subcutaneous Haematoma	0	0	0	0	1 (3.8)	0
Subdural Haematoma	2 (0.8)	0	1 (0.4)	2 (0.6)	0	0
Thermal Burn	1 (0.4)	0	0	2 (0.6)	0	0
Tooth Fracture	0	1 (0 3)	0	1 (0.3)	1 (3.8)	0
Toxicity To Various Agents	3 (1.2)	5 (1.4)	5 (2.2)	2 (0.6)	0	0
Transfusion Reaction	16 (6.6)	18 (5.0)	13 (5.8)	8 (2.5)	4 (15.4)	6 (18.8)
Transplant Failure	0	2 (0.6)	0	3 (1.0)	0	0
Traumatic Haematoma	1 (0.4)	0	0	1 (0.3)	0	0
Vaginal Laceration	0	0	1 (0.4)	0	0	0

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	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Vascular Injury	0	0	0	1 (0.3)	0	0
Wound	0	3 (0.8)	5 (2.2)	5 (1.6)	0	0
Wound Complication	0	2 (0.6)	0	0	0	0
Wound Haemorrhage	0	1 (0 3)	0	0	0	0
Wound Secretion	0	0	0	1 (0.3)	0	0
Investigations	**129 (52.9)**	**199 (55.1)**	**118 (52.7)**	**169 (53.7)**	**15 (57.7)**	**18 (56.3)**
Activated Partial Thromboplastin Time Prolonged	0	0	2 (0.9)	1 (0.3)	0	0
Activated Partial Thromboplastin Time Shortened	0	0	1 (0.4)	0	0	0
Alanine Aminotransferase Abnormal	0	1 (0.3)	0	2 (0.6)	0	0
Alanine Aminotransferase Decreased	0	1 (0.3)	0	0	0	0
Alanine Aminotransferase Increased	13 (5.3)	24 (6.6)	10 (4.5)	16 (5 1)	2 (7.7)	1 (3.1)
Ammonia Increased	0	1 (0.3)	0	0	0	0
Amylase Increased	0	0	0	1 (0.3)	0	0
Antithrombin III Decreased	1 (0.4)	0	0	0	0	0
Aspartate Aminotransferase Abnormal	0	1 (0.3)	0	1 (0.3)	0	0
Aspartate Aminotransferase Increased	8 (3.3)	11 (3.0)	5 (2.2)	12 (3.8)	2 (7.7)	1 (3.1)
Aspergillus Test Positive	0	0	1 (0.4)	1 (0.3)	0	0
Aspiration Bronchial	1 (0.4)	0	0	0	0	0
Aspiration Tracheal	0	0	0	1 (0.3)	0	0
Aspiration Tracheal Abnormal	0	0	0	1 (0.3)	0	0
Atrial Pressure Increased	0	0	0	1 (0.3)	0	0
Bacterial Test Positive	3 (1.2)	9 (2.5)	9 (4.0)	9 (2.9)	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Basophil Count Increased	0	1 (0.3)	0	0	0	0
Bilirubin Conjugated Increased	0	1 (0.3)	1 (0.4)	0	0	0
Blast Cells Present	0	1 (0 3)	0	0	0	0
Bleeding Time Prolonged	2 (0.8)	1 (0.3)	0	1 (0.3)	0	0
Blood Albumin Abnormal	0	1 (0 3)	0	0	0	0
Blood Albumin Decreased	2 (0.8)	4 (1.1)	1 (0.4)	5 (1.6)	1 (3.8)	0
Blood Albumin Increased	0	0	1 (0.4)	1 (0.3)	0	0
Blood Alkaline Phosphatase Decreased	0	0	0	0	1 (3.8)	0
Blood Alkaline Phosphatase Increased	7 (2.9)	9 (2.5)	5 (2.2)	14 (4.4)	0	1 (3.1)
Blood Bicarbonate Decreased	2 (0.8)	1 (0.3)	3 (1.3)	2 (0.6)	1 (3.8)	0
Blood Bilirubin Abnormal	0	1 (0.3)	0	0	0	0
Blood Bilirubin Increased	15 (6.1)	14 (3.9)	9 (4.0)	17 (5.4)	3 (11.5)	1 (3.1)
Blood Calcium Decreased	1 (0.4)	1 (0.3)	1 (0.4)	6 (1.9)	0	0
Blood Chloride Increased	0	1 (0.3)	0	0	0	0
Blood Cholesterol Increased	1 (0.4)	4 (1.1)	0	1 (0.3)	0	0
Blood Creatine Decreased	0	0	0	1 (0.3)	0	0
Blood Creatine Increased	1 (0.4)	1 (0.3)	0	0	0	0
Blood Creatine Phosphokinase Increased	0	1 (0.3)	0	0	0	0
Blood Creatinine Decreased	0	0	0	1 (0.3)	0	0
Blood Creatinine Increased	13 (5.3)	21 (5.8)	16 (7.1)	32 (10.2)	1 (3.8)	1 (3.1)
Blood Culture Positive	3 (1.2)	14 (3.9)	4 (1.8)	5 (1.6)	1 (3.8)	0
Blood Electrolytes Abnormal	0	0	0	1 (0.3)	0	0
Blood Gastrin Increased	0	0	1 (0.4)	0	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Blood Glucose Increased	2 (0.8)	3 (0.8)	3 (1.3)	3 (1.0)	0	0
Blood Immunoglobulin G Decreased	1 (0.4)	1 (0.3)	1 (0.4)	0	0	0
Blood Lactate Dehydrogenase	0	0	0	1 (0.3)	0	0
Blood Lactate Dehydrogenase Increased	5 (2.0)	13 (3.6)	5 (2.2)	12 (3.8)	0	0
Blood Magnesium Decreased	4 (1.6)	7 (1.9)	2 (0.9)	6 (1.9)	0	0
Blood Magnesium Increased	1 (0.4)	0	0	0	0	0
Blood Phosphorus Decreased	1 (0.4)	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Blood Phosphorus Increased	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Blood Potassium	0	1 (0.3)	0	0	0	0
Blood Potassium Abnormal	0	0	0	0	1 (3.8)	0
Blood Potassium Decreased	3 (1.2)	5 (1.4)	3 (1.3)	5 (1.6)	1 (3.8)	0
Blood Potassium Increased	0	0	1 (0.4)	1 (0.3)	0	0
Blood Pressure Decreased	0	0	0	1 (0.3)	0	0
Blood Pressure Diastolic Increased	0	1 (0.3)	0	0	0	0
Blood Pressure Increased	3 (1.2)	3 (0.8)	4 (1.8)	2 (0.6)	0	0
Blood Pressure Orthostatic	1 (0.4)	1 (0.3)	0	0	0	0
Blood Sodium Decreased	0	0	0	1 (0.3)	0	0
Blood Testosterone Decreased	0	1 (0.3)	0	1 (0.3)	0	0
Blood Thyroid Stimulating Hormone Decreased	0	1 (0.3)	0	0	0	0
Blood Triglycerides Increased	1 (0.4)	1 (0.3)	0	3 (1.0)	0	0
Blood Urea Decreased	0	0	0	1 (0.3)	0	0
Blood Urea Increased	2 (0.8)	3 (0.8)	3 (1.3)	10 (3 2)	0	0
Blood Uric Acid Decreased	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Blood Uric Acid Increased	1 (0.4)	4 (1.1)	1 (0.4)	4 (1.3)	0	0
Blood Urine Present	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Body Temperature	0	1 (0.3)	0	0	0	0
Body Temperature Increased	2 (0.8)	2 (0.6)	0	0	0	0
Breath Sounds Abnormal	3 (1.2)	15 (4.2)	6 (2.7)	5 (1.6)	0	0
Bronchoscopy	0	0	0	1 (0.3)	0	0
C-Reactive Protein Abnormal	0	1 (0.3)	0	0	0	0
C-Reactive Protein Increased	0	4 (1 1)	1 (0.4)	2 (0.6)	1 (3.8)	1 (3.1)
Carbon Dioxide Decreased	0	1 (0 3)	0	1 (0.3)	0	0
Carbon Monoxide Diffusing Capacity Decreased	0	0	0	1 (0.3)	0	0
Cardiac Murmur	5 (2.0)	9 (2 5)	6 (2.7)	1 (0.3)	0	0
Central Venous Pressure Decreased	0	1 (0 3)	0	0	0	0
Chest X-Ray Abnormal	4 (1.6)	2 (0.6)	2 (0.9)	4 (1.3)	0	0
Clostridium Test	1 (0.4)	0	1 (0.4)	0	0	0
Clostridium Test Positive	4 (1.6)	3 (0.8)	0	6 (1.9)	0	0
Coagulation Factor Decreased	1 (0.4)	0	0	0	0	0
Coagulation Factor XIII Level Decreased	0	0	0	1 (0.3)	0	0
Coagulation Test Abnormal	0	2 (0.6)	0	2 (0.6)	0	0
Coagulation Time Prolonged	0	1 (0 3)	0	1 (0.3)	0	0
Coagulation Time Shortened	0	1 (0 3)	0	1 (0.3)	0	0
Colour Vision Tests Abnormal	0	0	0	1 (0.3)	0	0
Computerised Tomogram Abnormal	1 (0.4)	0	3 (1.3)	1 (0.3)	1 (3.8)	0
Creatinine Renal Clearance Decreased	1 (0.4)	1 (0.3)	3 (1.3)	3 (1.0)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Culture	0	1 (0 3)	0	0	0	0
Culture Positive	0	1 (0 3)	0	0	0	0
Culture Stool Positive	0	1 (0 3)	0	1 (0.3)	0	0
Culture Urine Positive	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Culture Wound Positive	0	0	0	1 (0.3)	0	0
Cytomegalovirus Test	2 (0.8)	3 (0.8)	2 (0.9)	4 (1.3)	0	0
Cytomegalovirus Test Positive	10 (4.1)	17 (4.7)	8 (3.6)	14 (4.4)	0	0
Drug Level Changed	1 (0.4)	0	0	1 (0.3)	0	0
Drug Level Increased	2 (0.8)	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Echocardiogram Abnormal	0	1 (0 3)	0	0	0	0
Ejection Fraction Decreased	1 (0.4)	1 (0.3)	0	0	0	0
Electrocardiogram Abnormal	1 (0.4)	2 (0.6)	0	2 (0.6)	0	0
Electrocardiogram Qt Interval	0	0	0	0	0	1 (3.1)
Electrocardiogram Qt Prolonged	5 (2.0)	19 (5.3)	5 (2.2)	14 (4.4)	1 (3.8)	4 (12.5)
Electrocardiogram Repolarisation Abnormality	0	1 (0.3)	0	0	0	0
Electrocardiogram St Segment Abnormal	0	1 (0.3)	0	0	0	0
Electrocardiogram St-T Change	0	1 (0.3)	0	0	0	0
Electrocardiogram St-T Segment Abnormal	0	1 (0.3)	0	0	0	0
Electrocardiogram T Wave Abnormal	0	4 (1.1)	0	0	0	0
Electrocardiogram T Wave Inversion	0	1 (0.3)	0	0	0	0
Electroencephalogram Abnormal	0	1 (0 3)	1 (0.4)	0	0	0
Eosinophil Count Increased	1 (0.4)	0	0	0	0	0
Fibrinolysis	0	0	1 (0.4)	0	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Fungal Test	0	0	0	0	0	1 (3.1)
Fungal Test Positive	2 (0.8)	1 (0.3)	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	0	1 (0.3)	0	0
Gamma-Glutamyltransferase Increased	20 (8.2)	21 (5.8)	15 (6.7)	23 (7 3)	4 (15.4)	0
Gastric Ph Decreased	1 (0.4)	0	0	1 (0.3)	0	0
General Physical Condition	0	1 (0.3)	0	0	0	0
Glucose Urine	0	1 (0 3)	0	0	0	0
Haematocrit Decreased	0	0	1 (0.4)	1 (0.3)	0	0
Haemoglobin Decreased	2 (0.8)	6 (1.7)	1 (0.4)	1 (0.3)	0	1 (3.1)
Heart Rate Increased	0	0	2 (0.9)	0	0	0
Heart Rate Irregular	1 (0.4)	4 (1.1)	1 (0.4)	2 (0.6)	0	0
Heart Sounds Abnormal	1 (0.4)	0	0	0	0	0
Hepatic Enzyme Abnormal	1 (0.4)	0	2 (0.9)	0	0	0
Hepatic Enzyme Increased	3 (1.2)	6 (1.7)	3 (1.3)	9 (2.9)	0	0
Herpes Simplex Test Positive	1 (0.4)	0	0	0	0	0
High Density Lipoprotein Increased	1 (0.4)	0	0	0	0	0
Immunoglobulins Decreased	0	1 (0.3)	0	0	0	0
Immunosuppressant Drug Level Decreased	0	0	0	1 (0.3)	0	0
International Normalised Ratio Abnormal	2 (0.8)	0	0	0	0	0
International Normalised Ratio Increased	2 (0.8)	0	0	2 (0.6)	0	0
Liver Function Test Abnormal	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Liver Function Test Increased	9 (3.7)	9 (2.5)	10 (4.5)	6 (1.9)	0	1 (3.1)
Lymphocyte Count Decreased	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Lymphocyte Count Increased	0	0	0	1 (0.3)	0	0
Microbiology Test Normal	1 (0.4)	0	0	0	0	0
Neurological Examination Abnormal	0	0	1 (0.4)	0	0	0
Neutrophil Count Abnormal	0	2 (0.6)	0	0	0	0
Neutrophil Count Decreased	0	3 (0.8)	0	1 (0.3)	1 (3.8)	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	1 (0.4)	0	0	0
Nuclear Magnetic Resonance Imaging Brain Abnormal	1 (0.4)	0	0	0	0	0
Nutritional Condition Abnormal	0	0	1 (0.4)	1 (0.3)	0	0
Occult Blood Positive	3 (1.2)	4 (1.1)	1 (0.4)	6 (1.9)	1 (3.8)	0
Oxygen Consumption Decreased	0	0	1 (0.4)	0	0	0
Oxygen Saturation Decreased	2 (0.8)	7 (1 9)	7 (3.1)	2 (0.6)	0	0
Parvovirus B19 Test Positive	0	1 (0.3)	0	0	0	0
Pedal Pulse Abnormal	0	0	0	1 (0.3)	0	0
Platelet Count Decreased	2 (0.8)	7 (1 9)	1 (0.4)	5 (1.6)	1 (3.8)	0
Po2 Decreased	0	1 (0 3)	0	0	0	0
Protein Total Decreased	0	1 (0.3)	0	1 (0.3)	1 (3.8)	0
Protein Total Increased	0	0	1 (0.4)	0	0	0
Prothrombin Time Prolonged	3 (1.2)	2 (0.6)	4 (1.8)	8 (2.5)	2 (7.7)	1 (3.1)
Prothrombin Time Ratio Decreased	0	0	1 (0.4)	0	0	0
Prothrombin Time Shortened	1 (0.4)	2 (0.6)	0	2 (0.6)	1 (3.8)	0
Pulmonary Function Test Decreased	1 (0.4)	0	0	1 (0.3)	0	0
Pulse Absent	0	0	0	1 (0.3)	0	0
Qrs Axis Abnormal	0	0	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Red Blood Cell Count Decreased	0	1 (0 3)	0	0	0	0
Red Blood Cell Schistocytes Present	0	0	1 (0.4)	0	0	0
Respiratory Rate Increased	0	1 (0 3)	2 (0.9)	0	0	0
Romberg Test Positive	0	0	1 (0.4)	0	0	0
Rotavirus Test Positive	0	0	1 (0.4)	0	0	0
Salmonella Test Positive	0	1 (0.3)	0	0	0	0
Scan Bone Marrow Abnormal	1 (0.4)	0	0	0	0	0
Serum Ferritin Increased	0	1 (0.3)	0	0	0	0
Sputum Abnormal	0	1 (0 3)	0	0	0	0
Sputum Culture Positive	0	0	0	1 (0.3)	0	0
Thrombin Time Prolonged	0	1 (0.3)	0	0	0	0
Thyroid Function Test Abnormal	0	0	1 (0.4)	0	0	0
Total Lung Capacity Decreased	0	1 (0 3)	0	0	0	0
Toxoplasma Serology Positive	1 (0.4)	0	0	0	0	0
Transaminases Increased	8 (3.3)	5 (1.4)	6 (2.7)	8 (2.5)	0	0
Troponin I Increased	0	0	0	1 (0.3)	0	0
Troponin Increased	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Urine Output Decreased	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
Urine Output Increased	0	1 (0.3)	0	0	0	0
Viral Test Positive	0	1 (0.3)	0	1 (0.3)	0	0
Vitamin K Decreased	1 (0.4)	0	0	0	0	0
Volume Blood Decreased	0	0	0	0	0	1 (3.1)
Weight Decreased	15 (6.1)	26 (7.2)	12 (5.4)	38 (12.1)	1 (3.8)	3 (9.4)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Weight Increased	7 (2.9)	5 (1.4)	5 (2.2)	4 (1.3)	2 (7.7)	3 (9.4)
White Blood Cell Count Abnormal	0	1 (0 3)	0	0	0	0
White Blood Cell Count Decreased	0	1 (0.3)	2 (0.9)	1 (0.3)	1 (3.8)	0
White Blood Cell Count Increased	1 (0.4)	1 (0.3)	0	0	0	0
X-Ray Abnormal	1 (0.4)	0	0	0	0	0
Metabolism And Nutrition Disorders	**147 (60.2)**	**207 (57.3)**	**137 (61.2)**	**177 (56 2)**	**22 (84.6)**	**23 (71.9)**
Acidosis	6 (2.5)	5 (1.4)	3 (1.3)	3 (1.0)	2 (7.7)	0
Appetite Disorder	0	1 (0.3)	1 (0.4)	0	0	0
Cachexia	0	2 (0.6)	0	0	0	0
Calcium Deficiency	0	0	0	1 (0.3)	0	0
Decreased Appetite	36 (14.8)	52 (14.4)	35 (15.6)	52 (16.5)	8 (30.8)	9 (28.1)
Dehydration	7 (2.9)	19 (5.3)	11 (4.9)	16 (5 1)	1 (3.8)	1 (3.1)
Diabetes Mellitus	5 (2.0)	12 (3.3)	2 (0.9)	5 (1.6)	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	0	1 (3.1)
Electrolyte Depletion	1 (0.4)	0	0	0	0	0
Electrolyte Imbalance	0	6 (1.7)	1 (0.4)	2 (0.6)	2 (7.7)	2 (6.3)
Enzyme Abnormality	0	0	1 (0.4)	0	0	0
Failure To Thrive	0	1 (0 3)	1 (0.4)	3 (1.0)	0	0
Feeding Disorder	0	0	0	1 (0.3)	0	0
Fluid Imbalance	0	0	0	1 (0.3)	0	0
Fluid Overload	8 (3.3)	19 (5.3)	5 (2.2)	12 (3.8)	2 (7.7)	0
Fluid Retention	7 (2.9)	11 (3.0)	10 (4.5)	14 (4.4)	2 (7.7)	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Food Aversion	0	1 (0 3)	0	0	0	0
Food Craving	0	1 (0.3)	0	0	0	0
Food Intolerance	0	1 (0 3)	0	0	0	0
Glucose Tolerance Impaired	0	0	1 (0.4)	0	0	0
Gout	0	3 (0.8)	1 (0.4)	3 (1.0)	0	0
Haemochromatosis	0	0	0	1 (0.3)	0	0
Haemosiderosis	0	0	1 (0.4)	0	0	0
Hypercalcaemia	2 (0.8)	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Hyperchloraemia	0	1 (0 3)	0	0	0	0
Hypercholesterolaemia	0	4 (1 1)	0	0	0	0
Hypercreatininaemia	1 (0.4)	0	0	0	0	0
Hyperferritinaemia	0	0	0	1 (0.3)	0	0
Hyperglycaemia	27 (11.1)	39 (10.8)	34 (15.2)	37 (11.7)	0	2 (6.3)
Hyperhomocysteinaemia	0	1 (0.3)	0	0	0	0
Hyperinsulinaemic Hypoglycaemia	0	1 (0.3)	0	0	0	0
Hyperkalaemia	6 (2.5)	9 (2 5)	10 (4.5)	13 (4 1)	2 (7.7)	0
Hyperlipidaemia	0	0	0	1 (0.3)	0	0
Hypermagnesaemia	3 (1.2)	3 (0.8)	2 (0.9)	1 (0.3)	1 (3.8)	2 (6.3)
Hypernatraemia	4 (1.6)	2 (0.6)	1 (0.4)	3 (1.0)	1 (3.8)	1 (3.1)
Hyperosmolar State	1 (0.4)	0	0	0	0	0
Hyperphagia	0	1 (0 3)	0	0	0	0
Hyperphosphataemia	4 (1.6)	2 (0.6)	1 (0.4)	7 (2.2)	0	0
Hypertriglyceridaemia	0	2 (0.6)	1 (0.4)	0	0	0

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hyperuricaemia	0	4 (1.1)	3 (1.3)	7 (2.2)	0	0
Hypervolaemia	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Hypoalbuminaemia	13 (5.3)	15 (4.2)	6 (2.7)	12 (3.8)	1 (3.8)	1 (3.1)
Hypocalcaemia	25 (10.2)	28 (7.8)	22 (9.8)	24 (7.6)	3 (11.5)	2 (6.3)
Hypochloraemia	0	0	0	1 (0.3)	0	0
Hypoglycaemia	4 (1.6)	6 (1.7)	3 (1.3)	6 (1.9)	0	0
Hypokalaemia	77 (31.6)	95 (26 3)	69 (30.8)	67 (21.3)	14 (53.8)	15 (46.9)
Hypomagnesaemia	46 (18.9)	52 (14.4)	36 (16.1)	39 (12.4)	6 (23.1)	5 (15.6)
Hyponatraemia	12 (4.9)	18 (5.0)	13 (5.8)	16 (5 1)	2 (7.7)	1 (3.1)
Hypophagia	5 (2.0)	5 (1.4)	7 (3.1)	4 (1.3)	0	0
Hypophosphataemia	19 (7.8)	28 (7.8)	15 (6.7)	22 (7.0)	4 (15.4)	2 (6.3)
Hypoproteinaemia	1 (0.4)	4 (1 1)	0	3 (1.0)	0	1 (3.1)
Hypovitaminosis	1 (0.4)	1 (0.3)	0	0	0	0
Hypovolaemia	1 (0.4)	2 (0.6)	1 (0.4)	3 (1.0)	0	0
Lactose Intolerance	0	0	1 (0.4)	0	0	0
Magnesium Deficiency	0	1 (0 3)	1 (0.4)	0	0	0
Malnutrition	2 (0.8)	3 (0.8)	6 (2.7)	9 (2.9)	0	0
Metabolic Acidosis	6 (2.5)	4 (1 1)	4 (1.8)	2 (0.6)	1 (3.8)	1 (3.1)
Metabolic Alkalosis	0	0	2 (0.9)	0	0	0
Obesity	0	0	1 (0.4)	1 (0.3)	0	0
Phosphorus Metabolism Disorder	0	1 (0.3)	0	0	0	0
Polydipsia	2 (0.8)	1 (0.3)	0	0	0	0
Vitamin B12 Deficiency	0	1 (0 3)	0	0	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Vitamin B6 Deficiency	0	0	0	1 (0.3)	0	0
Vitamin C Deficiency	0	0	0	1 (0.3)	0	0
Vitamin K Deficiency	0	1 (0 3)	0	2 (0.6)	0	0
Musculoskeletal And Connective Tissue Disorders	**96 (39.3)**	**153 (42.4)**	**101 (45.1)**	**145 (46.0)**	**12 (46.2)**	**8 (25.0)**
Arthralgia	19 (7.8)	39 (10.8)	24 (10.7)	32 (10.2)	2 (7.7)	1 (3.1)
Arthritis	2 (0.8)	2 (0.6)	0	1 (0.3)	0	1 (3.1)
Axillary Mass	1 (0.4)	0	0	0	0	0
Back Pain	29 (11.9)	32 (8.9)	29 (12.9)	37 (11.7)	2 (7.7)	2 (6.3)
Bone Pain	9 (3.7)	17 (4.7)	5 (2.2)	6 (1.9)	2 (7.7)	1 (3.1)
Bursitis	1 (0.4)	0	0	1 (0.3)	0	0
Chondritis	1 (0.4)	0	0	0	0	0
Clubbing	0	0	0	1 (0.3)	0	0
Coccydynia	2 (0.8)	0	0	0	0	0
Flank Pain	4 (1.6)	5 (1.4)	1 (0.4)	6 (1.9)	1 (3.8)	0
Groin Pain	0	2 (0.6)	1 (0.4)	2 (0.6)	1 (3.8)	0
Haemarthrosis	2 (0.8)	0	1 (0.4)	0	0	0
Inguinal Mass	1 (0.4)	1 (0 3)	0	0	0	0
Intervertebral Disc Degeneration	0	0	0	1 (0.3)	0	0
Intervertebral Disc Protrusion	0	1 (0.3)	1 (0.4)	0	0	0
Joint Contracture	0	1 (0 3)	0	0	0	0
Joint Effusion	2 (0.8)	1 (0 3)	0	0	0	0
Joint Stiffness	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Joint Swelling	2 (0.8)	7 (1 9)	3 (1.3)	3 (1.0)	0	0
Kyphoscoliosis	1 (0.4)	0	0	0	0	0
Limb Discomfort	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Mobility Decreased	1 (0.4)	0	0	0	0	0
Muscle Atrophy	0	4 (1 1)	0	1 (0.3)	0	0
Muscle Contracture	1 (0.4)	0	0	0	0	0
Muscle Fatigue	1 (0.4)	0	1 (0.4)	0	0	0
Muscle Spasms	6 (2.5)	25 (6.9)	15 (6.7)	23 (7 3)	0	0
Muscle Swelling	0	0	1 (0.4)	0	1 (3.8)	0
Muscle Tightness	0	1 (0.3)	0	0	0	0
Muscle Twitching	2 (0.8)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Muscular Weakness	11 (4.5)	17 (4.7)	15 (6.7)	13 (4 1)	1 (3.8)	0
Musculoskeletal Chest Pain	5 (2.0)	7 (1.9)	7 (3.1)	5 (1.6)	0	0
Musculoskeletal Discomfort	1 (0.4)	3 (0.8)	2 (0.9)	1 (0.3)	0	0
Musculoskeletal Pain	6 (2.5)	10 (2.8)	8 (3.6)	12 (3.8)	2 (7.7)	2 (6.3)
Musculoskeletal Stiffness	2 (0.8)	3 (0.8)	6 (2.7)	4 (1.3)	1 (3.8)	0
Myalgia	12 (4.9)	19 (5.3)	14 (6.3)	19 (6.0)	1 (3.8)	0
Myopathy	8 (3.3)	12 (3.3)	6 (2.7)	5 (1.6)	0	0
Myositis	1 (0.4)	0	0	0	0	0
Neck Mass	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Neck Pain	6 (2.5)	3 (0.8)	12 (5.4)	8 (2.5)	1 (3.8)	0
Nuchal Rigidity	0	0	0	1 (0.3)	0	0
Osteoarthritis	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Osteolysis	0	0	0	1 (0.3)	0	0
Osteonecrosis	1 (0.4)	1 (0 3)	1 (0.4)	2 (0.6)	0	0
Osteopenia	1 (0.4)	1 (0 3)	0	0	0	0
Osteoporosis	0	0	2 (0.9)	0	0	0
Pain In Extremity	21 (8.6)	37 (10 2)	24 (10.7)	24 (7.6)	3 (11.5)	2 (6.3)
Pain In Jaw	2 (0.8)	4 (1 1)	1 (0.4)	1 (0.3)	1 (3.8)	0
Pathological Fracture	0	0	1 (0.4)	0	0	0
Plantar Fasciitis	0	1 (0 3)	0	0	0	0
Polychondritis	0	0	0	0	1 (3.8)	0
Scoliosis	0	1 (0 3)	0	0	0	0
Sjogren's Syndrome	0	3 (0.8)	0	1 (0.3)	0	0
Soft Tissue Disorder	0	0	0	3 (1.0)	0	0
Spinal Osteoarthritis	2 (0.8)	1 (0.3)	0	0	0	0
Spinal Pain	0	0	1 (0.4)	0	0	0
Temporomandibular Joint Syndrome	0	1 (0 3)	0	0	0	0
Tendon Pain	0	0	0	1 (0.3)	0	0
Tendonitis	1 (0.4)	2 (0.6)	0	0	2 (7.7)	0
Tenosynovitis	0	1 (0 3)	0	0	0	0
Torticollis	0	1 (0 3)	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**22 (9.0)**	**39 (10 8)**	**23 (10.3)**	**34 (10.8)**	**0**	**3 (9.4)**
Acute Lymphocytic Leukaemia Recurrent	0	0	4 (1.8)	2 (0.6)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Acute Myeloid Leukaemia	8 (3.3)	5 (1.4)	3 (1.3)	6 (1.9)	0	1 (3.1)
Acute Myeloid Leukaemia Recurrent	5 (2.0)	7 (1.9)	3 (1.3)	3 (1.0)	0	0
Adenoma Benign	0	0	0	1 (0.3)	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	1 (0.4)	0	0	0
Angiomyolipoma	0	0	1 (0.4)	0	0	0
Anogenital Warts	0	1 (0 3)	0	0	0	0
B-Cell Lymphoma	0	0	0	1 (0.3)	0	0
Basal Cell Carcinoma	0	0	0	1 (0.3)	0	0
Bowen's Disease	0	1 (0 3)	0	0	0	0
Breast Neoplasm	1 (0.4)	0	0	0	0	0
Chloroma	0	1 (0 3)	0	0	0	0
Chronic Lymphocytic Leukaemia Recurrent	0	0	0	1 (0.3)	0	0
Chronic Myeloid Leukaemia	0	1 (0 3)	0	0	0	0
Colon Adenoma	0	1 (0 3)	0	0	0	0
Haemangioma Of Liver	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Hodgkin's Disease	0	0	1 (0.4)	0	0	0
Hodgkin's Disease Recurrent	0	0	1 (0.4)	0	0	0
Leukaemia	0	4 (1 1)	2 (0.9)	1 (0.3)	0	0
Leukaemia Cutis	0	0	0	0	0	1 (3.1)
Leukaemia Recurrent	2 (0.8)	4 (1 1)	2 (0.9)	3 (1.0)	0	0
Lipoma	0	2 (0.6)	0	0	0	0
Lymphoma	0	6 (1.7)	0	2 (0.6)	0	0
Malignant Melanoma	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Melanocytic Naevus	0	0	1 (0.4)	0	0	0
Meningioma	1 (0.4)	0	0	1 (0.3)	0	0
Metastases To Kidney	0	0	0	1 (0.3)	0	0
Metastases To Liver	0	0	0	1 (0.3)	0	0
Metastatic Neoplasm	0	1 (0 3)	0	0	0	0
Myelodysplastic Syndrome	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Nasal Neoplasm	1 (0.4)	0	0	0	0	0
Neoplasm Malignant	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Neuroma	1 (0.4)	0	0	0	0	0
Non-Hodgkin's Lymphoma	0	1 (0.3)	1 (0.4)	3 (1.0)	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	0	2 (0.6)	0	0
Plasma Cell Myeloma	0	0	0	1 (0.3)	0	0
Post Transplant Lymphoproliferative Disorder	0	1 (0.3)	0	1 (0.3)	0	0
Pyogenic Granuloma	0	0	0	1 (0.3)	0	0
Renal Cancer	0	1 (0 3)	0	0	0	0
Renal Neoplasm	0	1 (0 3)	0	0	0	0
Seborrhoeic Keratosis	0	0	0	1 (0.3)	0	0
Skin Papilloma	0	1 (0 3)	0	0	0	0
Squamous Cell Carcinoma	0	2 (0.6)	0	1 (0.3)	0	0
Thyroid Adenoma	1 (0.4)	0	0	0	0	0
Tumour Associated Fever	0	0	0	0	0	1 (3.1)
Tumour Pain	0	2 (0.6)	0	0	0	0
Uterine Leiomyoma	2 (0.8)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Vaginal Neoplasm	1 (0.4)	0	0	0	0	0
Nervous System Disorders	**119 (48.8)**	**176 (48.8)**	**141 (62.9)**	**145 (46.0)**	**16 (61.5)**	**15 (46.9)**
Ageusia	1 (0.4)	0	0	2 (0.6)	0	0
Akathisia	0	0	0	1 (0.3)	0	0
Akinesia	0	0	1 (0.4)	0	0	0
Amnesia	0	3 (0.8)	0	1 (0.3)	0	0
Aphasia	1 (0.4)	0	0	1 (0.3)	0	0
Areflexia	0	2 (0.6)	0	0	0	0
Asterixis	0	1 (0.3)	0	0	0	0
Ataxia	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Athetosis	0	0	0	1 (0.3)	0	0
Balance Disorder	0	5 (1.4)	2 (0.9)	2 (0.6)	0	0
Brachial Plexopathy	0	0	0	1 (0.3)	0	0
Brain Compression	0	0	0	0	1 (3.8)	0
Brain Oedema	2 (0.8)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Burning Sensation	0	8 (2 2)	1 (0.4)	1 (0.3)	0	0
Central Nervous System Lesion	0	1 (0 3)	1 (0.4)	0	0	0
Cerebellar Haemorrhage	2 (0.8)	0	0	0	1 (3.8)	0
Cerebral Haemorrhage	5 (2.0)	0	2 (0.9)	3 (1.0)	0	0
Cerebral Hypoperfusion	0	0	1 (0.4)	0	0	0
Cerebral Infarction	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Cerebrovascular Accident	1 (0.4)	1 (0 3)	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Clonus	1 (0.4)	0	0	0	0	0
Cluster Headache	0	1 (0.3)	0	0	0	0
Cognitive Disorder	0	3 (0.8)	1 (0.4)	0	0	0
Coma	2 (0.8)	1 (0 3)	2 (0.9)	3 (1.0)	0	0
Demyelination	1 (0.4)	3 (0.8)	0	0	0	0
Depressed Level Of Consciousness	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	1 (3.1)
Disturbance In Attention	0	0	4 (1.8)	2 (0.6)	0	0
Dizziness	26 (10.7)	35 (9.7)	24 (10.7)	28 (8.9)	2 (7.7)	3 (9.4)
Dizziness Postural	1 (0.4)	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Dysaesthesia	0	1 (0 3)	0	0	0	0
Dysarthria	0	2 (0.6)	1 (0.4)	2 (0.6)	0	1 (3.1)
Dysgeusia	4 (1.6)	5 (1.4)	6 (2.7)	3 (1.0)	0	0
Encephalopathy	2 (0.8)	3 (0.8)	2 (0.9)	1 (0.3)	0	0
Epilepsy	0	0	1 (0.4)	0	0	0
Extrapyramidal Disorder	0	2 (0.6)	0	0	0	0
Facial Paralysis	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Facial Paresis	1 (0.4)	0	0	1 (0.3)	0	0
Generalised Tonic-Clonic Seizure	0	0	1 (0.4)	1 (0.3)	0	0
Guillain-Barre Syndrome	0	0	0	1 (0.3)	0	0
Haemorrhage Intracranial	0	2 (0.6)	4 (1.8)	2 (0.6)	0	0
Haemorrhagic Stroke	0	1 (0 3)	1 (0.4)	0	0	0
Head Discomfort	0	1 (0.3)	0	0	0	0
Headache	78 (32.0)	93 (25.8)	72 (32.1)	67 (21.3)	10 (38.5)	12 (37.5)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hemiparesis	0	0	5 (2.2)	2 (0.6)	0	0
Hemiplegia	1 (0.4)	0	2 (0.9)	1 (0.3)	0	0
Hydrocephalus	0	0	0	0	1 (3.8)	0
Hyperreflexia	0	0	1 (0.4)	1 (0.3)	0	0
Hypertonia	0	0	1 (0.4)	2 (0.6)	0	0
Hypoaesthesia	1 (0.4)	5 (1.4)	6 (2.7)	7 (2.2)	1 (3.8)	2 (6.3)
Hypogeusia	0	2 (0.6)	2 (0.9)	1 (0 3)	0	0
Hypoglycaemic Coma	1 (0.4)	0	0	0	0	0
Hypokinesia	0	0	0	1 (0.3)	0	0
Hyporeflexia	0	3 (0.8)	2 (0.9)	0	0	0
Hypotonia	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Incoherent	0	0	1 (0.4)	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	1 (3.8)	0
Intention Tremor	0	0	1 (0.4)	0	0	0
Intercostal Neuralgia	0	0	1 (0.4)	0	0	0
Intracranial Aneurysm	0	0	0	1 (0.3)	0	0
Lethargy	9 (3.7)	10 (2.8)	11 (4.9)	11 (3 5)	3 (11.5)	0
Leukoencephalopathy	2 (0.8)	0	0	0	0	0
Loss Of Consciousness	2 (0.8)	2 (0.6)	3 (1.3)	2 (0.6)	1 (3.8)	0
Memory Impairment	2 (0.8)	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Meningism	0	1 (0 3)	0	0	0	0
Mental Impairment	0	0	0	1 (0.3)	0	0
Metabolic Encephalopathy	2 (0.8)	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Migraine	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Myoclonus	0	2 (0.6)	1 (0.4)	0	0	0
Nerve Compression	0	1 (0 3)	0	0	0	0
Nervous System Disorder	1 (0.4)	1 (0.3)	0	0	0	0
Neuralgia	1 (0.4)	0	1 (0.4)	0	0	0
Neurological Symptom	1 (0.4)	0	0	0	0	0
Neuropathy Peripheral	4 (1.6)	5 (1.4)	8 (3.6)	4 (1.3)	0	0
Neurotoxicity	0	0	0	2 (0.6)	0	0
Nystagmus	0	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Paraesthesia	7 (2.9)	10 (2.8)	10 (4.5)	11 (3 5)	1 (3.8)	0
Paralysis	2 (0.8)	0	0	0	0	0
Paresis	0	0	0	1 (0.3)	0	0
Parosmia	1 (0.4)	0	0	0	0	0
Peripheral Sensory Neuropathy	0	0	0	1 (0.3)	1 (3.8)	0
Peroneal Nerve Palsy	1 (0.4)	1 (0 3)	0	1 (0.3)	0	0
Polyneuropathy	0	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Poor Quality Sleep	0	1 (0 3)	1 (0.4)	0	0	0
Post Herpetic Neuralgia	1 (0.4)	1 (0.3)	2 (0.9)	1 (0.3)	0	0
Presyncope	1 (0.4)	2 (0.6)	0	0	1 (3.8)	1 (3.1)
Psychomotor Hyperactivity	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Reflexes Abnormal	0	1 (0 3)	0	1 (0.3)	0	0
Sciatica	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Sedation	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Seizure	3 (1.2)	6 (1.7)	4 (1.8)	3 (1.0)	0	0
Sensory Disturbance	0	1 (0 3)	0	0	0	0
Sensory Loss	1 (0.4)	3 (0.8)	2 (0.9)	0	0	0
Sinus Headache	1 (0.4)	2 (0.6)	0	0	0	0
Somnolence	7 (2.9)	10 (2.8)	7 (3.1)	5 (1.6)	0	0
Speech Disorder	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Stupor	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Syncope	9 (3.7)	7 (1.9)	3 (1.3)	2 (0.6)	1 (3.8)	0
Tension Headache	0	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Tonic Convulsion	0	1 (0.3)	0	0	0	0
Toxic Neuropathy	1 (0.4)	0	0	0	0	0
Transient Ischaemic Attack	0	1 (0 3)	0	0	0	0
Tremor	15 (6.1)	33 (9.1)	23 (10.3)	21 (6.7)	1 (3.8)	1 (3.1)
Trigeminal Neuralgia	0	0	0	1 (0.3)	0	0
Unresponsive To Stimuli	0	1 (0.3)	2 (0.9)	1 (0 3)	0	0
Visual Field Defect	0	2 (0.6)	1 (0.4)	0	0	0
Pregnancy, Puerperium And Perinatal Conditions	**1 (0.4)**	**0**	**0**	**0**	**0**	**0**
Pregnancy	1 (0.4)	0	0	0	0	0
Product Issues	**9 (3.7)**	**7 (1.9)**	**9 (4.0)**	**5 (1.6)**	**0**	**0**
Device Breakage	0	0	0	1 (0.3)	0	0
Device Leakage	3 (1.2)	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Device Occlusion	5 (2.0)	5 (1.4)	4 (1.8)	3 (1.0)	0	0
Thrombosis In Device	1 (0.4)	2 (0.6)	4 (1.8)	1 (0.3)	0	0
Psychiatric Disorders	**89 (36.5)**	**131 (36.3)**	**92 (41.1)**	**108 (34.3)**	**15 (57.7)**	**12 (37.5)**
Abnormal Behaviour	0	0	1 (0.4)	0	0	0
Abnormal Dreams	0	0	1 (0.4)	0	0	0
Adjustment Disorder With Depressed Mood	1 (0.4)	0	0	1 (0.3)	0	0
Affect Lability	3 (1.2)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Affective Disorder	1 (0.4)	1 (0.3)	0	0	0	0
Aggression	0	1 (0 3)	0	0	0	0
Agitated Depression	1 (0.4)	0	0	0	0	0
Agitation	9 (3.7)	7 (1 9)	7 (3.1)	7 (2.2)	0	0
Anger	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Anxiety	19 (7.8)	34 (9.4)	31 (13.8)	25 (7.9)	6 (23.1)	3 (9.4)
Aversion	0	0	0	0	1 (3.8)	0
Claustrophobia	0	0	1 (0.4)	0	0	0
Confusional State	11 (4.5)	18 (5.0)	13 (5.8)	15 (4.8)	3 (11.5)	0
Delirium	0	5 (1.4)	1 (0.4)	1 (0.3)	0	0
Depressed Mood	0	5 (1.4)	3 (1.3)	1 (0.3)	0	1 (3.1)
Depression	19 (7.8)	32 (8.9)	21 (9.4)	24 (7.6)	1 (3.8)	2 (6.3)
Depression Suicidal	0	0	0	1 (0.3)	0	0
Disorientation	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Disturbance In Social Behaviour	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Eating Disorder	0	0	1 (0.4)	1 (0.3)	0	0
Emotional Disorder	0	0	0	1 (0.3)	0	0
Emotional Distress	1 (0.4)	0	1 (0.4)	0	0	0
Euphoric Mood	1 (0.4)	1 (0 3)	0	0	0	0
Fear	0	0	0	1 (0.3)	0	0
Feeling Of Despair	1 (0.4)	0	0	0	0	0
Flat Affect	0	2 (0.6)	0	1 (0.3)	0	0
Frustration Tolerance Decreased	1 (0.4)	0	0	0	0	0
Generalised Anxiety Disorder	0	1 (0.3)	0	1 (0.3)	0	0
Hallucination	3 (1.2)	3 (0.8)	2 (0.9)	3 (1.0)	1 (3.8)	0
Hallucination, Visual	1 (0.4)	1 (0.3)	1 (0.4)	0	0	2 (6.3)
Hypomania	0	1 (0 3)	0	0	0	0
Insomnia	36 (14.8)	65 (18.0)	41 (18.3)	53 (16.8)	5 (19.2)	7 (21.9)
Irritability	1 (0.4)	1 (0.3)	0	2 (0.6)	0	0
Mania	0	0	0	2 (0.6)	0	0
Mental Disorder	0	0	1 (0.4)	0	0	0
Mental Status Changes	5 (2.0)	5 (1.4)	4 (1.8)	7 (2.2)	0	0
Mood Altered	2 (0.8)	4 (1 1)	3 (1.3)	0	0	0
Mood Swings	0	0	2 (0.9)	1 (0.3)	0	0
Nervousness	1 (0.4)	1 (0 3)	0	0	1 (3.8)	0
Nightmare	1 (0.4)	2 (0.6)	0	2 (0.6)	0	0
Obsessive-Compulsive Disorder	0	1 (0 3)	0	0	0	0
Paranoia	0	0	1 (0.4)	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Phonophobia	0	0	1 (0.4)	0	0	0
Posturing	0	0	1 (0.4)	0	0	0
Psychotic Disorder	1 (0.4)	1 (0 3)	1 (0.4)	0	0	0
Restlessness	2 (0.8)	3 (0.8)	1 (0.4)	1 (0.3)	1 (3.8)	2 (6.3)
Sleep Disorder	1 (0.4)	2 (0.6)	0	4 (1.3)	0	0
Sleep Disorder Due To General Medical Condition, Insomnia Type	0	1 (0.3)	0	0	0	0
Stress	1 (0.4)	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Substance-Induced Psychotic Disorder	0	0	1 (0.4)	0	0	0
Suicidal Ideation	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Tachyphrenia	0	0	0	1 (0.3)	0	0
Tearfulness	0	0	1 (0.4)	0	0	0
Renal And Urinary Disorders	**66 (27.0)**	**102 (28.3)**	**63 (28.1)**	**92 (29.2)**	**7 (26.9)**	**8 (25.0)**
Acute Kidney Injury	6 (2.5)	8 (2 2)	4 (1.8)	8 (2.5)	2 (7.7)	0
Acute Prerenal Failure	1 (0.4)	0	0	0	0	0
Anuria	1 (0.4)	3 (0.8)	0	1 (0.3)	0	0
Azotaemia	1 (0.4)	0	0	1 (0.3)	0	0
Bilirubinuria	0	0	0	1 (0.3)	0	0
Bladder Dilatation	0	0	0	1 (0.3)	0	0
Bladder Pain	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Bladder Spasm	4 (1.6)	1 (0.3)	0	3 (1.0)	0	0
Choluria	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Chromaturia	0	2 (0.6)	3 (1.3)	0	0	0
Chronic Kidney Disease	1 (0.4)	0	0	1 (0.3)	0	0
Costovertebral Angle Tenderness	0	1 (0 3)	0	0	0	0
Cystitis Haemorrhagic	4 (1.6)	7 (1.9)	4 (1.8)	7 (2.2)	0	0
Dysuria	14 (5.7)	22 (6.1)	9 (4.0)	20 (6 3)	0	1 (3.1)
Glycosuria	0	1 (0.3)	1 (0.4)	0	0	0
Haematuria	16 (6.6)	23 (6.4)	16 (7.1)	22 (7.0)	4 (15.4)	3 (9.4)
Hydronephrosis	1 (0.4)	1 (0 3)	0	0	0	1 (3.1)
Incontinence	0	1 (0 3)	0	0	0	0
Kidney Enlargement	0	0	1 (0.4)	0	0	0
Micturition Disorder	1 (0.4)	0	0	0	0	0
Micturition Frequency Decreased	0	1 (0.3)	0	0	0	0
Micturition Urgency	3 (1.2)	1 (0 3)	0	2 (0.6)	0	0
Nephrolithiasis	3 (1.2)	1 (0 3)	0	0	0	0
Nephropathy	0	0	0	1 (0.3)	0	0
Nocturia	0	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Obstructive Nephropathy	0	0	0	1 (0.3)	0	0
Oliguria	4 (1.6)	6 (1.7)	2 (0.9)	1 (0.3)	0	1 (3.1)
Pollakiuria	5 (2.0)	12 (3.3)	4 (1.8)	8 (2.5)	0	0
Polyuria	5 (2.0)	3 (0.8)	0	1 (0.3)	0	0
Proteinuria	0	1 (0 3)	0	1 (0.3)	0	0
Renal Cyst	0	1 (0 3)	2 (0.9)	0	0	1 (3.1)
Renal Disorder	1 (0.4)	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Renal Failure	14 (5.7)	26 (7.2)	22 (9.8)	41 (13.0)	0	2 (6.3)
Renal Haematoma	0	1 (0 3)	0	0	0	0
Renal Hypertension	0	0	0	1 (0.3)	0	0
Renal Impairment	5 (2.0)	7 (1 9)	7 (3.1)	9 (2.9)	1 (3.8)	0
Renal Mass	0	0	0	0	0	1 (3.1)
Renal Pain	0	1 (0 3)	0	0	0	0
Renal Tubular Necrosis	0	0	2 (0.9)	1 (0.3)	0	0
Renal Vein Thrombosis	0	1 (0 3)	0	0	0	0
Stress Urinary Incontinence	1 (0.4)	1 (0 3)	0	0	0	0
Tubulointerstitial Nephritis	0	0	0	2 (0.6)	0	0
Urethral Discharge	0	0	0	1 (0.3)	0	0
Urethral Haemorrhage	0	1 (0 3)	0	0	0	0
Urinary Hesitation	0	1 (0 3)	0	2 (0.6)	0	0
Urinary Incontinence	6 (2.5)	6 (1.7)	8 (3.6)	3 (1.0)	0	0
Urinary Retention	0	8 (2 2)	4 (1.8)	5 (1.6)	1 (3.8)	1 (3.1)
Urine Abnormality	0	1 (0 3)	0	0	0	0
Urine Odour Abnormal	1 (0.4)	0	0	0	0	0
Urogenital Disorder	1 (0.4)	0	0	0	0	0
Reproductive System And Breast Disorders	**44 (18.0)**	**18 (5.0)**	**42 (18.8)**	**17 (5.4)**	**7 (26.9)**	**1 (3.1)**
Adnexa Uteri Cyst	1 (0.4)	0	0	0	0	0
Balanoposthitis	0	1 (0.3)	0	1 (0 3)	0	1 (3.1)
Bartholin's Cyst	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Benign Prostatic Hyperplasia	0	2 (0.6)	0	0	0	0
Breast Mass	0	1 (0.3)	0	0	0	0
Breast Pain	1 (0.4)	0	0	1 (0.3)	0	0
Dysfunctional Uterine Bleeding	1 (0.4)	0	0	0	0	0
Dysmenorrhoea	2 (0.8)	0	4 (1.8)	0	0	0
Dyspareunia	1 (0.4)	0	0	0	0	0
Epididymal Disorder	0	1 (0 3)	0	0	0	0
Erectile Dysfunction	0	1 (0.3)	0	1 (0.3)	0	0
Genital Erosion	0	0	0	1 (0.3)	0	0
Genital Erythema	0	0	0	2 (0.6)	0	0
Genital Lesion	0	0	1 (0.4)	1 (0.3)	0	0
Genital Swelling	0	0	1 (0.4)	0	2 (7.7)	0
Genital Ulceration	1 (0.4)	0	1 (0.4)	0	0	0
Gynaecomastia	0	1 (0.3)	0	0	0	0
Menopausal Symptoms	2 (0.8)	0	0	0	0	0
Menorrhagia	2 (0.8)	0	5 (2.2)	0	1 (3.8)	0
Menstrual Disorder	2 (0.8)	0	1 (0.4)	0	1 (3.8)	0
Metrorrhagia	5 (2.0)	0	6 (2.7)	0	0	0
Pelvic Discomfort	1 (0.4)	0	0	1 (0.3)	0	0
Pelvic Haematoma	0	1 (0 3)	0	0	0	0
Pelvic Pain	2 (0.8)	0	1 (0.4)	0	0	0
Penile Discharge	0	0	0	1 (0.3)	0	0
Penile Haemorrhage	0	1 (0 3)	0	1 (0.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Penile Necrosis	0	1 (0.3)	0	0	0	0
Penile Oedema	0	1 (0.3)	0	1 (0.3)	0	0
Penile Pain	0	1 (0 3)	0	2 (0.6)	0	0
Perineal Pain	0	1 (0 3)	0	0	0	0
Postmenopausal Haemorrhage	1 (0.4)	0	0	0	0	0
Prostatism	0	1 (0 3)	0	0	0	0
Prostatitis	0	1 (0.3)	0	1 (0 3)	0	0
Pruritus Genital	2 (0.8)	0	0	0	0	0
Scrotal Oedema	0	2 (0.6)	0	3 (1.0)	0	0
Scrotal Pain	0	0	0	1 (0.3)	0	0
Scrotal Swelling	0	1 (0 3)	0	1 (0.3)	0	0
Sexual Dysfunction	0	0	0	1 (0.3)	0	0
Testicular Pain	0	1 (0 3)	0	2 (0.6)	0	0
Testicular Swelling	0	1 (0.3)	0	0	0	0
Uterine Disorder	1 (0.4)	0	0	0	0	0
Uterine Haemorrhage	0	0	1 (0.4)	0	0	0
Vaginal Discharge	0	0	2 (0.9)	0	1 (3.8)	0
Vaginal Dysplasia	0	0	1 (0.4)	0	0	0
Vaginal Haemorrhage	24 (9.8)	0	20 (8.9)	0	3 (11.5)	0
Vulval Oedema	1 (0.4)	0	0	0	0	0
Vulval Ulceration	0	0	1 (0.4)	0	0	0
Vulvovaginal Burning Sensation	2 (0.8)	0	0	0	0	0
Vulvovaginal Discomfort	1 (0.4)	0	2 (0.9)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Vulvovaginal Dryness	1 (0.4)	0	0	0	0	0
Vulvovaginal Pain	1 (0.4)	0	0	0	0	0
Vulvovaginal Pruritus	1 (0.4)	0	1 (0.4)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**146 (59.8)**	**216 (59.8)**	**145 (64.7)**	**181 (57 5)**	**19 (73.1)**	**25 (78.1)**
Acute Promyelocytic Leukaemia Differentiation Syndrome	1 (0.4)	0	0	0	0	1 (3.1)
Acute Pulmonary Oedema	1 (0.4)	1 (0.3)	0	2 (0.6)	0	0
Acute Respiratory Distress Syndrome	1 (0.4)	5 (1.4)	6 (2.7)	1 (0.3)	1 (3.8)	0
Acute Respiratory Failure	3 (1.2)	2 (0.6)	0	1 (0.3)	0	0
Apnoea	1 (0.4)	1 (0 3)	0	0	0	0
Asthma	2 (0.8)	2 (0.6)	1 (0.4)	0	0	0
Atelectasis	7 (2.9)	18 (5.0)	2 (0.9)	10 (3 2)	3 (11.5)	0
Bronchial Hyperreactivity	0	0	1 (0.4)	0	0	0
Bronchial Obstruction	0	0	1 (0.4)	1 (0.3)	0	0
Bronchial Wall Thickening	0	1 (0.3)	0	0	0	0
Bronchitis Chronic	0	0	0	1 (0.3)	0	0
Bronchopneumopathy	1 (0.4)	0	0	0	0	0
Bronchospasm	3 (1.2)	6 (1.7)	5 (2.2)	4 (1.3)	0	0
Chronic Obstructive Pulmonary Disease	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Cough	66 (27.0)	90 (24.9)	64 (28.6)	74 (23.5)	6 (23.1)	10 (31.3)
Diaphragmalgia	1 (0.4)	0	0	0	0	0
Diaphragmatic Disorder	0	0	0	1 (0.3)	0	0
Diffuse Alveolar Damage	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Dry Throat	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Dysphonia	3 (1.2)	3 (0.8)	3 (1.3)	5 (1.6)	0	0
Dyspnoea	38 (15.6)	63 (17 5)	44 (19.6)	62 (19.7)	7 (26.9)	6 (18.8)
Dyspnoea Exertional	7 (2.9)	16 (4.4)	9 (4.0)	9 (2.9)	1 (3.8)	0
Dyspnoea Paroxysmal Nocturnal	0	0	0	1 (0.3)	0	0
Emphysema	0	1 (0 3)	1 (0.4)	0	0	0
Epiglottis Ulcer	0	1 (0 3)	0	0	0	0
Epistaxis	33 (13.5)	47 (13.0)	42 (18.8)	30 (9.5)	6 (23.1)	6 (18.8)
Haemoptysis	5 (2.0)	17 (4.7)	8 (3.6)	12 (3.8)	1 (3.8)	2 (6.3)
Haemothorax	0	0	0	2 (0.6)	0	0
Hiccups	2 (0.8)	10 (2.8)	3 (1.3)	4 (1.3)	0	1 (3.1)
Hydrothorax	0	1 (0 3)	0	1 (0.3)	0	0
Hypercapnia	1 (0.4)	0	0	0	0	0
Hyperventilation	2 (0.8)	1 (0.3)	0	0	0	0
Hypocapnia	1 (0.4)	0	0	0	0	0
Hypoxia	10 (4.1)	12 (3.3)	13 (5.8)	21 (6.7)	4 (15.4)	3 (9.4)
Increased Bronchial Secretion	3 (1.2)	1 (0.3)	1 (0.4)	0	0	0
Increased Upper Airway Secretion	1 (0.4)	1 (0 3)	3 (1.3)	1 (0.3)	0	0
Increased Viscosity Of Bronchial Secretion	1 (0.4)	2 (0.6)	3 (1.3)	0	0	0
Interstitial Lung Disease	1 (0.4)	3 (0.8)	0	2 (0.6)	0	0
Laryngeal Infiltration	0	0	0	1 (0.3)	0	0
Laryngeal Oedema	1 (0.4)	0	0	0	0	1 (3.1)
Lung Consolidation	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	2 (7.7)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Lung Disorder	2 (0.8)	2 (0.6)	1 (0.4)	0	0	1 (3.1)
Lung Infiltration	8 (3.3)	13 (3.6)	13 (5.8)	10 (3.2)	0	0
Nasal Congestion	12 (4.9)	13 (3.6)	10 (4.5)	11 (3 5)	1 (3.8)	1 (3.1)
Nasal Discomfort	0	3 (0.8)	1 (0.4)	0	0	0
Nasal Dryness	1 (0.4)	0	4 (1.8)	0	0	0
Nasal Inflammation	0	0	1 (0.4)	0	0	0
Nasal Necrosis	0	0	0	1 (0.3)	0	0
Nasal Obstruction	0	2 (0.6)	1 (0.4)	0	0	0
Nasal Septum Disorder	1 (0.4)	0	0	0	0	0
Nasal Ulcer	0	0	1 (0.4)	0	0	0
Nocturnal Dyspnoea	0	1 (0 3)	0	0	0	0
Obliterative Bronchiolitis	0	0	1 (0.4)	1 (0.3)	0	0
Obstructive Airways Disorder	0	0	1 (0.4)	0	0	0
Organising Pneumonia	0	2 (0.6)	0	0	0	0
Oropharyngeal Pain	23 (9.4)	41 (11.4)	25 (11.2)	29 (9.2)	7 (26.9)	4 (12.5)
Oropharyngeal Swelling	1 (0.4)	0	0	0	0	0
Orthopnoea	0	1 (0.3)	1 (0.4)	2 (0.6)	0	0
Painful Respiration	1 (0.4)	1 (0.3)	0	0	0	0
Paranasal Sinus Discomfort	1 (0.4)	2 (0.6)	0	0	0	0
Paranasal Sinus Hypersecretion	0	1 (0.3)	0	0	0	0
Pharyngeal Erythema	1 (0.4)	4 (1 1)	0	2 (0.6)	1 (3.8)	0
Pharyngeal Lesion	0	1 (0 3)	0	0	0	0
Pharyngeal Ulceration	0	0	0	1 (0.3)	0	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Pleural Effusion	16 (6.6)	31 (8.6)	13 (5.8)	26 (8 3)	2 (7.7)	2 (6.3)
Pleural Rub	0	0	0	1 (0.3)	0	0
Pleurisy	0	1 (0.3)	1 (0.4)	0	0	0
Pleuritic Pain	4 (1.6)	2 (0.6)	4 (1.8)	3 (1.0)	0	0
Pneumomediastinum	0	0	0	1 (0.3)	0	0
Pneumonia Aspiration	0	3 (0.8)	2 (0.9)	1 (0.3)	0	0
Pneumonitis	3 (1.2)	4 (1.1)	1 (0.4)	3 (1.0)	0	0
Pneumothorax	3 (1.2)	2 (0.6)	1 (0.4)	4 (1.3)	1 (3.8)	0
Productive Cough	8 (3.3)	22 (6.1)	9 (4.0)	24 (7.6)	2 (7.7)	0
Prolonged Expiration	0	1 (0 3)	0	0	0	0
Pulmonary Alveolar Haemorrhage	3 (1.2)	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Pulmonary Congestion	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Pulmonary Embolism	1 (0.4)	6 (1.7)	2 (0.9)	0	0	0
Pulmonary Fibrosis	0	0	0	1 (0.3)	0	0
Pulmonary Haemorrhage	2 (0.8)	5 (1.4)	3 (1.3)	3 (1.0)	0	0
Pulmonary Haemosiderosis	0	0	0	1 (0.3)	0	0
Pulmonary Hypertension	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
Pulmonary Mass	4 (1.6)	4 (1 1)	4 (1.8)	4 (1.3)	0	0
Pulmonary Oedema	6 (2.5)	10 (2.8)	11 (4.9)	8 (2.5)	2 (7.7)	1 (3.1)
Rales	10 (4.1)	25 (6.9)	8 (3.6)	22 (7.0)	2 (7.7)	3 (9.4)
Respiratory Acidosis	1 (0.4)	1 (0 3)	2 (0.9)	0	0	0
Respiratory Alkalosis	0	0	0	2 (0.6)	0	0
Respiratory Arrest	0	1 (0 3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Respiratory Disorder	1 (0.4)	1 (0 3)	1 (0.4)	0	1 (3.8)	0
Respiratory Distress	6 (2.5)	4 (1 1)	4 (1.8)	3 (1.0)	0	2 (6.3)
Respiratory Failure	13 (5.3)	12 (3.3)	18 (8.0)	19 (6.0)	0	2 (6.3)
Respiratory Tract Congestion	1 (0.4)	3 (0.8)	0	1 (0.3)	1 (3.8)	0
Respiratory Tract Haemorrhage	0	1 (0 3)	0	0	0	0
Restrictive Pulmonary Disease	1 (0.4)	0	0	1 (0.3)	0	0
Rhinalgia	0	1 (0 3)	1 (0.4)	0	0	0
Rhinitis Allergic	0	0	1 (0.4)	0	0	0
Rhinorrhoea	6 (2.5)	24 (6.6)	9 (4.0)	13 (4 1)	2 (7.7)	2 (6.3)
Rhonchi	2 (0.8)	5 (1.4)	4 (1.8)	6 (1.9)	0	0
Sinus Congestion	3 (1.2)	14 (3.9)	5 (2.2)	9 (2.9)	0	0
Sinus Disorder	0	1 (0.3)	2 (0.9)	0	0	0
Sinus Pain	0	4 (1 1)	6 (2.7)	4 (1.3)	0	0
Sinus Polyp	1 (0.4)	1 (0 3)	0	0	0	0
Sleep Apnoea Syndrome	0	0	0	1 (0.3)	0	0
Sneezing	1 (0.4)	1 (0 3)	1 (0.4)	2 (0.6)	0	1 (3.1)
Sputum Discoloured	0	3 (0.8)	0	1 (0.3)	0	0
Sputum Increased	1 (0.4)	0	1 (0.4)	0	0	0
Tachypnoea	10 (4.1)	8 (2 2)	4 (1.8)	11 (3 5)	2 (7.7)	3 (9.4)
Throat Irritation	1 (0.4)	0	0	1 (0.3)	0	0
Throat Lesion	0	1 (0 3)	0	0	0	0
Throat Tightness	0	1 (0 3)	0	1 (0.3)	0	0
Tonsillar Disorder	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Tonsillar Ulcer	0	1 (0.3)	0	0	0	0
Upper-Airway Cough Syndrome	6 (2.5)	3 (0.8)	1 (0.4)	3 (1.0)	0	0
Vocal Cord Inflammation	0	1 (0 3)	0	0	0	0
Wheezing	3 (1.2)	16 (4.4)	6 (2.7)	17 (5.4)	4 (15.4)	2 (6.3)
Skin And Subcutaneous Tissue Disorders	**130 (53.3)**	**178 (49.3)**	**117 (52.2)**	**150 (47.6)**	**19 (73.1)**	**23 (71.9)**
Acne	0	2 (0.6)	2 (0.9)	6 (1.9)	0	0
Actinic Cheilitis	0	1 (0.3)	0	0	0	0
Acute Febrile Neutrophilic Dermatosis	0	0	1 (0.4)	0	1 (3.8)	0
Alopecia	19 (7.8)	12 (3.3)	13 (5.8)	11 (3 5)	3 (11.5)	0
Alopecia Totalis	1 (0.4)	0	0	0	0	0
Angioedema	0	1 (0 3)	0	1 (0.3)	0	0
Blister	2 (0.8)	8 (2.2)	2 (0.9)	3 (1.0)	0	0
Blood Blister	2 (0.8)	3 (0.8)	0	2 (0.6)	2 (7.7)	0
Cold Sweat	1 (0.4)	1 (0 3)	0	0	0	0
Cutaneous Vasculitis	1 (0.4)	0	0	0	0	0
Decubitus Ulcer	2 (0.8)	3 (0.8)	4 (1.8)	4 (1.3)	0	0
Dermal Cyst	0	0	0	1 (0.3)	0	0
Dermatitis	3 (1.2)	4 (1.1)	1 (0.4)	4 (1.3)	1 (3.8)	0
Dermatitis Acneiform	1 (0.4)	0	0	0	0	0
Dermatitis Allergic	7 (2.9)	5 (1.4)	4 (1.8)	2 (0.6)	0	0
Dermatitis Bullous	0	0	0	2 (0.6)	0	0
Dermatitis Contact	1 (0.4)	1 (0 3)	0	0	0	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Dermatitis Exfoliative	0	0	0	1 (0.3)	0	0
Drug Eruption	3 (1.2)	2 (0.6)	3 (1.3)	4 (1.3)	1 (3.8)	1 (3.1)
Dry Skin	7 (2.9)	9 (2 5)	8 (3.6)	5 (1.6)	0	1 (3.1)
Ecchymosis	4 (1.6)	4 (1 1)	10 (4.5)	7 (2.2)	2 (7.7)	1 (3.1)
Eczema	2 (0.8)	2 (0.6)	0	0	0	0
Erythema	11 (4.5)	30 (8.3)	7 (3.1)	25 (7 9)	4 (15.4)	1 (3.1)
Erythema Multiforme	0	0	0	1 (0.3)	0	0
Erythema Nodosum	0	0	0	0	1 (3.8)	0
Erythrosis	1 (0.4)	0	0	0	0	0
Exfoliative Rash	0	0	0	1 (0.3)	0	0
Generalised Erythema	0	1 (0 3)	0	0	0	0
Hangnail	0	1 (0 3)	0	1 (0.3)	0	0
Hidradenitis	2 (0.8)	1 (0 3)	0	0	0	0
Hirsutism	1 (0.4)	1 (0 3)	0	0	0	0
Hyperhidrosis	4 (1.6)	16 (4.4)	7 (3.1)	12 (3.8)	1 (3.8)	2 (6.3)
Hypersensitivity Vasculitis	1 (0.4)	1 (0 3)	0	0	0	0
Hypertrichosis	2 (0.8)	0	1 (0.4)	0	0	0
Ingrowing Nail	2 (0.8)	2 (0.6)	0	1 (0.3)	0	0
Leukoplakia	0	1 (0.3)	1 (0.4)	0	0	0
Lichenification	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Lichenoid Keratosis	0	0	1 (0.4)	0	0	0
Lipohypertrophy	0	0	0	1 (0.3)	0	0
Livedo Reticularis	0	0	1 (0.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Macule	1 (0.4)	0	1 (0.4)	0	0	0
Madarosis	0	0	1 (0.4)	0	0	0
Nail Disorder	0	1 (0 3)	0	0	0	0
Neurodermatitis	0	1 (0.3)	0	0	0	0
Night Sweats	10 (4.1)	8 (2.2)	2 (0.9)	8 (2.5)	0	1 (3.1)
Onychoclasis	0	1 (0 3)	0	0	0	0
Onychomadesis	0	1 (0 3)	0	1 (0.3)	0	0
Pain Of Skin	4 (1.6)	0	4 (1.8)	2 (0.6)	0	0
Palmar Erythema	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	1 (3.8)	0
Palmar-Plantar Erythrodysaesthesia Syndrome	4 (1.6)	0	1 (0.4)	0	0	0
Papule	2 (0.8)	0	1 (0.4)	2 (0.6)	2 (7.7)	1 (3.1)
Penile Ulceration	0	0	0	1 (0.3)	0	0
Petechiae	26 (10.7)	33 (9.1)	26 (11.6)	26 (8.3)	4 (15.4)	5 (15.6)
Photosensitivity Reaction	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Pigmentation Disorder	0	2 (0.6)	1 (0.4)	3 (1.0)	0	0
Prurigo	0	1 (0.3)	0	0	0	0
Pruritus	28 (11.5)	32 (8.9)	33 (14.7)	23 (7.3)	3 (11.5)	6 (18.8)
Pruritus Allergic	0	0	1 (0.4)	1 (0.3)	0	0
Pruritus Generalised	4 (1.6)	2 (0.6)	1 (0.4)	2 (0.6)	0	1 (3.1)
Psoriasis	0	0	0	1 (0.3)	0	0
Purpura	3 (1.2)	7 (1 9)	3 (1.3)	2 (0.6)	1 (3.8)	1 (3.1)
Purpura Senile	1 (0.4)	0	0	0	0	0
Rash	44 (18.0)	56 (15 5)	38 (17.0)	50 (15.9)	11 (42.3)	12 (37.5)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Rash Erythematous	3 (1.2)	5 (1.4)	2 (0.9)	4 (1.3)	0	1 (3.1)
Rash Follicular	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Rash Generalised	2 (0.8)	3 (0.8)	2 (0.9)	3 (1.0)	1 (3.8)	1 (3.1)
Rash Macular	2 (0.8)	3 (0.8)	1 (0.4)	1 (0.3)	1 (3.8)	1 (3.1)
Rash Maculo-Papular	6 (2.5)	8 (2 2)	1 (0.4)	6 (1.9)	0	1 (3.1)
Rash Papular	2 (0.8)	2 (0.6)	3 (1.3)	1 (0.3)	0	0
Rash Pruritic	1 (0.4)	6 (1.7)	4 (1.8)	8 (2.5)	0	0
Rash Vesicular	1 (0.4)	0	1 (0.4)	0	0	0
Red Man Syndrome	0	1 (0 3)	0	0	0	0
Rosacea	0	1 (0 3)	0	0	0	0
Scab	0	2 (0.6)	0	2 (0.6)	0	0
Skin Burning Sensation	0	1 (0 3)	0	1 (0.3)	0	0
Skin Discolouration	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Skin Disorder	3 (1.2)	4 (1 1)	3 (1.3)	6 (1.9)	0	1 (3.1)
Skin Dystrophy	0	0	1 (0.4)	0	0	0
Skin Exfoliation	3 (1.2)	5 (1.4)	4 (1.8)	5 (1.6)	1 (3.8)	0
Skin Fissures	0	0	1 (0.4)	0	0	0
Skin Haemorrhage	0	1 (0 3)	0	0	0	0
Skin Hyperpigmentation	2 (0.8)	5 (1.4)	4 (1.8)	0	0	0
Skin Hypopigmentation	0	1 (0 3)	0	0	0	0
Skin Irritation	0	0	1 (0.4)	0	0	0
Skin Lesion	7 (2.9)	13 (3.6)	4 (1.8)	10 (3 2)	1 (3.8)	2 (6.3)
Skin Mass	3 (1.2)	2 (0.6)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Skin Necrosis	0	0	1 (0.4)	0	0	0
Skin Oedema	1 (0.4)	0	0	0	0	0
Skin Striae	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Skin Ulcer	1 (0.4)	4 (1 1)	1 (0.4)	1 (0.3)	0	0
Subcutaneous Emphysema	0	1 (0.3)	0	0	0	0
Swelling Face	3 (1.2)	4 (1 1)	0	1 (0.3)	1 (3.8)	0
Transient Acantholytic Dermatosis	1 (0.4)	0	0	0	0	0
Urticaria	5 (2.0)	8 (2 2)	7 (3.1)	3 (1.0)	0	1 (3.1)
Vascular Skin Disorder	0	1 (0.3)	0	0	0	0
Vitiligo	0	0	0	1 (0.3)	0	0
Xanthomatosis	0	0	0	1 (0.3)	0	0
Social Circumstances	**1 (0.4)**	**1 (0.3)**	**0**	**2 (0.6)**	**0**	**0**
Loss Of Personal Independence In Daily Activities	0	0	0	1 (0.3)	0	0
Menopause	1 (0.4)	0	0	0	0	0
Social Problem	0	1 (0 3)	0	0	0	0
Treatment Noncompliance	0	0	0	1 (0.3)	0	0
Surgical And Medical Procedures	**8 (3.3)**	**9 (2.5)**	**7 (3.1)**	**9 (2.9)**	**1 (3.8)**	**2 (6.3)**
Abscess Drainage	0	0	0	1 (0.3)	0	0
Analgesic Therapy	0	0	1 (0.4)	0	0	0
Artificial Crown Procedure	0	0	1 (0.4)	0	0	0
Astringent Therapy	1 (0.4)	0	0	0	1 (3.8)	1 (3.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Blood Stem Cell Harvest	1 (0.4)	0	0	0	0	0
Bone Marrow Transplant	1 (0.4)	1 (0 3)	0	0	0	0
Central Venous Catheter Removal	0	0	0	1 (0.3)	0	0
Central Venous Catheterisation	0	0	1 (0.4)	0	0	0
Chemotherapy	0	0	1 (0.4)	1 (0.3)	0	0
Fluid Replacement	0	1 (0.3)	1 (0.4)	0	0	0
Incisional Drainage	0	0	1 (0.4)	0	0	0
Mitral Valve Replacement	1 (0.4)	0	0	0	0	0
Oesophageal Dilation Procedure	0	1 (0 3)	0	0	0	0
Oxygen Therapy	0	0	0	1 (0.3)	0	0
Parenteral Nutrition	1 (0.4)	0	0	0	0	0
Prophylaxis	0	0	0	1 (0.3)	0	0
Sinus Operation	2 (0.8)	3 (0.8)	0	3 (1.0)	0	0
Stem Cell Transplant	0	1 (0.3)	0	0	0	0
Surgery	0	0	0	0	0	1 (3.1)
Therapeutic Procedure	1 (0.4)	0	0	0	0	0
Tooth Extraction	0	1 (0.3)	0	1 (0.3)	0	0
Wisdom Teeth Removal	0	1 (0.3)	1 (0.4)	0	0	0
Vascular Disorders	**99 (40.6)**	**132 (36.6)**	**94 (42.0)**	**122 (38.7)**	**16 (61.5)**	**8 (25.0)**
Air Embolism	0	1 (0 3)	0	0	0	0
Angiodysplasia	0	0	0	0	0	1 (3.1)
Arteriovenous Fistula	0	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Capillary Leak Syndrome	0	1 (0.3)	0	0	0	0
Circulatory Collapse	2 (0.8)	0	3 (1.3)	3 (1.0)	0	0
Deep Vein Thrombosis	5 (2.0)	2 (0.6)	4 (1.8)	4 (1.3)	1 (3.8)	0
Diastolic Hypertension	0	0	1 (0.4)	0	0	0
Embolism Arterial	0	0	0	1 (0.3)	0	0
Flushing	2 (0.8)	3 (0.8)	6 (2.7)	4 (1.3)	2 (7.7)	1 (3.1)
Haematoma	9 (3.7)	7 (1.9)	9 (4.0)	7 (2.2)	5 (19.2)	0
Haemodynamic Instability	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Haemorrhage	3 (1.2)	3 (0.8)	1 (0.4)	4 (1.3)	0	0
Haemorrhagic Infarction	0	0	0	1 (0.3)	0	0
Hot Flush	1 (0.4)	0	2 (0.9)	0	0	0
Hyperaemia	0	1 (0 3)	0	0	0	0
Hypertension	40 (16.4)	70 (19.4)	43 (19.2)	52 (16.5)	3 (11.5)	2 (6.3)
Hypertensive Crisis	1 (0.4)	0	1 (0.4)	0	0	0
Hypotension	35 (14.3)	49 (13.6)	26 (11.6)	53 (16.8)	8 (30.8)	3 (9.4)
Hypovolaemic Shock	0	2 (0.6)	3 (1.3)	1 (0.3)	0	0
Intermittent Claudication	0	1 (0 3)	0	0	0	0
Ischaemia	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Jugular Vein Thrombosis	0	0	0	1 (0.3)	0	0
Labile Hypertension	0	0	0	1 (0.3)	0	0
Microangiopathy	0	1 (0 3)	0	0	0	0
Orthostatic Hypotension	6 (2.5)	10 (2.8)	6 (2.7)	1 (0.3)	0	1 (3.1)
Pallor	5 (2.0)	2 (0.6)	2 (0.9)	1 (0.3)	1 (3.8)	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Peripheral Circulatory Failure	0	1 (0 3)	0	0	0	0
Peripheral Coldness	0	0	1 (0.4)	0	0	0
Peripheral Vascular Disorder	1 (0.4)	0	0	0	0	0
Peripheral Venous Disease	0	1 (0 3)	0	0	0	0
Phlebitis	4 (1.6)	3 (0.8)	4 (1.8)	4 (1.3)	1 (3.8)	0
Poor Peripheral Circulation	0	0	0	2 (0.6)	0	0
Postpartum Venous Thrombosis	0	1 (0.3)	0	0	0	0
Reperfusion Injury	0	0	0	1 (0.3)	0	0
Secondary Hypertension	0	0	0	1 (0.3)	0	0
Shock	0	0	2 (0.9)	2 (0.6)	0	0
Subclavian Vein Thrombosis	0	2 (0.6)	0	0	0	0
Superior Vena Cava Stenosis	0	0	0	1 (0.3)	0	0
Thrombophlebitis	3 (1.2)	2 (0.6)	1 (0.4)	5 (1.6)	0	0
Thrombophlebitis Superficial	0	0	0	1 (0.3)	1 (3.8)	0
Thrombosis	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Varicose Vein	0	1 (0 3)	0	0	0	0
Vasculitis	0	1 (0.3)	0	0	1 (3.8)	0
Vasodilatation	0	0	1 (0.4)	0	0	1 (3.1)
Vein Disorder	1 (0.4)	0	0	0	0	0
Vena Cava Embolism	0	0	1 (0.4)	0	0	0
Venous Thrombosis	2 (0.8)	1 (0 3)	2 (0.9)	4 (1.3)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Venous Thrombosis Limb	1 (0.4)	0	0	1 (0.3)	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 2.7.4-167　　性別ごとの重度／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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Subjects Reporting Any Adverse Event	**182 (74.6)**	**266 (73.7)**	**165 (73.7)**	**216 (68.6)**	**22 (84.6)**	**25 (78.1)**
Blood And Lymphatic System Disorders	**94 (38.5)**	**145 (40.2)**	**103 (46.0)**	**108 (34 3)**	**12 (46.2)**	**16 (50.0)**
Anaemia	24 (9.8)	43 (11 9)	24 (10.7)	24 (7.6)	4 (15.4)	8 (25.0)
Bone Marrow Disorder	0	0	0	1 (0.3)	0	0
Bone Marrow Failure	1 (0.4)	2 (0.6)	0	0	0	0
Coagulopathy	0	0	2 (0.9)	2 (0.6)	1 (3.8)	0
Disseminated Intravascular Coagulation	0	2 (0.6)	3 (1.3)	1 (0.3)	0	0
Febrile Neutropenia	21 (8.6)	28 (7.8)	21 (9.4)	19 (6.0)	5 (19.2)	2 (6.3)
Granulocytopenia	0	1 (0 3)	0	1 (0.3)	0	0
Haemolysis	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Haemolytic Uraemic Syndrome	1 (0.4)	4 (1.1)	1 (0.4)	0	0	0
Haemorrhagic Diathesis	0	0	1 (0.4)	1 (0.3)	0	0
Leukocytosis	0	1 (0.3)	0	1 (0 3)	0	0
Leukopenia	6 (2.5)	13 (3.6)	12 (5.4)	8 (2 5)	3 (11.5)	2 (6.3)
Lymphadenitis	0	0	0	1 (0.3)	0	0
Lymphadenopathy	0	1 (0 3)	1 (0.4)	1 (0.3)	1 (3.8)	0
Lymphopenia	0	0	0	1 (0.3)	0	0
Microangiopathic Haemolytic Anaemia	0	0	1 (0.4)	0	0	0
Neutropenia	39 (16.0)	56 (15 5)	42 (18.8)	37 (11.7)	6 (23.1)	13 (40.6)
Pancytopenia	3 (1.2)	6 (1.7)	5 (2.2)	8 (2.5)	0	1 (3.1)
Splenomegaly	0	0	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Thrombocytopenia	54 (22.1)	89 (24.7)	57 (25.4)	60 (19.0)	9 (34.6)	7 (21.9)
Thrombocytosis	0	0	0	1 (0.3)	0	0
Thrombotic Microangiopathy	0	0	0	1 (0.3)	0	0
Thrombotic Thrombocytopenic Purpura	3 (1.2)	5 (1.4)	2 (0.9)	0	0	0
Cardiac Disorders	**12 (4.9)**	**34 (9.4)**	**17 (7.6)**	**23 (7 3)**	**2 (7.7)**	**3 (9.4)**
Acute Myocardial Infarction	0	1 (0.3)	0	0	0	0
Angina Pectoris	0	1 (0 3)	0	0	0	0
Arrhythmia	0	2 (0.6)	0	0	0	0
Arrhythmia Supraventricular	0	0	0	1 (0.3)	0	0
Atrial Fibrillation	2 (0.8)	6 (1.7)	3 (1.3)	5 (1.6)	1 (3.8)	1 (3.1)
Atrial Flutter	0	1 (0 3)	0	2 (0.6)	0	0
Atrioventricular Block	0	0	1 (0.4)	0	0	0
Atrioventricular Block Complete	0	1 (0.3)	0	0	0	0
Bradycardia	1 (0.4)	3 (0.8)	0	1 (0.3)	0	0
Bundle Branch Block Left	0	0	0	1 (0.3)	0	0
Bundle Branch Block Right	0	0	0	1 (0.3)	0	0
Cardiac Arrest	2 (0.8)	5 (1.4)	3 (1.3)	3 (1.0)	0	1 (3.1)
Cardiac Failure	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Cardiac Failure Congestive	0	2 (0.6)	2 (0.9)	2 (0.6)	0	0
Cardio-Respiratory Arrest	1 (0.4)	2 (0.6)	3 (1.3)	3 (1.0)	0	0
Cardiomegaly	0	1 (0 3)	0	0	0	0
Cardiomyopathy	0	0	0	0	0	1 (3.1)

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Cardiopulmonary Failure	0	1 (0 3)	0	0	0	0
Cardiotoxicity	0	0	0	1 (0.3)	0	0
Cardiovascular Disorder	0	0	1 (0.4)	0	0	0
Cardiovascular Insufficiency	0	3 (0.8)	1 (0.4)	0	0	0
Congestive Cardiomyopathy	0	1 (0 3)	0	0	0	0
Endocarditis Noninfective	0	0	0	1 (0.3)	0	0
Intracardiac Mass	0	0	0	1 (0.3)	0	0
Left Atrial Dilatation	0	1 (0 3)	0	0	0	0
Left Ventricular Dysfunction	0	1 (0.3)	0	0	0	0
Left Ventricular Hypertrophy	0	1 (0.3)	0	0	0	0
Mitral Valve Incompetence	0	1 (0.3)	0	0	0	0
Myocardial Infarction	0	3 (0.8)	0	0	0	0
Myocardial Ischaemia	0	1 (0 3)	0	0	0	0
Myocarditis	0	1 (0 3)	0	0	0	0
Palpitations	0	1 (0 3)	0	0	0	0
Pericardial Effusion	0	0	2 (0.9)	1 (0.3)	0	0
Pericarditis	0	1 (0 3)	0	0	0	0
Sinus Tachycardia	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Subendocardial Ischaemia	0	0	0	1 (0.3)	0	0
Supraventricular Tachycardia	2 (0.8)	1 (0.3)	0	2 (0.6)	0	1 (3.1)
Tachycardia	3 (1.2)	3 (0.8)	2 (0.9)	2 (0.6)	1 (3.8)	2 (6.3)
Torsade De Pointes	1 (0.4)	0	0	1 (0.3)	0	0
Ventricular Extrasystoles	1 (0.4)	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Ear And Labyrinth Disorders	**1 (0.4)**	**2 (0.6)**	**0**	**2 (0.6)**	**0**	**0**
Deafness	0	0	0	1 (0.3)	0	0
Ear Discomfort	0	0	0	1 (0.3)	0	0
Hypoacusis	1 (0.4)	1 (0 3)	0	0	0	0
Vertigo	0	1 (0 3)	0	0	0	0
Endocrine Disorders	**0**	**1 (0.3)**	**0**	**0**	**0**	**1 (3.1)**
Adrenal Insufficiency	0	0	0	0	0	1 (3.1)
Cushing's Syndrome	0	1 (0 3)	0	0	0	0
Eye Disorders	**2 (0.8)**	**2 (0.6)**	**9 (4.0)**	**5 (1.6)**	**0**	**0**
Choroiditis	0	0	0	1 (0.3)	0	0
Conjunctival Haemorrhage	0	0	1 (0.4)	1 (0.3)	0	0
Corneal Degeneration	0	0	1 (0.4)	0	0	0
Diplopia	0	0	1 (0.4)	0	0	0
Dry Eye	0	0	1 (0.4)	0	0	0
Eye Haemorrhage	0	0	1 (0.4)	0	0	0
Eye Oedema	0	0	1 (0.4)	0	0	0
Eye Pain	0	0	0	1 (0.3)	0	0
Eye Pruritus	1 (0.4)	0	0	0	0	0
Glaucoma	0	1 (0 3)	0	0	0	0
Mydriasis	0	0	1 (0.4)	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Photophobia	0	0	0	1 (0.3)	0	0
Pupils Unequal	1 (0.4)	0	1 (0.4)	0	0	0
Scleral Haemorrhage	0	0	1 (0.4)	0	0	0
Vision Blurred	0	1 (0 3)	0	0	0	0
Visual Acuity Reduced	0	0	1 (0.4)	0	0	0
Visual Impairment	0	1 (0 3)	0	0	0	0
Gastrointestinal Disorders	**41 (16.8)**	**70 (19.4)**	**48 (21.4)**	**54 (17.1)**	**7 (26.9)**	**5 (15.6)**
Abdominal Compartment Syndrome	0	0	1 (0.4)	0	0	0
Abdominal Discomfort	0	0	0	1 (0.3)	0	0
Abdominal Distension	0	3 (0.8)	2 (0.9)	2 (0.6)	0	0
Abdominal Pain	4 (1.6)	12 (3.3)	9 (4.0)	8 (2.5)	0	0
Abdominal Pain Lower	1 (0.4)	0	0	0	0	0
Abdominal Pain Upper	3 (1.2)	2 (0.6)	3 (1.3)	2 (0.6)	0	0
Abdominal Rigidity	0	0	0	1 (0.3)	0	0
Abdominal Tenderness	0	1 (0 3)	0	1 (0.3)	0	0
Acute Abdomen	0	1 (0.3)	0	1 (0.3)	0	0
Anal Fissure	1 (0.4)	1 (0 3)	0	0	0	0
Anal Fistula	0	0	0	0	0	1 (3.1)
Anal Incontinence	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Anal Ulcer	0	1 (0 3)	0	0	0	0
Anorectal Discomfort	1 (0.4)	0	0	0	0	0
Ascites	2 (0.8)	3 (0.8)	1 (0.4)	5 (1.6)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Change Of Bowel Habit	0	1 (0 3)	0	0	0	0
Colitis	1 (0.4)	1 (0 3)	3 (1.3)	2 (0.6)	0	1 (3.1)
Colitis Ulcerative	0	1 (0 3)	0	0	0	0
Constipation	1 (0.4)	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Crohn's Disease	0	1 (0 3)	0	0	0	0
Diarrhoea	8 (3.3)	14 (3.9)	10 (4.5)	14 (4.4)	3 (11.5)	0
Diarrhoea Haemorrhagic	1 (0.4)	2 (0.6)	5 (2.2)	0	0	0
Dry Mouth	0	1 (0 3)	0	0	0	0
Duodenal Perforation	0	1 (0.3)	0	0	0	0
Duodenitis Haemorrhagic	0	0	0	1 (0.3)	0	0
Dyspepsia	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Dysphagia	1 (0.4)	1 (0 3)	4 (1.8)	2 (0.6)	0	0
Enteritis	1 (0.4)	0	0	0	0	0
Erosive Oesophagitis	0	1 (0 3)	0	0	0	0
Gastric Disorder	0	1 (0 3)	0	0	0	0
Gastric Haemorrhage	0	1 (0 3)	0	0	0	0
Gastric Ulcer	0	1 (0 3)	1 (0.4)	0	0	0
Gastric Ulcer Haemorrhage	0	2 (0.6)	1 (0.4)	0	0	0
Gastritis	0	0	1 (0.4)	2 (0.6)	0	0
Gastritis Erosive	0	1 (0.3)	0	0	0	0
Gastritis Haemorrhagic	0	1 (0 3)	0	0	0	0
Gastrointestinal Haemorrhage	5 (2.0)	8 (2.2)	7 (3.1)	7 (2.2)	0	0
Gastrointestinal Pain	0	1 (0 3)	0	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Gastrointestinal Sounds Abnormal	0	0	1 (0.4)	0	0	0
Gastrointestinal Ulcer Haemorrhage	0	1 (0 3)	0	0	0	0
Gastrooesophageal Reflux Disease	0	1 (0 3)	0	1 (0.3)	0	0
Gingival Bleeding	0	1 (0 3)	0	1 (0.3)	0	0
Glossitis	0	0	1 (0.4)	0	0	0
Haematemesis	2 (0.8)	3 (0.8)	4 (1.8)	0	0	0
Haematochezia	0	1 (0 3)	3 (1.3)	0	0	0
Haemorrhoidal Haemorrhage	0	0	0	1 (0.3)	0	0
Haemorrhoids	1 (0.4)	3 (0.8)	0	0	1 (3.8)	0
Ileus	0	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Ileus Paralytic	0	0	2 (0.9)	0	0	0
Inguinal Hernia	0	0	0	1 (0.3)	0	0
Intestinal Haemorrhage	0	1 (0 3)	1 (0.4)	0	0	0
Intestinal Infarction	0	1 (0 3)	0	0	0	0
Intestinal Ischaemia	0	1 (0 3)	0	0	0	0
Intestinal Mass	0	0	0	1 (0.3)	0	0
Intestinal Obstruction	0	1 (0.3)	1 (0.4)	0	0	0
Intestinal Ulcer	0	1 (0 3)	0	1 (0.3)	0	0
Intra-Abdominal Fluid Collection	0	0	0	1 (0.3)	0	0
Malabsorption	0	1 (0 3)	0	0	0	0
Melaena	1 (0.4)	3 (0.8)	2 (0.9)	0	0	1 (3.1)
Mouth Haemorrhage	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Nausea	12 (4.9)	14 (3.9)	6 (2.7)	4 (1.3)	1 (3.8)	2 (6.3)

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Neutropenic Colitis	2 (0.8)	2 (0.6)	1 (0.4)	0	0	1 (3.1)
Odynophagia	0	0	1 (0.4)	0	0	0
Oesophageal Ulcer	1 (0.4)	0	0	0	0	0
Oesophagitis	0	2 (0.6)	1 (0.4)	0	0	0
Oral Mucosal Blistering	0	0	0	0	1 (3.8)	0
Oral Pain	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	1 (3.8)	0
Pancreatitis	0	1 (0 3)	1 (0.4)	0	0	0
Pancreatitis Acute	0	1 (0 3)	0	0	0	0
Proctalgia	0	0	0	2 (0.6)	0	1 (3.1)
Rectal Haemorrhage	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Rectal Tenesmus	1 (0.4)	0	0	0	0	0
Small Intestinal Obstruction	0	1 (0.3)	0	0	0	0
Stomatitis	1 (0.4)	0	1 (0.4)	0	0	0
Subileus	0	1 (0.3)	0	0	0	0
Swollen Tongue	0	0	1 (0.4)	0	0	0
Upper Gastrointestinal Haemorrhage	1 (0.4)	1 (0 3)	0	0	0	0
Vomiting	9 (3.7)	7 (1.9)	7 (3.1)	7 (2.2)	0	0
General Disorders And Administration Site Conditions	**44 (18.0)**	**77 (21 3)**	**40 (17.9)**	**64 (20.3)**	**7 (26.9)**	**8 (25.0)**
Adverse Drug Reaction	0	1 (0.3)	0	0	0	0
Asthenia	2 (0.8)	10 (2.8)	5 (2.2)	7 (2.2)	0	1 (3.1)
Catheter Site Bruise	0	0	1 (0.4)	0	0	0
Catheter Site Erythema	0	0	0	0	1 (3.8)	0

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Catheter Site Haematoma	1 (0.4)	0	0	0	0	0
Catheter Site Haemorrhage	0	1 (0.3)	0	0	0	0
Catheter Site Inflammation	0	0	0	0	0	1 (3.1)
Chest Pain	3 (1.2)	3 (0.8)	3 (1.3)	3 (1.0)	0	0
Chills	1 (0.4)	7 (1 9)	2 (0.9)	0	1 (3.8)	1 (3.1)
Death	0	0	1 (0.4)	0	0	0
Disease Progression	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Drug Interaction	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Drug Intolerance	0	0	1 (0.4)	1 (0.3)	0	0
Fatigue	6 (2.5)	10 (2.8)	6 (2.7)	2 (0.6)	0	0
Gait Disturbance	0	0	2 (0.9)	0	0	0
General Physical Health Deterioration	1 (0.4)	1 (0.3)	1 (0.4)	0	0	0
Generalised Oedema	1 (0.4)	1 (0 3)	2 (0.9)	2 (0.6)	0	0
Hyperpyrexia	0	0	0	0	0	1 (3.1)
Hyperthermia	0	1 (0 3)	0	1 (0.3)	0	0
Hypothermia	0	1 (0 3)	0	1 (0.3)	0	0
Malaise	0	0	1 (0.4)	0	0	0
Mucosal Haemorrhage	0	0	0	1 (0.3)	0	0
Mucosal Inflammation	9 (3.7)	8 (2.2)	4 (1.8)	10 (3 2)	0	1 (3.1)
Multi-Organ Disorder	1 (0.4)	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	5 (2.0)	10 (2.8)	3 (1.3)	6 (1.9)	2 (7.7)	0
Necrosis	0	1 (0 3)	0	0	0	0
Nodule	0	0	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Oedema	1 (0.4)	0	2 (0.9)	3 (1.0)	0	0
Oedema Peripheral	0	4 (1.1)	1 (0.4)	1 (0.3)	0	0
Pain	1 (0.4)	3 (0.8)	2 (0.9)	0	0	0
Performance Status Decreased	2 (0.8)	0	0	0	0	0
Peripheral Swelling	1 (0.4)	1 (0.3)	0	0	0	0
Pyrexia	16 (6.6)	29 (8.0)	19 (8.5)	33 (10.5)	6 (23.1)	4 (12.5)
Sudden Death	0	0	0	1 (0.3)	0	0
Therapy Non-Responder	0	4 (1 1)	1 (0.4)	1 (0.3)	0	0
Thirst	0	0	1 (0.4)	0	0	0
Hepatobiliary Disorders	**16 (6.6)**	**21 (5.8)**	**10 (4.5)**	**18 (5.7)**	**1 (3.8)**	**4 (12.5)**
Acute Hepatic Failure	0	1 (0.3)	0	0	0	0
Cholecystitis	0	0	1 (0.4)	0	0	0
Cholecystitis Acute	0	0	0	0	0	1 (3.1)
Cholelithiasis	1 (0.4)	0	0	0	0	0
Cholestasis	1 (0.4)	1 (0.3)	0	0	0	0
Drug-Induced Liver Injury	0	0	0	1 (0.3)	0	0
Hepatic Failure	3 (1.2)	4 (1 1)	1 (0.4)	3 (1.0)	0	0
Hepatic Function Abnormal	1 (0.4)	1 (0 3)	0	3 (1.0)	0	0
Hepatic Necrosis	0	1 (0 3)	0	0	0	0
Hepatitis	0	0	1 (0.4)	1 (0.3)	0	0
Hepatitis Acute	0	1 (0.3)	0	0	0	0
Hepatocellular Injury	1 (0.4)	2 (0.6)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hepatotoxicity	2 (0.8)	1 (0 3)	0	0	0	0
Hyperbilirubinaemia	8 (3.3)	8 (2 2)	4 (1.8)	9 (2.9)	1 (3.8)	3 (9.4)
Hypertransaminasaemia	0	1 (0.3)	0	0	0	0
Jaundice	1 (0.4)	5 (1.4)	2 (0.9)	3 (1.0)	0	0
Liver Disorder	0	0	1 (0.4)	0	0	0
Liver Injury	0	1 (0.3)	0	0	0	0
Ocular Icterus	0	1 (0.3)	0	0	0	0
Immune System Disorders	**8 (3.3)**	**42 (11.6)**	**22 (9.8)**	**31 (9 8)**	**0**	**2 (6.3)**
Acute Graft Versus Host Disease In Liver	0	0	1 (0.4)	0	0	0
Anaphylactic Reaction	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Chronic Graft Versus Host Disease	1 (0.4)	0	0	1 (0.3)	0	0
Drug Hypersensitivity	1 (0.4)	0	1 (0.4)	0	0	2 (6.3)
Graft Versus Host Disease	4 (1.6)	27 (7.5)	16 (7.1)	12 (3.8)	0	0
Graft Versus Host Disease In Gastrointestinal Tract	0	15 (4.2)	2 (0.9)	10 (3.2)	0	0
Graft Versus Host Disease In Liver	1 (0.4)	9 (2.5)	2 (0.9)	3 (1.0)	0	0
Graft Versus Host Disease In Lung	0	0	1 (0.4)	2 (0.6)	0	0
Graft Versus Host Disease In Skin	1 (0.4)	8 (2.2)	1 (0.4)	5 (1.6)	0	0
Hypogammaglobulinaemia	0	1 (0 3)	0	0	0	0
Immune System Disorder	0	0	1 (0.4)	0	0	0
Transplant Rejection	0	2 (0.6)	0	0	0	0
Infections And Infestations	**74 (30.3)**	**117 (32.4)**	**69 (30.8)**	**97 (30.8)**	**12 (46.2)**	**12 (37.5)**

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Abscess Fungal	0	0	1 (0.4)	0	0	0
Abscess Limb	0	0	0	1 (0.3)	0	0
Acid Fast Bacilli Infection	1 (0.4)	0	0	0	0	0
Acinetobacter Infection	0	0	1 (0.4)	0	0	0
Acute Sinusitis	0	1 (0.3)	0	0	0	0
Anal Abscess	0	1 (0 3)	0	0	0	0
Anorectal Infection	0	1 (0 3)	0	0	0	0
Aspergilloma	0	0	0	1 (0.3)	0	0
Aspergillus Infection	2 (0.8)	1 (0.3)	4 (1.8)	6 (1 9)	0	1 (3.1)
Atypical Pneumonia	0	1 (0.3)	0	0	0	0
Bacteraemia	18 (7.4)	18 (5.0)	9 (4.0)	10 (3 2)	4 (15.4)	2 (6.3)
Bacterial Infection	1 (0.4)	4 (1.1)	1 (0.4)	2 (0.6)	1 (3.8)	0
Bacterial Sepsis	2 (0.8)	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Bk Virus Infection	0	1 (0.3)	0	0	0	0
Bronchitis	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Bronchopulmonary Aspergillosis	3 (1.2)	0	7 (3.1)	2 (0.6)	2 (7.7)	0
Candida Infection	1 (0.4)	0	2 (0.9)	2 (0.6)	0	0
Candida Sepsis	0	1 (0 3)	0	0	0	0
Catheter Site Cellulitis	0	0	0	1 (0.3)	0	0
Catheter Site Infection	1 (0.4)	0	0	3 (1.0)	0	0
Cavernous Sinus Thrombosis	0	0	1 (0.4)	0	0	0
Cellulitis	1 (0.4)	3 (0.8)	2 (0.9)	2 (0.6)	0	0
Cerebral Toxoplasmosis	0	0	0	2 (0.6)	0	0

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Chronic Sinusitis	0	1 (0 3)	0	0	0	0
Clostridial Infection	0	2 (0.6)	0	0	0	0
Clostridium Bacteraemia	0	0	0	1 (0.3)	0	0
Clostridium Difficile Colitis	0	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Clostridium Difficile Infection	0	1 (0.3)	0	0	0	0
Conjunctivitis	0	1 (0 3)	0	1 (0.3)	0	0
Corynebacterium Infection	0	0	0	1 (0.3)	0	0
Corynebacterium Sepsis	0	1 (0 3)	0	0	0	0
Cystitis	0	2 (0.6)	0	0	0	0
Cystitis Klebsiella	0	1 (0.3)	0	0	0	0
Cytomegalovirus Colitis	0	1 (0.3)	0	2 (0.6)	0	0
Cytomegalovirus Gastritis	0	0	1 (0.4)	0	0	0
Cytomegalovirus Gastroenteritis	0	1 (0 3)	0	2 (0.6)	0	0
Cytomegalovirus Infection	4 (1.6)	7 (1.9)	5 (2.2)	6 (1.9)	0	0
Cytomegalovirus Viraemia	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Device Related Infection	4 (1.6)	7 (1.9)	5 (2.2)	5 (1.6)	1 (3.8)	1 (3.1)
Device Related Sepsis	2 (0.8)	0	1 (0.4)	0	1 (3.8)	0
Ear Infection	0	1 (0 3)	0	0	0	0
Emphysematous Cystitis	1 (0.4)	0	0	0	0	0
Encephalitis	0	2 (0.6)	0	1 (0.3)	0	0
Encephalitis Viral	0	0	1 (0.4)	0	0	0
Enterobacter Bacteraemia	0	1 (0 3)	0	0	0	0
Enterobacter Infection	1 (0.4)	0	0	0	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Enterobacter Sepsis	1 (0.4)	0	0	0	0	0
Enterococcal Bacteraemia	1 (0.4)	1 (0.3)	0	0	0	3 (9.4)
Enterococcal Infection	1 (0.4)	0	1 (0.4)	3 (1.0)	0	0
Enterococcal Sepsis	0	0	1 (0.4)	0	0	0
Epstein-Barr Virus Infection	0	0	0	4 (1.3)	0	0
Erysipelas	0	0	1 (0.4)	0	0	1 (3.1)
Escherichia Bacteraemia	1 (0.4)	2 (0.6)	1 (0.4)	0	0	0
Escherichia Infection	0	0	0	1 (0.3)	0	0
Escherichia Sepsis	1 (0.4)	0	2 (0.9)	0	0	0
Escherichia Urinary Tract Infection	0	0	1 (0.4)	0	0	0
Fungaemia	0	0	1 (0.4)	0	0	0
Fungal Infection	1 (0.4)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Fungal Rhinitis	0	0	0	1 (0.3)	0	0
Fungal Sepsis	1 (0.4)	0	0	1 (0.3)	0	0
Fusobacterium Infection	0	0	1 (0.4)	0	0	0
Gangrene	0	0	0	1 (0.3)	0	0
Gastroenteritis	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Gastroenteritis Rotavirus	0	0	0	1 (0.3)	0	0
Gastrointestinal Infection	1 (0.4)	0	0	0	0	0
Herpes Dermatitis	0	0	1 (0.4)	0	0	0
Herpes Pharyngitis	0	0	1 (0.4)	0	0	0
Herpes Simplex	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Herpes Virus Infection	0	0	0	1 (0.3)	0	0

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Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Herpes Zoster	1 (0.4)	2 (0.6)	0	1 (0.3)	0	0
Human Herpesvirus 6 Infection	0	0	0	1 (0.3)	0	0
Infection	0	1 (0 3)	1 (0.4)	0	0	0
Influenza	0	0	0	1 (0.3)	0	0
Infusion Site Infection	0	0	1 (0.4)	0	0	0
Klebsiella Bacteraemia	1 (0.4)	1 (0.3)	3 (1.3)	1 (0.3)	0	1 (3.1)
Klebsiella Infection	0	0	2 (0.9)	0	0	0
Klebsiella Sepsis	0	1 (0.3)	0	0	0	0
Leptotrichia Infection	0	0	0	1 (0.3)	0	0
Liver Abscess	0	0	0	1 (0.3)	0	0
Localised Infection	0	1 (0 3)	1 (0.4)	0	0	0
Lower Respiratory Tract Infection	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Lung Abscess	1 (0.4)	0	0	0	0	0
Mastoiditis	0	1 (0 3)	0	0	0	0
Meningitis Listeria	0	0	0	1 (0.3)	0	0
Meningococcal Infection	0	0	0	1 (0.3)	0	0
Micrococcus Infection	1 (0.4)	0	0	0	0	0
Mycobacterial Infection	0	0	0	1 (0.3)	0	0
Mycobacterium Avium Complex Infection	0	0	1 (0.4)	0	0	0
Neutropenic Sepsis	2 (0.8)	0	1 (0.4)	0	1 (3.8)	2 (6.3)
Nocardiosis	0	1 (0 3)	1 (0.4)	0	0	0
Oesophageal Candidiasis	0	0	2 (0.9)	0	0	0
Oral Candidiasis	0	0	0	0	1 (3.8)	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Oral Herpes	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Oropharyngeal Candidiasis	0	0	0	0	1 (3.8)	0
Peritonitis	0	0	1 (0.4)	0	0	0
Peritonitis Bacterial	0	0	0	1 (0.3)	0	0
Pharyngitis	0	1 (0 3)	0	1 (0.3)	0	0
Pneumocystis Jirovecii Pneumonia	0	1 (0.3)	1 (0.4)	0	0	0
Pneumonia	11 (4.5)	15 (4.2)	13 (5.8)	11 (3 5)	1 (3.8)	2 (6.3)
Pneumonia Bacterial	0	3 (0.8)	0	0	0	0
Pneumonia Cytomegaloviral	0	3 (0.8)	0	0	0	0
Pneumonia Fungal	1 (0.4)	3 (0.8)	0	2 (0.6)	0	1 (3.1)
Pneumonia Klebsiella	1 (0.4)	1 (0.3)	2 (0.9)	2 (0.6)	0	0
Pneumonia Necrotising	0	0	0	1 (0.3)	0	0
Pneumonia Pseudomonal	0	1 (0.3)	1 (0.4)	0	0	0
Pneumonia Staphylococcal	1 (0.4)	1 (0.3)	1 (0.4)	0	0	0
Pneumonia Streptococcal	0	0	0	1 (0.3)	0	0
Pneumonia Viral	1 (0.4)	0	0	0	0	0
Pseudomembranous Colitis	0	2 (0.6)	0	0	0	0
Pseudomonal Bacteraemia	0	2 (0.6)	1 (0.4)	2 (0.6)	0	0
Pseudomonal Sepsis	3 (1.2)	0	2 (0.9)	0	0	0
Pseudomonas Infection	1 (0.4)	1 (0.3)	0	4 (1.3)	0	0
Pulmonary Mycosis	1 (0.4)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Relapsing Fever	0	0	0	1 (0.3)	0	0
Respiratory Syncytial Virus Infection	0	0	1 (0.4)	0	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Rhinovirus Infection	0	0	0	0	1 (3.8)	0
Scedosporium Infection	0	0	1 (0.4)	0	0	0
Sepsis	5 (2.0)	9 (2 5)	7 (3.1)	8 (2.5)	2 (7.7)	1 (3.1)
Sepsis Syndrome	0	1 (0.3)	0	0	0	0
Septic Embolus	0	1 (0 3)	0	0	0	0
Septic Shock	5 (2.0)	11 (3.0)	5 (2.2)	9 (2.9)	2 (7.7)	4 (12.5)
Sinusitis	2 (0.8)	2 (0.6)	0	1 (0.3)	0	0
Sinusitis Bacterial	0	1 (0.3)	0	0	0	0
Sinusitis Fungal	0	0	0	0	0	1 (3.1)
Staphylococcal Bacteraemia	3 (1.2)	4 (1.1)	1 (0.4)	4 (1.3)	1 (3.8)	0
Staphylococcal Infection	2 (0.8)	0	1 (0.4)	0	0	0
Staphylococcal Sepsis	2 (0.8)	0	1 (0.4)	2 (0.6)	0	0
Streptococcal Bacteraemia	0	1 (0.3)	2 (0.9)	0	1 (3.8)	0
Streptococcal Infection	1 (0.4)	0	0	2 (0.6)	0	0
Streptococcal Sepsis	2 (0.8)	1 (0.3)	0	0	0	0
Superinfection	1 (0.4)	0	0	0	0	0
Systemic Candida	3 (1.2)	1 (0.3)	0	2 (0.6)	0	0
Systemic Mycosis	0	1 (0.3)	1 (0.4)	2 (0.6)	0	0
Tracheobronchitis	0	1 (0 3)	0	1 (0.3)	0	0
Upper Respiratory Tract Infection	0	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Urinary Tract Infection	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Urinary Tract Infection Pseudomonal	0	1 (0.3)	0	0	0	0
Urinary Tract Infection Viral	0	0	0	1 (0.3)	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Varicella Zoster Pneumonia	0	1 (0.3)	0	0	0	0
Varicella Zoster Virus Infection	0	2 (0.6)	0	0	0	0
Viral Haemorrhagic Cystitis	0	1 (0 3)	0	0	0	0
Viral Infection	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Injury, Poisoning And Procedural Complications	**6 (2.5)**	**11 (3.0)**	**13 (5.8)**	**9 (2.9)**	**1 (3.8)**	**0**
Accidental Overdose	0	0	1 (0.4)	0	0	0
Back Injury	0	1 (0 3)	0	0	0	0
Brain Herniation	0	0	0	0	1 (3.8)	0
Complications Of Transplant Surgery	0	1 (0.3)	0	0	0	0
Compression Fracture	1 (0.4)	0	0	0	0	0
Contusion	0	0	0	1 (0.3)	0	0
Fall	0	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Femoral Neck Fracture	0	1 (0 3)	1 (0.4)	0	0	0
Head Injury	0	0	0	1 (0.3)	0	0
Hip Fracture	0	1 (0 3)	1 (0.4)	0	0	0
Lumbar Vertebral Fracture	0	1 (0 3)	0	0	0	0
Overdose	0	0	0	1 (0.3)	0	0
Post Procedural Haemorrhage	1 (0.4)	0	2 (0.9)	0	0	0
Postoperative Fever	0	0	1 (0.4)	0	0	0
Sedation Complication	0	1 (0 3)	0	0	0	0
Spinal Fracture	1 (0.4)	0	0	0	0	0
Subarachnoid Haemorrhage	1 (0.4)	1 (0 3)	0	0	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Subdural Haematoma	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Toxicity To Various Agents	1 (0.4)	1 (0.3)	2 (0.9)	0	0	0
Transfusion Reaction	0	1 (0.3)	2 (0.9)	0	0	0
Transplant Failure	0	2 (0.6)	0	3 (1.0)	0	0
Investigations	**40 (16.4)**	**59 (16 3)**	**35 (15.6)**	**54 (17.1)**	**3 (11.5)**	**2 (6.3)**
Activated Partial Thromboplastin Time Prolonged	0	0	1 (0.4)	0	0	0
Alanine Aminotransferase Abnormal	0	1 (0.3)	0	1 (0.3)	0	0
Alanine Aminotransferase Increased	5 (2.0)	7 (1.9)	7 (3.1)	7 (2.2)	1 (3.8)	0
Ammonia Increased	0	1 (0.3)	0	0	0	0
Aspartate Aminotransferase Increased	1 (0.4)	2 (0.6)	3 (1.3)	5 (1.6)	0	0
Bacterial Test Positive	0	4 (1.1)	2 (0.9)	4 (1.3)	0	0
Basophil Count Increased	0	1 (0.3)	0	0	0	0
Bilirubin Conjugated Increased	0	1 (0.3)	1 (0.4)	0	0	0
Blast Cells Present	0	1 (0 3)	0	0	0	0
Bleeding Time Prolonged	1 (0.4)	1 (0.3)	0	0	0	0
Blood Albumin Abnormal	0	1 (0 3)	0	0	0	0
Blood Alkaline Phosphatase Increased	2 (0.8)	3 (0.8)	0	0	0	0
Blood Bicarbonate Decreased	1 (0.4)	0	0	1 (0.3)	0	0
Blood Bilirubin Increased	3 (1.2)	4 (1.1)	6 (2.7)	8 (2.5)	1 (3.8)	1 (3.1)
Blood Calcium Decreased	0	0	0	1 (0.3)	0	0
Blood Cholesterol Increased	0	1 (0 3)	0	0	0	0
Blood Creatinine Increased	1 (0.4)	1 (0.3)	1 (0.4)	3 (1.0)	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Blood Culture Positive	0	1 (0.3)	2 (0.9)	2 (0.6)	0	0
Blood Glucose Increased	0	0	1 (0.4)	0	0	0
Blood Lactate Dehydrogenase	0	0	0	1 (0.3)	0	0
Blood Lactate Dehydrogenase Increased	0	2 (0.6)	4 (1.8)	4 (1.3)	0	0
Blood Magnesium Decreased	1 (0.4)	0	0	0	0	0
Blood Potassium Decreased	0	1 (0.3)	0	0	0	0
Blood Pressure Decreased	0	0	0	1 (0.3)	0	0
Blood Pressure Increased	1 (0.4)	0	0	1 (0.3)	0	0
Blood Urea Increased	1 (0.4)	1 (0 3)	0	2 (0.6)	0	0
Blood Uric Acid Increased	1 (0.4)	1 (0.3)	0	0	0	0
Body Temperature	0	1 (0.3)	0	0	0	0
Breath Sounds Abnormal	0	1 (0 3)	0	1 (0.3)	0	0
Bronchoscopy	0	0	0	1 (0.3)	0	0
C-Reactive Protein Abnormal	0	1 (0.3)	0	0	0	0
C-Reactive Protein Increased	0	0	0	1 (0.3)	1 (3.8)	0
Central Venous Pressure Decreased	0	1 (0 3)	0	0	0	0
Chest X-Ray Abnormal	0	0	1 (0.4)	0	0	0
Clostridium Test Positive	0	1 (0.3)	0	0	0	0
Coagulation Test Abnormal	0	0	0	1 (0.3)	0	0
Computerised Tomogram Abnormal	0	0	1 (0.4)	0	0	0
Cytomegalovirus Test	0	1 (0.3)	0	2 (0.6)	0	0
Cytomegalovirus Test Positive	2 (0.8)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Drug Level Changed	1 (0.4)	0	0	0	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Drug Level Increased	1 (0.4)	1 (0.3)	0	2 (0.6)	0	0
Ejection Fraction Decreased	1 (0.4)	0	0	0	0	0
Electrocardiogram Abnormal	1 (0.4)	0	0	0	0	0
Electrocardiogram Qt Prolonged	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)	0	0
Electrocardiogram T Wave Abnormal	0	1 (0.3)	0	0	0	0
Electroencephalogram Abnormal	0	1 (0 3)	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	0	1 (0.3)	0	0
Gamma-Glutamyltransferase Increased	11 (4.5)	9 (2.5)	8 (3.6)	14 (4.4)	0	0
Haematocrit Decreased	0	0	0	1 (0.3)	0	0
Haemoglobin Decreased	1 (0.4)	1 (0.3)	1 (0.4)	0	0	1 (3.1)
Heart Sounds Abnormal	1 (0.4)	0	0	0	0	0
Hepatic Enzyme Abnormal	1 (0.4)	0	2 (0.9)	0	0	0
Hepatic Enzyme Increased	1 (0.4)	3 (0.8)	0	3 (1.0)	0	0
Liver Function Test Abnormal	0	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Liver Function Test Increased	3 (1.2)	3 (0.8)	3 (1.3)	3 (1.0)	0	0
Lymphocyte Count Decreased	0	0	1 (0.4)	0	0	0
Lymphocyte Count Increased	0	0	0	1 (0.3)	0	0
Neutrophil Count Abnormal	0	1 (0 3)	0	0	0	0
Neutrophil Count Decreased	0	1 (0.3)	0	1 (0.3)	0	0
Nutritional Condition Abnormal	0	0	0	1 (0.3)	0	0
Occult Blood Positive	1 (0.4)	0	0	0	0	0
Oxygen Saturation Decreased	1 (0.4)	4 (1 1)	1 (0.4)	1 (0.3)	0	0
Platelet Count Decreased	0	3 (0.8)	0	1 (0.3)	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Protein Total Decreased	0	1 (0.3)	0	0	0	0
Prothrombin Time Prolonged	0	0	1 (0.4)	0	0	0
Pulse Absent	0	0	0	1 (0.3)	0	0
Red Blood Cell Count Decreased	0	1 (0 3)	0	0	0	0
Respiratory Rate Increased	0	1 (0 3)	0	0	0	0
Salmonella Test Positive	0	1 (0.3)	0	0	0	0
Serum Ferritin Increased	0	1 (0.3)	0	0	0	0
Transaminases Increased	4 (1.6)	5 (1.4)	2 (0.9)	3 (1.0)	0	0
Troponin I Increased	0	0	0	1 (0.3)	0	0
Troponin Increased	0	1 (0 3)	0	0	0	0
Urine Output Decreased	0	1 (0 3)	0	0	0	0
Weight Decreased	1 (0.4)	6 (1.7)	0	5 (1.6)	0	0
Weight Increased	0	0	0	1 (0.3)	0	0
White Blood Cell Count Abnormal	0	1 (0 3)	0	0	0	0
Metabolism And Nutrition Disorders	**35 (14.3)**	**57 (15 8)**	**26 (11.6)**	**43 (13.7)**	**6 (23.1)**	**4 (12.5)**
Acidosis	2 (0.8)	4 (1.1)	0	1 (0.3)	2 (7.7)	0
Cachexia	0	1 (0 3)	0	0	0	0
Decreased Appetite	4 (1.6)	3 (0.8)	3 (1.3)	8 (2.5)	0	0
Dehydration	2 (0.8)	5 (1.4)	0	4 (1.3)	0	0
Diabetes Mellitus	1 (0.4)	3 (0.8)	0	2 (0.6)	0	0
Electrolyte Depletion	1 (0.4)	0	0	0	0	0
Electrolyte Imbalance	0	2 (0.6)	0	1 (0.3)	0	0

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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Failure To Thrive	0	1 (0 3)	0	0	0	0
Feeding Disorder	0	0	0	1 (0.3)	0	0
Fluid Overload	0	0	0	5 (1.6)	1 (3.8)	0
Fluid Retention	0	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Gout	0	1 (0 3)	0	0	0	0
Hypercholesterolaemia	0	1 (0 3)	0	0	0	0
Hyperglycaemia	4 (1.6)	13 (3.6)	7 (3.1)	10 (3 2)	0	0
Hyperinsulinaemic Hypoglycaemia	0	1 (0.3)	0	0	0	0
Hyperkalaemia	0	4 (1 1)	1 (0.4)	4 (1.3)	0	0
Hypermagnesaemia	1 (0.4)	1 (0.3)	0	0	0	0
Hypernatraemia	0	1 (0 3)	0	0	1 (3.8)	0
Hyperphosphataemia	0	0	0	1 (0.3)	0	0
Hypertriglyceridaemia	0	1 (0 3)	1 (0.4)	0	0	0
Hyperuricaemia	0	1 (0.3)	0	0	0	0
Hypoalbuminaemia	1 (0.4)	4 (1 1)	0	2 (0.6)	1 (3.8)	0
Hypocalcaemia	3 (1.2)	5 (1.4)	1 (0.4)	1 (0.3)	1 (3.8)	0
Hypoglycaemia	2 (0.8)	2 (0.6)	0	0	0	0
Hypokalaemia	14 (5.7)	13 (3.6)	9 (4.0)	9 (2.9)	2 (7.7)	3 (9.4)
Hypomagnesaemia	5 (2.0)	3 (0.8)	0	3 (1.0)	0	0
Hyponatraemia	1 (0.4)	3 (0.8)	4 (1.8)	0	0	1 (3.1)
Hypophagia	1 (0.4)	2 (0.6)	0	0	0	0
Hypophosphataemia	1 (0.4)	6 (1.7)	0	3 (1.0)	1 (3.8)	0
Hypoproteinaemia	0	1 (0.3)	0	0	0	0

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	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hypovolaemia	0	0	0	2 (0.6)	0	0
Malnutrition	2 (0.8)	2 (0.6)	1 (0.4)	3 (1.0)	0	0
Metabolic Acidosis	4 (1.6)	1 (0 3)	2 (0.9)	2 (0.6)	1 (3.8)	1 (3.1)
Metabolic Alkalosis	0	0	1 (0.4)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**17 (7.0)**	**16 (4.4)**	**13 (5.8)**	**9 (2.9)**	**1 (3.8)**	**1 (3.1)**
Arthralgia	1 (0.4)	4 (1 1)	3 (1.3)	1 (0.3)	0	0
Back Pain	4 (1.6)	4 (1.1)	2 (0.9)	2 (0.6)	0	1 (3.1)
Bone Pain	4 (1.6)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Flank Pain	2 (0.8)	0	0	1 (0.3)	0	0
Intervertebral Disc Degeneration	0	0	0	1 (0.3)	0	0
Intervertebral Disc Protrusion	0	0	1 (0.4)	0	0	0
Muscle Contracture	1 (0.4)	0	0	0	0	0
Muscle Spasms	1 (0.4)	1 (0 3)	1 (0.4)	0	0	0
Muscular Weakness	2 (0.8)	3 (0.8)	3 (1.3)	0	1 (3.8)	0
Musculoskeletal Pain	0	0	1 (0.4)	1 (0.3)	0	0
Musculoskeletal Stiffness	0	0	0	1 (0.3)	0	0
Myalgia	2 (0.8)	1 (0 3)	1 (0.4)	2 (0.6)	0	0
Myopathy	3 (1.2)	5 (1.4)	1 (0.4)	0	0	0
Neck Pain	1 (0.4)	0	1 (0.4)	0	0	0
Osteonecrosis	0	0	1 (0.4)	0	0	0
Pain In Extremity	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)	1 (3.8)	0
Pathological Fracture	0	0	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**17 (7.0)**	**27 (7.5)**	**16 (7.1)**	**23 (7 3)**	**0**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	4 (1.8)	1 (0.3)	0	0
Acute Myeloid Leukaemia	8 (3.3)	5 (1.4)	3 (1.3)	6 (1.9)	0	0
Acute Myeloid Leukaemia Recurrent	5 (2.0)	7 (1.9)	3 (1.3)	3 (1.0)	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	1 (0.4)	0	0	0
B-Cell Lymphoma	0	0	0	1 (0.3)	0	0
Chronic Myeloid Leukaemia	0	1 (0 3)	0	0	0	0
Hodgkin's Disease	0	0	1 (0.4)	0	0	0
Hodgkin's Disease Recurrent	0	0	1 (0.4)	0	0	0
Leukaemia	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Leukaemia Recurrent	2 (0.8)	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Lymphoma	0	5 (1.4)	0	2 (0.6)	0	0
Meningioma	1 (0.4)	0	0	0	0	0
Metastases To Kidney	0	0	0	1 (0.3)	0	0
Metastases To Liver	0	0	0	1 (0.3)	0	0
Metastatic Neoplasm	0	1 (0 3)	0	0	0	0
Myelodysplastic Syndrome	0	1 (0.3)	0	0	0	0
Neoplasm Malignant	1 (0.4)	0	1 (0.4)	2 (0.6)	0	0
Non-Hodgkin's Lymphoma	0	1 (0.3)	0	3 (1.0)	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	0	2 (0.6)	0	0
Plasma Cell Myeloma	0	0	0	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Post Transplant Lymphoproliferative Disorder	0	1 (0.3)	0	0	0	0
Renal Cancer	0	1 (0 3)	0	0	0	0
Squamous Cell Carcinoma	0	0	0	1 (0.3)	0	0
Tumour Pain	0	1 (0 3)	0	0	0	0
Uterine Leiomyoma	1 (0.4)	0	0	0	0	0
Nervous System Disorders	**29 (11.9)**	**35 (9.7)**	**29 (12.9)**	**26 (8 3)**	**3 (11.5)**	**1 (3.1)**
Amnesia	0	1 (0 3)	0	0	0	0
Ataxia	0	1 (0 3)	0	0	0	0
Balance Disorder	0	0	1 (0.4)	0	0	0
Brain Compression	0	0	0	0	1 (3.8)	0
Brain Oedema	2 (0.8)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Central Nervous System Lesion	0	1 (0 3)	1 (0.4)	0	0	0
Cerebellar Haemorrhage	2 (0.8)	0	0	0	1 (3.8)	0
Cerebral Haemorrhage	5 (2.0)	0	2 (0.9)	3 (1.0)	0	0
Cerebral Hypoperfusion	0	0	1 (0.4)	0	0	0
Cerebral Infarction	1 (0.4)	0	1 (0.4)	1 (0.3)	0	0
Cerebrovascular Accident	0	1 (0 3)	1 (0.4)	0	0	0
Cognitive Disorder	0	2 (0.6)	0	0	0	0
Coma	2 (0.8)	1 (0 3)	2 (0.9)	3 (1.0)	0	0
Demyelination	1 (0.4)	0	0	0	0	0
Depressed Level Of Consciousness	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Dizziness	0	2 (0.6)	2 (0.9)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Encephalopathy	1 (0.4)	3 (0.8)	1 (0.4)	1 (0.3)	0	0
Facial Paresis	0	0	0	1 (0.3)	0	0
Generalised Tonic-Clonic Seizure	0	0	1 (0.4)	1 (0.3)	0	0
Guillain-Barre Syndrome	0	0	0	1 (0.3)	0	0
Haemorrhage Intracranial	0	2 (0.6)	4 (1.8)	1 (0.3)	0	0
Haemorrhagic Stroke	0	1 (0 3)	1 (0.4)	0	0	0
Headache	8 (3.3)	7 (1 9)	8 (3.6)	4 (1.3)	1 (3.8)	1 (3.1)
Hemiparesis	0	0	3 (1.3)	1 (0.3)	0	0
Hemiplegia	1 (0.4)	0	2 (0.9)	0	0	0
Hydrocephalus	0	0	0	0	1 (3.8)	0
Hypoglycaemic Coma	1 (0.4)	0	0	0	0	0
Hypokinesia	0	0	0	1 (0.3)	0	0
Hyporeflexia	0	1 (0 3)	0	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	1 (3.8)	0
Lethargy	1 (0.4)	2 (0.6)	0	0	1 (3.8)	0
Leukoencephalopathy	1 (0.4)	0	0	0	0	0
Loss Of Consciousness	2 (0.8)	2 (0.6)	3 (1.3)	2 (0.6)	1 (3.8)	0
Meningism	0	1 (0 3)	0	0	0	0
Metabolic Encephalopathy	0	1 (0 3)	0	0	0	0
Migraine	1 (0.4)	0	0	0	0	0
Myoclonus	0	1 (0 3)	0	0	0	0
Nervous System Disorder	1 (0.4)	0	0	0	0	0
Neuropathy Peripheral	0	1 (0.3)	1 (0.4)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Neurotoxicity	0	0	0	1 (0.3)	0	0
Nystagmus	0	0	0	0	1 (3.8)	0
Paralysis	1 (0.4)	0	0	0	0	0
Paresis	0	0	0	1 (0.3)	0	0
Peroneal Nerve Palsy	1 (0.4)	0	0	0	0	0
Post Herpetic Neuralgia	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Psychomotor Hyperactivity	1 (0.4)	0	0	0	0	0
Seizure	3 (1.2)	6 (1.7)	2 (0.9)	3 (1.0)	0	0
Sensory Loss	0	1 (0.3)	0	0	0	0
Somnolence	0	2 (0.6)	3 (1.3)	0	0	0
Stupor	1 (0.4)	1 (0 3)	1 (0.4)	1 (0.3)	0	0
Syncope	5 (2.0)	4 (1.1)	1 (0.4)	1 (0.3)	1 (3.8)	0
Tonic Convulsion	0	1 (0.3)	0	0	0	0
Transient Ischaemic Attack	0	1 (0 3)	0	0	0	0
Tremor	0	0	0	2 (0.6)	0	0
Trigeminal Neuralgia	0	0	0	1 (0.3)	0	0
Unresponsive To Stimuli	0	1 (0.3)	2 (0.9)	1 (0 3)	0	0
Visual Field Defect	0	0	1 (0.4)	0	0	0
Product Issues	**0**	**0**	**0**	**1 (0 3)**	**0**	**0**
Device Breakage	0	0	0	1 (0.3)	0	0
Psychiatric Disorders	**9 (3.7)**	**15 (4.2)**	**11 (4.9)**	**9 (2.9)**	**1 (3.8)**	**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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Abnormal Behaviour	0	0	1 (0.4)	0	0	0
Agitation	1 (0.4)	0	2 (0.9)	0	0	0
Anxiety	1 (0.4)	0	0	4 (1.3)	0	0
Confusional State	2 (0.8)	4 (1 1)	2 (0.9)	2 (0.6)	1 (3.8)	0
Delirium	0	1 (0 3)	0	0	0	0
Depression	2 (0.8)	3 (0.8)	3 (1.3)	2 (0.6)	0	0
Depression Suicidal	0	0	0	1 (0.3)	0	0
Disorientation	0	0	1 (0.4)	0	0	0
Eating Disorder	0	0	0	1 (0.3)	0	0
Fear	0	0	0	1 (0.3)	0	0
Flat Affect	0	1 (0 3)	0	0	0	0
Hallucination	1 (0.4)	0	2 (0.9)	0	0	0
Hallucination, Visual	0	1 (0 3)	0	0	0	0
Hypomania	0	1 (0 3)	0	0	0	0
Insomnia	0	1 (0 3)	0	1 (0.3)	0	0
Mental Status Changes	2 (0.8)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Mood Altered	0	0	1 (0.4)	0	0	0
Stress	0	1 (0 3)	1 (0.4)	0	0	0
Suicidal Ideation	0	1 (0 3)	0	1 (0.3)	0	0
Renal And Urinary Disorders	**14 (5.7)**	**29 (8.0)**	**18 (8.0)**	**25 (7 9)**	**1 (3.8)**	**0**
Acute Kidney Injury	5 (2.0)	4 (1 1)	3 (1.3)	5 (1.6)	1 (3.8)	0
Anuria	0	3 (0.8)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Azotaemia	0	0	0	1 (0.3)	0	0
Bladder Spasm	2 (0.8)	0	0	0	0	0
Choluria	1 (0.4)	0	0	0	0	0
Cystitis Haemorrhagic	0	3 (0.8)	1 (0.4)	2 (0.6)	0	0
Dysuria	0	2 (0.6)	0	3 (1.0)	0	0
Haematuria	3 (1.2)	5 (1.4)	1 (0.4)	6 (1.9)	0	0
Hydronephrosis	1 (0.4)	1 (0 3)	0	0	0	0
Obstructive Nephropathy	0	0	0	1 (0.3)	0	0
Oliguria	1 (0.4)	4 (1 1)	1 (0.4)	0	0	0
Polyuria	0	1 (0 3)	0	0	0	0
Renal Failure	5 (2.0)	12 (3.3)	8 (3.6)	14 (4.4)	0	0
Renal Haematoma	0	1 (0 3)	0	0	0	0
Renal Impairment	2 (0.8)	1 (0 3)	2 (0.9)	1 (0.3)	0	0
Renal Tubular Necrosis	0	0	1 (0.4)	1 (0.3)	0	0
Tubulointerstitial Nephritis	0	0	0	1 (0.3)	0	0
Urethral Discharge	0	0	0	1 (0.3)	0	0
Urinary Incontinence	0	1 (0 3)	2 (0.9)	0	0	0
Urinary Retention	0	1 (0 3)	0	0	0	0
Reproductive System And Breast Disorders	**9 (3.7)**	**3 (0.8)**	**6 (2.7)**	**2 (0.6)**	**0**	**0**
Erectile Dysfunction	0	1 (0.3)	0	0	0	0
Menorrhagia	1 (0.4)	0	2 (0.9)	0	0	0
Menstrual Disorder	1 (0.4)	0	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Penile Pain	0	0	0	1 (0.3)	0	0
Prostatitis	0	1 (0.3)	0	0	0	0
Scrotal Oedema	0	1 (0.3)	0	0	0	0
Testicular Pain	0	0	0	1 (0.3)	0	0
Uterine Haemorrhage	0	0	1 (0.4)	0	0	0
Vaginal Haemorrhage	6 (2.5)	0	3 (1.3)	0	0	0
Vulval Oedema	1 (0.4)	0	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**44 (18.0)**	**57 (15 8)**	**53 (23.7)**	**55 (17.5)**	**7 (26.9)**	**7 (21.9)**
Acute Pulmonary Oedema	1 (0.4)	1 (0.3)	0	2 (0.6)	0	0
Acute Respiratory Distress Syndrome	1 (0.4)	5 (1.4)	6 (2.7)	1 (0.3)	1 (3.8)	0
Acute Respiratory Failure	3 (1.2)	2 (0.6)	0	1 (0.3)	0	0
Apnoea	1 (0.4)	1 (0 3)	0	0	0	0
Asthma	0	0	1 (0.4)	0	0	0
Atelectasis	0	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Bronchial Hyperreactivity	0	0	1 (0.4)	0	0	0
Bronchial Obstruction	0	0	1 (0.4)	1 (0.3)	0	0
Bronchopneumopathy	1 (0.4)	0	0	0	0	0
Bronchospasm	0	0	2 (0.9)	0	0	0
Chronic Obstructive Pulmonary Disease	0	0	1 (0.4)	0	0	0
Cough	0	3 (0.8)	0	3 (1.0)	0	0
Diffuse Alveolar Damage	0	0	1 (0.4)	0	0	0
Dyspnoea	13 (5.3)	18 (5.0)	15 (6.7)	14 (4.4)	3 (11.5)	1 (3.1)

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

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Emphysema	0	1 (0 3)	0	0	0	0
Epiglottis Ulcer	0	1 (0 3)	0	0	0	0
Epistaxis	6 (2.5)	3 (0.8)	2 (0.9)	3 (1.0)	0	0
Haemoptysis	2 (0.8)	2 (0.6)	2 (0.9)	1 (0.3)	0	0
Haemothorax	0	0	0	2 (0.6)	0	0
Hydrothorax	0	1 (0 3)	0	1 (0.3)	0	0
Hypercapnia	1 (0.4)	0	0	0	0	0
Hypoxia	3 (1.2)	6 (1.7)	6 (2.7)	14 (4.4)	4 (15.4)	3 (9.4)
Interstitial Lung Disease	1 (0.4)	3 (0.8)	0	1 (0.3)	0	0
Laryngeal Oedema	0	0	0	0	0	1 (3.1)
Lung Consolidation	0	0	1 (0.4)	0	1 (3.8)	0
Lung Disorder	2 (0.8)	0	1 (0.4)	0	0	0
Lung Infiltration	3 (1.2)	1 (0.3)	4 (1.8)	3 (1.0)	0	0
Nasal Congestion	1 (0.4)	0	0	0	0	0
Nasal Necrosis	0	0	0	1 (0.3)	0	0
Obliterative Bronchiolitis	0	0	1 (0.4)	0	0	0
Organising Pneumonia	0	2 (0.6)	0	0	0	0
Oropharyngeal Pain	0	0	1 (0.4)	3 (1.0)	0	0
Pleural Effusion	2 (0.8)	4 (1.1)	1 (0.4)	5 (1.6)	0	0
Pleurisy	0	0	1 (0.4)	0	0	0
Pleuritic Pain	2 (0.8)	0	0	1 (0.3)	0	0
Pneumonia Aspiration	0	3 (0.8)	2 (0.9)	1 (0.3)	0	0
Pneumonitis	1 (0.4)	3 (0.8)	0	1 (0.3)	0	0

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All Randomized Subjects
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	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Pneumothorax	1 (0.4)	2 (0.6)	1 (0.4)	1 (0.3)	0	0
Productive Cough	1 (0.4)	0	2 (0.9)	2 (0.6)	0	0
Pulmonary Alveolar Haemorrhage	3 (1.2)	0	1 (0.4)	0	1 (3.8)	0
Pulmonary Congestion	1 (0.4)	0	0	0	0	0
Pulmonary Embolism	0	3 (0.8)	2 (0.9)	0	0	0
Pulmonary Fibrosis	0	0	0	1 (0.3)	0	0
Pulmonary Haemorrhage	2 (0.8)	4 (1 1)	2 (0.9)	2 (0.6)	0	0
Pulmonary Haemosiderosis	0	0	0	1 (0.3)	0	0
Pulmonary Hypertension	1 (0.4)	1 (0.3)	0	0	0	0
Pulmonary Mass	1 (0.4)	2 (0.6)	2 (0.9)	2 (0.6)	0	0
Pulmonary Oedema	4 (1.6)	4 (1.1)	5 (2.2)	4 (1.3)	0	1 (3.1)
Rales	0	1 (0 3)	0	0	0	0
Respiratory Acidosis	0	1 (0 3)	1 (0.4)	0	0	0
Respiratory Arrest	0	1 (0 3)	0	0	0	0
Respiratory Disorder	0	1 (0 3)	1 (0.4)	0	1 (3.8)	0
Respiratory Distress	5 (2.0)	4 (1 1)	4 (1.8)	1 (0.3)	0	2 (6.3)
Respiratory Failure	13 (5.3)	11 (3.0)	18 (8.0)	19 (6.0)	0	2 (6.3)
Respiratory Tract Haemorrhage	0	1 (0 3)	0	0	0	0
Restrictive Pulmonary Disease	1 (0.4)	0	0	0	0	0
Rhinalgia	0	0	1 (0.4)	0	0	0
Sinus Congestion	0	0	0	1 (0.3)	0	0
Sinus Disorder	0	1 (0.3)	0	0	0	0
Tachypnoea	4 (1.6)	3 (0.8)	1 (0.4)	4 (1.3)	0	0

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Tonsillar Disorder	1 (0.4)	0	0	0	0	0
Wheezing	0	0	1 (0.4)	0	0	0
Skin And Subcutaneous Tissue Disorders	**11 (4.5)**	**15 (4.2)**	**12 (5.4)**	**5 (1.6)**	**2 (7.7)**	**1 (3.1)**
Alopecia	1 (0.4)	0	2 (0.9)	0	0	0
Alopecia Totalis	1 (0.4)	0	0	0	0	0
Blister	0	2 (0.6)	1 (0.4)	0	0	0
Cold Sweat	0	1 (0 3)	0	0	0	0
Decubitus Ulcer	0	0	0	1 (0.3)	0	0
Dry Skin	1 (0.4)	0	1 (0.4)	0	0	0
Erythema	1 (0.4)	1 (0 3)	0	0	0	0
Exfoliative Rash	0	0	0	1 (0.3)	0	0
Hypersensitivity Vasculitis	0	1 (0 3)	0	0	0	0
Night Sweats	1 (0.4)	1 (0.3)	0	0	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome	1 (0.4)	0	0	0	0	0
Petechiae	1 (0.4)	1 (0 3)	2 (0.9)	0	0	0
Pruritus	0	2 (0.6)	2 (0.9)	0	0	0
Rash	3 (1.2)	2 (0.6)	2 (0.9)	1 (0.3)	1 (3.8)	0
Rash Erythematous	0	1 (0 3)	0	0	0	0
Rash Generalised	0	0	0	0	1 (3.8)	1 (3.1)
Rash Maculo-Papular	2 (0.8)	1 (0 3)	0	0	0	0
Rash Pruritic	0	0	1 (0.4)	2 (0.6)	0	0
Skin Disorder	0	1 (0 3)	1 (0.4)	0	0	0

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All Randomized Subjects
Summary of Severe/Life Threatening Treatment Emergent Adverse Events by Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Skin Exfoliation	0	0	0	1 (0.3)	0	0
Skin Hypopigmentation	0	1 (0 3)	0	0	0	0
Skin Lesion	0	0	1 (0.4)	1 (0.3)	0	0
Skin Oedema	1 (0.4)	0	0	0	0	0
Skin Ulcer	0	0	0	1 (0.3)	0	0
Subcutaneous Emphysema	0	1 (0.3)	0	0	0	0
Social Circumstances	**0**	**1 (0.3)**	**0**	**0**	**0**	**0**
Social Problem	0	1 (0 3)	0	0	0	0
Surgical And Medical Procedures	**1 (0.4)**	**2 (0.6)**	**1 (0.4)**	**0**	**0**	**1 (3.1)**
Bone Marrow Transplant	1 (0.4)	1 (0 3)	0	0	0	0
Chemotherapy	0	0	1 (0.4)	0	0	0
Stem Cell Transplant	0	1 (0.3)	0	0	0	0
Surgery	0	0	0	0	0	1 (3.1)
Vascular Disorders	**24 (9.8)**	**35 (9.7)**	**29 (12.9)**	**40 (12.7)**	**5 (19.2)**	**2 (6.3)**
Circulatory Collapse	1 (0.4)	0	3 (1.3)	1 (0.3)	0	0
Deep Vein Thrombosis	2 (0.8)	0	1 (0.4)	1 (0.3)	1 (3.8)	0
Embolism Arterial	0	0	0	1 (0.3)	0	0
Haemodynamic Instability	1 (0.4)	1 (0.3)	0	1 (0.3)	0	0
Haemorrhage	1 (0.4)	1 (0 3)	0	3 (1.0)	0	0
Haemorrhagic Infarction	0	0	0	1 (0.3)	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 Sex
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Female n = 244	Male n = 361	Female n = 224	Male n = 315	Female n = 26	Male n = 32
Hypertension	4 (1.6)	7 (1 9)	7 (3.1)	9 (2.9)	2 (7.7)	0
Hypertensive Crisis	1 (0.4)	0	1 (0.4)	0	0	0
Hypotension	15 (6.1)	23 (6.4)	15 (6.7)	25 (7 9)	3 (11.5)	2 (6.3)
Hypovolaemic Shock	0	2 (0.6)	3 (1.3)	0	0	0
Ischaemia	0	0	1 (0.4)	0	0	0
Microangiopathy	0	1 (0 3)	0	0	0	0
Orthostatic Hypotension	0	2 (0.6)	0	0	0	0
Pallor	0	1 (0 3)	0	0	0	0
Peripheral Circulatory Failure	0	1 (0 3)	0	0	0	0
Peripheral Vascular Disorder	1 (0.4)	0	0	0	0	0
Shock	0	0	2 (0.9)	2 (0.6)	0	0
Subclavian Vein Thrombosis	0	1 (0.3)	0	0	0	0
Vasodilatation	0	0	1 (0.4)	0	0	0
Vena Cava Embolism	0	0	1 (0.4)	0	0	0
Venous Thrombosis	0	0	1 (0.4)	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 2.7.4-168　　性別ごと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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Subjects Reporting Any Adverse Event	**77 (97.5)**	**44 (97 8)**	**191 (96.5)**	**100 (94 3)**	**268 (96.8)**	**144 (95.4)**
Blood And Lymphatic System Disorders	**37 (46.8)**	**18 (40.0)**	**75 (37.9)**	**33 (31.1)**	**112 (40.4)**	**51 (33.8)**
Anaemia	15 (19.0)	6 (13.3)	46 (23.2)	14 (13.2)	61 (22.0)	20 (13.2)
Anaemia Megaloblastic	0	0	1 (0.5)	0	1 (0.4)	0
Aplastic Anaemia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Autoimmune Haemolytic Anaemia	0	0	0	1 (0.9)	0	1 (0.7)
Bandaemia	0	0	0	1 (0.9)	0	1 (0.7)
Coagulopathy	0	3 (6.7)	2 (1.0)	2 (1.9)	2 (0.7)	5 (3.3)
Disseminated Intravascular Coagulation	0	1 (2 2)	3 (1.5)	1 (0.9)	3 (1.1)	2 (1.3)
Eosinophilia	0	0	1 (0.5)	0	1 (0.4)	0
Febrile Neutropenia	2 (2.5)	3 (6.7)	11 (5.6)	6 (5.7)	13 (4.7)	9 (6.0)
Haemolysis	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Haemolytic Anaemia	0	1 (2 2)	0	2 (1.9)	0	3 (2.0)
Haemolytic Uraemic Syndrome	3 (3.8)	1 (2.2)	0	0	3 (1.1)	1 (0.7)
Hypercoagulation	0	0	0	1 (0.9)	0	1 (0.7)
Leukocytosis	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Leukopenia	2 (2.5)	2 (4.4)	3 (1.5)	4 (3.8)	5 (1.8)	6 (4.0)
Lymphadenopathy	2 (2.5)	0	4 (2.0)	3 (2.8)	6 (2.2)	3 (2.0)
Neutropenia	8 (10.1)	4 (8.9)	15 (7.6)	12 (11.3)	23 (8.3)	16 (10.6)
Pancytopenia	4 (5.1)	2 (4.4)	6 (3.0)	7 (6.6)	10 (3.6)	9 (6.0)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Polycythaemia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Retroperitoneal Lymphadenopathy	1 (1.3)	0	0	0	1 (0.4)	0
Splenic Infarction	0	0	0	1 (0.9)	0	1 (0.7)
Splenic Lesion	0	0	1 (0.5)	0	1 (0.4)	0
Splenomegaly	4 (5.1)	1 (2 2)	3 (1.5)	1 (0.9)	7 (2.5)	2 (1.3)
Thrombocytopenia	14 (17.7)	8 (17.8)	31 (15.7)	12 (11.3)	45 (16.2)	20 (13.2)
Thrombocytosis	0	0	1 (0.5)	0	1 (0.4)	0
Thrombotic Thrombocytopenic Purpura	4 (5.1)	1 (2.2)	0	1 (0.9)	4 (1.4)	2 (1.3)
Cardiac Disorders	**34 (43.0)**	**22 (48 9)**	**49 (24.7)**	**30 (28.3)**	**83 (30.0)**	**52 (34.4)**
Angina Pectoris	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Aortic Valve Incompetence	0	0	0	1 (0.9)	0	1 (0.7)
Aortic Valve Sclerosis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Arrhythmia	0	0	2 (1.0)	0	2 (0.7)	0
Arrhythmia Supraventricular	0	2 (4.4)	0	0	0	2 (1.3)
Arteriosclerosis Coronary Artery	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Atrial Fibrillation	6 (7.6)	1 (2.2)	9 (4.5)	2 (1 9)	15 (5.4)	3 (2.0)
Atrial Flutter	4 (5.1)	0	1 (0.5)	2 (1.9)	5 (1.8)	2 (1.3)
Atrioventricular Block	0	1 (2.2)	0	0	0	1 (0.7)
Atrioventricular Block First Degree	0	0	2 (1.0)	0	2 (0.7)	0
Bradycardia	1 (1.3)	1 (2 2)	6 (3.0)	2 (1.9)	7 (2.5)	3 (2.0)
Bundle Branch Block	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Bundle Branch Block Left	1 (1.3)	0	0	0	1 (0.4)	0
Bundle Branch Block Right	0	0	0	2 (1.9)	0	2 (1.3)
Cardiac Arrest	1 (1.3)	1 (2 2)	0	6 (5.7)	1 (0.4)	7 (4.6)
Cardiac Failure	3 (3.8)	1 (2 2)	0	2 (1.9)	3 (1.1)	3 (2.0)
Cardiac Failure Congestive	1 (1.3)	1 (2 2)	7 (3.5)	4 (3.8)	8 (2.9)	5 (3.3)
Cardiac Valve Disease	0	0	0	1 (0.9)	0	1 (0.7)
Cardio-Respiratory Arrest	1 (1.3)	7 (15.6)	5 (2.5)	4 (3.8)	6 (2.2)	11 (7.3)
Cardiogenic Shock	0	0	0	1 (0.9)	0	1 (0.7)
Cardiomegaly	1 (1.3)	2 (4.4)	0	0	1 (0.4)	2 (1.3)
Cardiomyopathy	2 (2.5)	2 (4.4)	1 (0.5)	0	3 (1.1)	2 (1.3)
Cardiopulmonary Failure	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Coronary Artery Occlusion	0	0	0	1 (0.9)	0	1 (0.7)
Cyanosis	0	0	0	2 (1.9)	0	2 (1.3)
Defect Conduction Intraventricular	1 (1.3)	0	0	0	1 (0.4)	0
Dilatation Atrial	0	0	1 (0.5)	0	1 (0.4)	0
Extrasystoles	0	0	2 (1.0)	0	2 (0.7)	0
Left Atrial Enlargement	1 (1.3)	0	0	0	1 (0.4)	0
Left Ventricular Dysfunction	0	0	0	1 (0.9)	0	1 (0.7)
Left Ventricular Hypertrophy	0	0	1 (0.5)	0	1 (0.4)	0
Mitral Valve Calcification	0	0	1 (0.5)	0	1 (0.4)	0
Mitral Valve Incompetence	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Mitral Valve Stenosis	0	0	0	1 (0.9)	0	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Myocardial Infarction	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Palpitations	3 (3.8)	0	3 (1.5)	0	6 (2.2)	0
Pericardial Effusion	5 (6.3)	4 (8.9)	5 (2.5)	0	10 (3.6)	4 (2.6)
Pericardial Rub	3 (3.8)	0	0	0	3 (1.1)	0
Pericarditis	1 (1.3)	1 (2 2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Pulseless Electrical Activity	0	1 (2 2)	0	0	0	1 (0.7)
Sinus Bradycardia	0	0	0	1 (0.9)	0	1 (0.7)
Sinus Tachycardia	5 (6.3)	0	1 (0.5)	3 (2.8)	6 (2.2)	3 (2.0)
Supraventricular Tachycardia	5 (6.3)	1 (2.2)	3 (1.5)	5 (4.7)	8 (2.9)	6 (4.0)
Tachycardia	16 (20.3)	9 (20.0)	13 (6.6)	10 (9.4)	29 (10.5)	19 (12.6)
Tricuspid Valve Incompetence	1 (1.3)	0	0	0	1 (0.4)	0
Ventricular Extrasystoles	0	1 (2.2)	5 (2.5)	0	5 (1.8)	1 (0.7)
Ventricular Fibrillation	0	1 (2.2)	1 (0.5)	1 (0 9)	1 (0.4)	2 (1.3)
Ventricular Hypertrophy	0	0	1 (0.5)	0	1 (0.4)	0
Ventricular Tachycardia	1 (1.3)	1 (2.2)	2 (1.0)	2 (1.9)	3 (1.1)	3 (2.0)
Congenital, Familial And Genetic Disorders	**0**	**0**	**2 (1.0)**	**0**	**2 (0.7)**	**0**
Aplasia	0	0	1 (0.5)	0	1 (0.4)	0
Fanconi Syndrome	0	0	1 (0.5)	0	1 (0.4)	0
Ear And Labyrinth Disorders	**8 (10.1)**	**5 (11.1)**	**11 (5.6)**	**9 (8.5)**	**19 (6.9)**	**14 (9.3)**
Cerumen Impaction	1 (1.3)	0	3 (1.5)	0	4 (1.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Conductive Deafness	0	0	1 (0.5)	0	1 (0.4)	0
Deafness	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Ear Discomfort	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Ear Pain	3 (3.8)	3 (6.7)	0	6 (5.7)	3 (1.1)	9 (6.0)
Ear Pruritus	1 (1.3)	0	0	0	1 (0.4)	0
Excessive Cerumen Production	1 (1.3)	0	0	0	1 (0.4)	0
External Ear Inflammation	1 (1.3)	0	0	0	1 (0.4)	0
Hypoacusis	0	1 (2 2)	2 (1.0)	1 (0.9)	2 (0.7)	2 (1.3)
Middle Ear Effusion	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Tinnitus	0	2 (4.4)	0	1 (0.9)	0	3 (2.0)
Vertigo	1 (1.3)	0	4 (2.0)	1 (0.9)	5 (1.8)	1 (0.7)
Vertigo Labyrinthine	0	0	1 (0.5)	0	1 (0.4)	0
Endocrine Disorders	**6 (7.6)**	**3 (6.7)**	**7 (3.5)**	**1 (0.9)**	**13 (4.7)**	**4 (2.6)**
Adrenal Insufficiency	3 (3.8)	0	3 (1.5)	1 (0.9)	6 (2.2)	1 (0.7)
Adrenocortical Insufficiency Acute	0	0	1 (0.5)	0	1 (0.4)	0
Cushingoid	1 (1.3)	1 (2 2)	3 (1.5)	0	4 (1.4)	1 (0.7)
Hyperthyroidism	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Hypogonadism	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Hypothyroidism	1 (1.3)	2 (4.4)	1 (0.5)	0	2 (0.7)	2 (1.3)
Eye Disorders	**20 (25.3)**	**15 (33 3)**	**34 (17.2)**	**21 (19.8)**	**54 (19.5)**	**36 (23.8)**

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Blepharitis	1 (1.3)	0	0	0	1 (0.4)	0
Blindness	0	1 (2.2)	0	1 (0 9)	0	2 (1.3)
Cataract	2 (2.5)	0	1 (0.5)	1 (0.9)	3 (1.1)	1 (0.7)
Conjunctival Haemorrhage	0	1 (2 2)	3 (1.5)	0	3 (1.1)	1 (0.7)
Conjunctival Hyperaemia	0	0	1 (0.5)	0	1 (0.4)	0
Conjunctival Irritation	0	1 (2 2)	0	0	0	1 (0.7)
Conjunctival Oedema	1 (1.3)	2 (4.4)	0	1 (0.9)	1 (0.4)	3 (2.0)
Conjunctivitis Allergic	0	0	1 (0.5)	0	1 (0.4)	0
Corneal Epithelium Defect	0	0	1 (0.5)	0	1 (0.4)	0
Corneal Erosion	1 (1.3)	0	0	0	1 (0.4)	0
Corneal Perforation	0	0	0	1 (0.9)	0	1 (0.7)
Dacryostenosis Acquired	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Diplopia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Dry Eye	4 (5.1)	2 (4.4)	1 (0.5)	1 (0.9)	5 (1.8)	3 (2.0)
Erythema Of Eyelid	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Exophthalmos	0	1 (2 2)	0	0	0	1 (0.7)
Eye Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Eye Irritation	2 (2.5)	0	5 (2.5)	2 (1.9)	7 (2.5)	2 (1.3)
Eye Movement Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Eye Oedema	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Eye Pain	2 (2.5)	1 (2 2)	2 (1.0)	3 (2.8)	4 (1.4)	4 (2.6)
Eye Pruritus	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Eye Swelling	0	1 (2.2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Eyelid Cyst	0	0	0	1 (0.9)	0	1 (0.7)
Eyelid Oedema	1 (1.3)	0	0	0	1 (0.4)	0
Eyelid Ptosis	1 (1.3)	0	0	0	1 (0.4)	0
Hypoaesthesia Eye	0	1 (2 2)	0	0	0	1 (0.7)
Iridocyclitis	0	1 (2.2)	0	0	0	1 (0.7)
Keratopathy	0	1 (2 2)	0	0	0	1 (0.7)
Lacrimation Increased	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Mydriasis	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Myopia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Ocular Hyperaemia	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Optic Atrophy	0	0	1 (0.5)	0	1 (0.4)	0
Papilloedema	0	0	1 (0.5)	0	1 (0.4)	0
Periorbital Oedema	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Photophobia	2 (2.5)	1 (2 2)	1 (0.5)	0	3 (1.1)	1 (0.7)
Photopsia	0	0	0	1 (0.9)	0	1 (0.7)
Pinguecula	0	0	0	1 (0.9)	0	1 (0.7)
Pupillary Reflex Impaired	0	1 (2.2)	0	0	0	1 (0.7)
Pupils Unequal	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Retinal Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Retinal Exudates	0	0	0	1 (0.9)	0	1 (0.7)
Scleral Discolouration	0	0	0	1 (0.9)	0	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Scleral Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Scleral Oedema	0	1 (2 2)	0	0	0	1 (0.7)
Uveitis	0	1 (2 2)	0	0	0	1 (0.7)
Vision Blurred	8 (10.1)	3 (6.7)	9 (4.5)	7 (6.6)	17 (6.1)	10 (6.6)
Visual Impairment	1 (1.3)	1 (2 2)	2 (1.0)	3 (2.8)	3 (1.1)	4 (2.6)
Gastrointestinal Disorders	**57 (72.2)**	**31 (68 9)**	**133 (67.2)**	**73 (68.9)**	**190 (68.6)**	**104 (68.9)**
Abdominal Discomfort	2 (2.5)	0	3 (1.5)	0	5 (1.8)	0
Abdominal Distension	9 (11.4)	8 (17.8)	8 (4.0)	8 (7 5)	17 (6.1)	16 (10.6)
Abdominal Hernia	0	0	1 (0.5)	0	1 (0.4)	0
Abdominal Pain	18 (22.8)	9 (20.0)	21 (10.6)	13 (12.3)	39 (14.1)	22 (14.6)
Abdominal Pain Lower	0	2 (4.4)	2 (1.0)	0	2 (0.7)	2 (1.3)
Abdominal Pain Upper	9 (11.4)	5 (11.1)	18 (9.1)	11 (10.4)	27 (9.7)	16 (10.6)
Abdominal Rigidity	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Abdominal Tenderness	1 (1.3)	1 (2 2)	3 (1.5)	1 (0.9)	4 (1.4)	2 (1.3)
Abdominal Wall Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Abnormal Faeces	1 (1.3)	0	0	0	1 (0.4)	0
Anal Incontinence	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Anorectal Discomfort	0	0	1 (0.5)	0	1 (0.4)	0
Ascites	5 (6.3)	3 (6.7)	5 (2.5)	1 (0.9)	10 (3.6)	4 (2.6)
Barrett's Oesophagus	0	0	1 (0.5)	0	1 (0.4)	0
Cheilitis	1 (1.3)	0	0	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Colitis	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Constipation	12 (15.2)	6 (13.3)	22 (11.1)	17 (16.0)	34 (12.3)	23 (15.2)
Dental Caries	0	0	1 (0.5)	0	1 (0.4)	0
Dental Discomfort	0	0	1 (0.5)	0	1 (0.4)	0
Diarrhoea	30 (38.0)	13 (28 9)	50 (25.3)	27 (25.5)	80 (28.9)	40 (26.5)
Diarrhoea Haemorrhagic	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Dry Mouth	3 (3.8)	1 (2 2)	4 (2.0)	1 (0.9)	7 (2.5)	2 (1.3)
Duodenal Ulcer	3 (3.8)	0	0	0	3 (1.1)	0
Duodenitis	2 (2.5)	1 (2.2)	0	0	2 (0.7)	1 (0.7)
Dyspepsia	5 (6.3)	2 (4.4)	7 (3.5)	6 (5.7)	12 (4.3)	8 (5.3)
Dysphagia	3 (3.8)	1 (2 2)	7 (3.5)	5 (4.7)	10 (3.6)	6 (4.0)
Enteritis	0	0	1 (0.5)	0	1 (0.4)	0
Eructation	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Faecaloma	0	0	1 (0.5)	0	1 (0.4)	0
Faeces Discoloured	0	0	0	1 (0.9)	0	1 (0.7)
Faeces Soft	0	0	1 (0.5)	0	1 (0.4)	0
Flatulence	2 (2.5)	2 (4.4)	10 (5.1)	4 (3.8)	12 (4.3)	6 (4.0)
Food Poisoning	0	0	2 (1.0)	0	2 (0.7)	0
Gastric Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Gastric Haemorrhage	0	0	1 (0.5)	0	1 (0.4)	0
Gastric Perforation	0	1 (2.2)	0	0	0	1 (0.7)
Gastric Polyps	1 (1.3)	0	0	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Gastric Ulcer	0	1 (2 2)	0	0	0	1 (0.7)
Gastritis	3 (3.8)	1 (2 2)	1 (0.5)	2 (1.9)	4 (1.4)	3 (2.0)
Gastrointestinal Haemorrhage	4 (5.1)	2 (4.4)	3 (1.5)	1 (0.9)	7 (2.5)	3 (2.0)
Gastrointestinal Hypermotility	1 (1.3)	0	0	0	1 (0.4)	0
Gastrointestinal Pain	0	0	1 (0.5)	0	1 (0.4)	0
Gastrointestinal Sounds Abnormal	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Gastrooesophageal Reflux Disease	1 (1.3)	0	2 (1.0)	2 (1.9)	3 (1.1)	2 (1.3)
Gingival Bleeding	2 (2.5)	0	3 (1.5)	2 (1.9)	5 (1.8)	2 (1.3)
Gingival Hypertrophy	0	0	1 (0.5)	0	1 (0.4)	0
Gingival Pain	0	0	1 (0.5)	0	1 (0.4)	0
Gingival Swelling	1 (1.3)	0	0	0	1 (0.4)	0
Glossitis	0	0	1 (0.5)	0	1 (0.4)	0
Glossodynia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Haematemesis	4 (5.1)	0	3 (1.5)	0	7 (2.5)	0
Haematochezia	2 (2.5)	0	4 (2.0)	1 (0.9)	6 (2.2)	1 (0.7)
Haemorrhoidal Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Haemorrhoids	1 (1.3)	1 (2.2)	4 (2.0)	4 (3.8)	5 (1.8)	5 (3.3)
Hiatus Hernia	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Hypoaesthesia Oral	1 (1.3)	3 (6.7)	1 (0.5)	1 (0.9)	2 (0.7)	4 (2.6)
Ileus	1 (1.3)	0	4 (2.0)	1 (0.9)	5 (1.8)	1 (0.7)
Ileus Paralytic	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Intestinal Dilatation	1 (1.3)	0	0	0	1 (0.4)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Intestinal Infarction	0	1 (2 2)	0	0	0	1 (0.7)
Intestinal Ischaemia	0	1 (2 2)	0	0	0	1 (0.7)
Intestinal Obstruction	0	0	1 (0.5)	0	1 (0.4)	0
Intestinal Ulcer	0	0	1 (0.5)	0	1 (0.4)	0
Irritable Bowel Syndrome	0	0	1 (0.5)	0	1 (0.4)	0
Leukoplakia Oral	0	0	1 (0.5)	0	1 (0.4)	0
Lip Dry	1 (1.3)	0	6 (3.0)	1 (0.9)	7 (2.5)	1 (0.7)
Lip Swelling	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Mallory-Weiss Syndrome	0	0	1 (0.5)	0	1 (0.4)	0
Melaena	0	1 (2 2)	0	0	0	1 (0.7)
Mouth Haemorrhage	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Mouth Ulceration	0	2 (4.4)	3 (1.5)	0	3 (1.1)	2 (1.3)
Nausea	21 (26.6)	15 (33 3)	50 (25.3)	41 (38.7)	71 (25.6)	56 (37.1)
Neutropenic Colitis	0	0	1 (0.5)	0	1 (0.4)	0
Obstruction Gastric	0	0	0	1 (0.9)	0	1 (0.7)
Odynophagia	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Oesophageal Pain	1 (1.3)	0	0	0	1 (0.4)	0
Oesophageal Perforation	0	0	0	1 (0.9)	0	1 (0.7)
Oesophageal Stenosis	1 (1.3)	0	0	0	1 (0.4)	0
Oesophageal Ulcer	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Oesophagitis	1 (1.3)	1 (2 2)	2 (1.0)	2 (1.9)	3 (1.1)	3 (2.0)
Oesophagitis Ulcerative	1 (1.3)	0	0	0	1 (0.4)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Oral Discomfort	0	1 (2.2)	0	0	0	1 (0.7)
Oral Disorder	0	2 (4.4)	1 (0.5)	1 (0.9)	1 (0.4)	3 (2.0)
Oral Mucosal Blistering	0	0	2 (1.0)	0	2 (0.7)	0
Oral Mucosal Erythema	1 (1.3)	0	0	0	1 (0.4)	0
Oral Pain	0	0	1 (0.5)	0	1 (0.4)	0
Palatal Swelling	1 (1.3)	0	0	0	1 (0.4)	0
Pancreatic Atrophy	1 (1.3)	0	0	0	1 (0.4)	0
Pancreatic Failure	0	0	1 (0.5)	0	1 (0.4)	0
Pancreatitis	1 (1.3)	0	1 (0.5)	3 (2.8)	2 (0.7)	3 (2.0)
Pancreatitis Acute	0	0	1 (0.5)	0	1 (0.4)	0
Pancreatitis Haemorrhagic	1 (1.3)	0	0	0	1 (0.4)	0
Pneumatosis Intestinalis	1 (1.3)	0	0	0	1 (0.4)	0
Proctalgia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Rectal Haemorrhage	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Rectal Lesion	1 (1.3)	0	0	0	1 (0.4)	0
Retching	1 (1.3)	1 (2 2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Salivary Hypersecretion	1 (1.3)	0	0	0	1 (0.4)	0
Stomatitis	0	1 (2 2)	3 (1.5)	1 (0.9)	3 (1.1)	2 (1.3)
Submaxillary Gland Enlargement	0	0	1 (0.5)	0	1 (0.4)	0
Tongue Coated	2 (2.5)	1 (2 2)	1 (0.5)	0	3 (1.1)	1 (0.7)
Tongue Oedema	1 (1.3)	0	0	0	1 (0.4)	0
Tongue Ulceration	2 (2.5)	2 (4.4)	0	0	2 (0.7)	2 (1.3)

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All Randomized Subjects
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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Tooth Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Toothache	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Umbilical Hernia	0	0	1 (0.5)	0	1 (0.4)	0
Upper Gastrointestinal Haemorrhage	0	0	2 (1.0)	0	2 (0.7)	0
Vomiting	20 (25.3)	15 (33 3)	43 (21.7)	34 (32.1)	63 (22.7)	49 (32.5)
General Disorders And Administration Site Conditions	**59 (74.7)**	**33 (73 3)**	**131 (66.2)**	**70 (66.0)**	**190 (68.6)**	**103 (68.2)**
Asthenia	12 (15.2)	8 (17.8)	26 (13.1)	23 (21.7)	38 (13.7)	31 (20.5)
Brain Death	0	1 (2.2)	0	0	0	1 (0.7)
Catheter Site Discharge	1 (1.3)	0	0	0	1 (0.4)	0
Catheter Site Erythema	1 (1.3)	0	6 (3.0)	0	7 (2.5)	0
Catheter Site Haematoma	0	0	1 (0.5)	0	1 (0.4)	0
Catheter Site Haemorrhage	0	0	1 (0.5)	0	1 (0.4)	0
Catheter Site Pain	1 (1.3)	1 (2.2)	3 (1.5)	2 (1.9)	4 (1.4)	3 (2.0)
Catheter Site Related Reaction	0	0	1 (0.5)	0	1 (0.4)	0
Catheter Site Swelling	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Chest Discomfort	1 (1.3)	0	0	0	1 (0.4)	0
Chest Pain	10 (12.7)	7 (15.6)	22 (11.1)	21 (19.8)	32 (11.6)	28 (18.5)
Chills	9 (11.4)	6 (13.3)	19 (9.6)	9 (8 5)	28 (10.1)	15 (9.9)
Crepitations	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Crying	0	1 (2 2)	0	0	0	1 (0.7)
Cyst	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Death	0	0	1 (0.5)	0	1 (0.4)	0
Discomfort	0	0	0	1 (0.9)	0	1 (0.7)
Disease Progression	11 (13.9)	3 (6.7)	9 (4.5)	6 (5.7)	20 (7.2)	9 (6.0)
Drug Interaction	0	0	0	1 (0.9)	0	1 (0.7)
Drug Intolerance	0	0	1 (0.5)	0	1 (0.4)	0
Early Satiety	0	0	0	1 (0.9)	0	1 (0.7)
Face Oedema	4 (5.1)	0	1 (0.5)	1 (0.9)	5 (1.8)	1 (0.7)
Facial Pain	1 (1.3)	3 (6.7)	0	2 (1.9)	1 (0.4)	5 (3.3)
Fatigue	17 (21.5)	3 (6.7)	23 (11.6)	9 (8.5)	40 (14.4)	12 (7.9)
Feeling Cold	1 (1.3)	1 (2 2)	0	0	1 (0.4)	1 (0.7)
Feeling Jittery	0	0	1 (0.5)	0	1 (0.4)	0
Gait Disturbance	2 (2.5)	0	5 (2.5)	4 (3.8)	7 (2.5)	4 (2.6)
Gait Inability	0	0	1 (0.5)	0	1 (0.4)	0
General Physical Health Deterioration	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Generalised Oedema	4 (5.1)	5 (11.1)	5 (2.5)	1 (0.9)	9 (3.2)	6 (4.0)
Granuloma	1 (1.3)	0	0	0	1 (0.4)	0
Hyperthermia	1 (1.3)	0	0	0	1 (0.4)	0
Hypothermia	2 (2.5)	0	0	0	2 (0.7)	0
Inflammation	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Influenza Like Illness	0	0	3 (1.5)	2 (1.9)	3 (1.1)	2 (1.3)
Infusion Site Erythema	0	0	1 (0.5)	0	1 (0.4)	0
Infusion Site Inflammation	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Infusion Site Phlebitis	0	0	0	1 (0.9)	0	1 (0.7)
Injection Site Pain	1 (1.3)	0	0	0	1 (0.4)	0
Localised Oedema	0	0	1 (0.5)	0	1 (0.4)	0
Malaise	3 (3.8)	1 (2 2)	7 (3.5)	4 (3.8)	10 (3.6)	5 (3.3)
Mass	0	0	1 (0.5)	0	1 (0.4)	0
Mucosal Dryness	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Mucosal Inflammation	5 (6.3)	1 (2.2)	18 (9.1)	6 (5.7)	23 (8.3)	7 (4.6)
Multi-Organ Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Multiple Organ Dysfunction Syndrome	5 (6.3)	4 (8.9)	3 (1.5)	3 (2.8)	8 (2.9)	7 (4.6)
Nodule	3 (3.8)	0	1 (0.5)	1 (0.9)	4 (1.4)	1 (0.7)
Oedema	3 (3.8)	2 (4.4)	9 (4.5)	5 (4.7)	12 (4.3)	7 (4.6)
Oedema Peripheral	15 (19.0)	9 (20.0)	25 (12.6)	13 (12.3)	40 (14.4)	22 (14.6)
Pain	3 (3.8)	2 (4.4)	11 (5.6)	3 (2.8)	14 (5.1)	5 (3.3)
Peripheral Swelling	3 (3.8)	3 (6.7)	9 (4.5)	4 (3.8)	12 (4.3)	7 (4.6)
Pseudocyst	0	1 (2.2)	0	0	0	1 (0.7)
Puncture Site Pain	0	0	1 (0.5)	0	1 (0.4)	0
Pyrexia	28 (35.4)	15 (33 3)	69 (34.8)	31 (29.2)	97 (35.0)	46 (30.5)
Secretion Discharge	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Sluggishness	1 (1.3)	0	0	0	1 (0.4)	0
Suprapubic Pain	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Swelling	0	1 (2 2)	1 (0.5)	1 (0.9)	1 (0.4)	2 (1.3)
Vessel Puncture Site Haematoma	0	0	1 (0.5)	0	1 (0.4)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Vessel Puncture Site Pain	0	0	1 (0.5)	0	1 (0.4)	0
Hepatobiliary Disorders	**12 (15.2)**	**7 (15.6)**	**22 (11.1)**	**10 (9.4)**	**34 (12.3)**	**17 (11.3)**
Cholecystitis	1 (1.3)	1 (2 2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Cholelithiasis	4 (5.1)	0	2 (1.0)	1 (0.9)	6 (2.2)	1 (0.7)
Cholestasis	0	2 (4.4)	0	0	0	2 (1.3)
Deficiency Of Bile Secretion	0	0	0	1 (0.9)	0	1 (0.7)
Gallbladder Enlargement	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Gallbladder Polyp	0	0	0	1 (0.9)	0	1 (0.7)
Hepatic Cyst	1 (1.3)	0	0	0	1 (0.4)	0
Hepatic Failure	1 (1.3)	0	4 (2.0)	1 (0.9)	5 (1.8)	1 (0.7)
Hepatic Function Abnormal	2 (2.5)	1 (2 2)	0	2 (1.9)	2 (0.7)	3 (2.0)
Hepatic Lesion	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Hepatic Necrosis	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Hepatic Steatosis	0	0	0	1 (0.9)	0	1 (0.7)
Hepatitis Acute	0	0	1 (0.5)	0	1 (0.4)	0
Hepatocellular Injury	0	1 (2 2)	0	0	0	1 (0.7)
Hepatomegaly	1 (1.3)	1 (2 2)	3 (1.5)	2 (1.9)	4 (1.4)	3 (2.0)
Hepatosplenomegaly	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Hepatotoxicity	0	0	1 (0.5)	0	1 (0.4)	0
Hyperbilirubinaemia	3 (3.8)	1 (2 2)	4 (2.0)	1 (0.9)	7 (2.5)	2 (1.3)
Jaundice	4 (5.1)	0	7 (3.5)	0	11 (4.0)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Liver Disorder	0	0	0	1 (0.9)	0	1 (0.7)
Ocular Icterus	1 (1.3)	2 (4.4)	2 (1.0)	3 (2.8)	3 (1.1)	5 (3.3)
Immune System Disorders	**28 (35.4)**	**13 (28 9)**	**14 (7.1)**	**6 (5.7)**	**42 (15.2)**	**19 (12.6)**
Acute Graft Versus Host Disease In Intestine	0	1 (2.2)	0	0	0	1 (0.7)
Acute Graft Versus Host Disease In Liver	1 (1.3)	0	0	0	1 (0.4)	0
Chronic Graft Versus Host Disease	0	1 (2.2)	0	0	0	1 (0.7)
Drug Hypersensitivity	2 (2.5)	1 (2 2)	1 (0.5)	2 (1.9)	3 (1.1)	3 (2.0)
Graft Versus Host Disease	7 (8.9)	9 (20.0)	3 (1.5)	0	10 (3.6)	9 (6.0)
Graft Versus Host Disease In Gastrointestinal Tract	5 (6.3)	2 (4.4)	1 (0.5)	0	6 (2.2)	2 (1.3)
Graft Versus Host Disease In Liver	6 (7.6)	0	0	0	6 (2.2)	0
Graft Versus Host Disease In Lung	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Graft Versus Host Disease In Skin	15 (19.0)	5 (11.1)	3 (1.5)	0	18 (6.5)	5 (3.3)
Hypersensitivity	1 (1.3)	0	4 (2.0)	2 (1.9)	5 (1.8)	2 (1.3)
Hypogammaglobulinaemia	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Iodine Allergy	0	0	1 (0.5)	0	1 (0.4)	0
Kidney Transplant Rejection	0	0	1 (0.5)	0	1 (0.4)	0
Seasonal Allergy	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Transplant Rejection	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Infections And Infestations	**56 (70.9)**	**37 (82 2)**	**123 (62.1)**	**64 (60.4)**	**179 (64.6)**	**101 (66.9)**
Abdominal Abscess	0	0	1 (0.5)	0	1 (0.4)	0

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Abdominal Infection	0	0	0	1 (0.9)	0	1 (0.7)
Abscess	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Abscess Limb	2 (2.5)	0	0	0	2 (0.7)	0
Abscess Neck	0	0	0	1 (0.9)	0	1 (0.7)
Abscess Of Eyelid	0	0	0	1 (0.9)	0	1 (0.7)
Abscess Oral	1 (1.3)	0	0	0	1 (0.4)	0
Acarodermatitis	0	0	2 (1.0)	0	2 (0.7)	0
Acid Fast Bacilli Infection	1 (1.3)	0	0	0	1 (0.4)	0
Acinetobacter Infection	0	0	1 (0.5)	0	1 (0.4)	0
Acquired Immunodeficiency Syndrome	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Actinomycosis	0	0	0	1 (0.9)	0	1 (0.7)
Adenovirus Infection	2 (2.5)	1 (2.2)	0	0	2 (0.7)	1 (0.7)
Aids Related Complication	0	0	0	1 (0.9)	0	1 (0.7)
Alpha Haemolytic Streptococcal Infection	1 (1.3)	0	0	2 (1.9)	1 (0.4)	2 (1.3)
Anal Abscess	0	0	0	1 (0.9)	0	1 (0.7)
Arthritis Bacterial	0	0	1 (0.5)	0	1 (0.4)	0
Arthritis Infective	0	0	1 (0.5)	0	1 (0.4)	0
Aspergilloma	2 (2.5)	0	0	0	2 (0.7)	0
Aspergillus Infection	2 (2.5)	2 (4.4)	1 (0.5)	2 (1 9)	3 (1.1)	4 (2.6)
Atypical Pneumonia	0	0	0	1 (0.9)	0	1 (0.7)
Bacteraemia	7 (8.9)	3 (6.7)	9 (4.5)	2 (1.9)	16 (5.8)	5 (3.3)
Bacterial Disease Carrier	0	0	1 (0.5)	0	1 (0.4)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Bacterial Infection	3 (3.8)	3 (6.7)	8 (4.0)	3 (2.8)	11 (4.0)	6 (4.0)
Brain Abscess	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Bronchiolitis	0	0	1 (0.5)	0	1 (0.4)	0
Bronchitis	3 (3.8)	1 (2 2)	10 (5.1)	1 (0.9)	13 (4.7)	2 (1.3)
Bronchitis Bacterial	0	0	1 (0.5)	0	1 (0.4)	0
Bronchitis Viral	1 (1.3)	0	0	0	1 (0.4)	0
Bronchopulmonary Aspergillosis	0	1 (2 2)	1 (0.5)	4 (3.8)	1 (0.4)	5 (3.3)
Candida Infection	2 (2.5)	2 (4.4)	0	1 (0.9)	2 (0.7)	3 (2.0)
Catheter Site Cellulitis	0	0	0	1 (0.9)	0	1 (0.7)
Catheter Site Infection	1 (1.3)	0	0	0	1 (0.4)	0
Cellulitis	1 (1.3)	2 (4.4)	8 (4.0)	3 (2.8)	9 (3.2)	5 (3.3)
Cellulitis Of Male External Genital Organ	0	0	1 (0.5)	0	1 (0.4)	0
Cellulitis Orbital	0	1 (2.2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Cerebral Aspergillosis	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Cerebral Toxoplasmosis	0	1 (2 2)	0	0	0	1 (0.7)
Chronic Sinusitis	1 (1.3)	0	0	0	1 (0.4)	0
Clostridium Difficile Colitis	2 (2.5)	1 (2.2)	2 (1.0)	2 (1 9)	4 (1.4)	3 (2.0)
Clostridium Difficile Infection	0	0	1 (0.5)	0	1 (0.4)	0
Conjunctivitis	2 (2.5)	2 (4.4)	9 (4.5)	1 (0.9)	11 (4.0)	3 (2.0)
Corynebacterium Infection	0	0	2 (1.0)	0	2 (0.7)	0
Corynebacterium Sepsis	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Cystitis Bacterial	1 (1.3)	0	0	0	1 (0.4)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Cytomegalovirus Chorioretinitis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Cytomegalovirus Colitis	0	0	0	1 (0.9)	0	1 (0.7)
Cytomegalovirus Duodenitis	1 (1.3)	0	0	0	1 (0.4)	0
Cytomegalovirus Infection	3 (3.8)	7 (15.6)	2 (1.0)	1 (0.9)	5 (1.8)	8 (5.3)
Dacryocystitis	0	0	1 (0.5)	0	1 (0.4)	0
Device Related Infection	2 (2.5)	2 (4.4)	7 (3.5)	0	9 (3.2)	2 (1.3)
Disseminated Tuberculosis	0	0	1 (0.5)	0	1 (0.4)	0
Diverticulitis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Ear Infection	0	0	1 (0.5)	0	1 (0.4)	0
Empyema	0	0	1 (0.5)	0	1 (0.4)	0
Encephalitis	0	1 (2.2)	0	0	0	1 (0.7)
End Stage Aids	0	0	1 (0.5)	0	1 (0.4)	0
Endocarditis Bacterial	0	1 (2.2)	0	0	0	1 (0.7)
Endophthalmitis	0	0	0	1 (0.9)	0	1 (0.7)
Enterobacter Infection	1 (1.3)	0	0	0	1 (0.4)	0
Enterococcal Bacteraemia	0	0	3 (1.5)	2 (1.9)	3 (1.1)	2 (1.3)
Enterococcal Infection	7 (8.9)	7 (15.6)	5 (2.5)	3 (2.8)	12 (4.3)	10 (6.6)
Enterococcal Sepsis	0	1 (2 2)	1 (0.5)	1 (0.9)	1 (0.4)	2 (1.3)
Escherichia Bacteraemia	1 (1.3)	0	0	0	1 (0.4)	0
Escherichia Infection	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Escherichia Sepsis	0	0	0	1 (0.9)	0	1 (0.7)
Escherichia Urinary Tract Infection	0	1 (2.2)	0	0	0	1 (0.7)

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Eye Infection Staphylococcal	0	0	1 (0.5)	0	1 (0.4)	0
Eyelid Infection	0	0	1 (0.5)	0	1 (0.4)	0
Folliculitis	1 (1.3)	0	0	0	1 (0.4)	0
Fungaemia	1 (1.3)	0	0	0	1 (0.4)	0
Fungal Infection	0	1 (2 2)	0	4 (3.8)	0	5 (3.3)
Fungal Rhinitis	0	0	0	1 (0.9)	0	1 (0.7)
Fungal Sepsis	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Fungal Skin Infection	0	0	0	1 (0.9)	0	1 (0.7)
Furuncle	0	0	2 (1.0)	0	2 (0.7)	0
Fusarium Infection	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Gastroenteritis	0	0	1 (0.5)	0	1 (0.4)	0
Gastroenteritis Viral	0	0	1 (0.5)	0	1 (0.4)	0
Genital Herpes	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Gingival Abscess	1 (1.3)	0	0	0	1 (0.4)	0
Gingivitis	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Helicobacter Gastritis	1 (1.3)	0	0	0	1 (0.4)	0
Hepatic Candidiasis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Hepatosplenic Candidiasis	0	0	1 (0.5)	0	1 (0.4)	0
Herpes Simplex	0	3 (6.7)	1 (0.5)	0	1 (0.4)	3 (2.0)
Herpes Simplex Pneumonia	0	0	1 (0.5)	0	1 (0.4)	0
Herpes Zoster	3 (3.8)	0	6 (3.0)	0	9 (3.2)	0
Hiv Wasting Syndrome	0	0	1 (0.5)	0	1 (0.4)	0

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Hordeolum	0	0	0	1 (0.9)	0	1 (0.7)
Human Polyomavirus Infection	1 (1.3)	0	0	0	1 (0.4)	0
Infection Parasitic	0	0	1 (0.5)	0	1 (0.4)	0
Influenza	0	0	3 (1.5)	3 (2.8)	3 (1.1)	3 (2.0)
Infusion Site Cellulitis	0	0	1 (0.5)	0	1 (0.4)	0
Intervertebral Discitis	0	2 (4.4)	0	0	0	2 (1.3)
Klebsiella Bacteraemia	0	0	1 (0.5)	0	1 (0.4)	0
Klebsiella Infection	0	0	1 (0.5)	0	1 (0.4)	0
Klebsiella Sepsis	0	0	1 (0.5)	0	1 (0.4)	0
Localised Infection	0	0	2 (1.0)	0	2 (0.7)	0
Lower Respiratory Tract Infection	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Lung Abscess	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Lung Infection	0	0	0	1 (0.9)	0	1 (0.7)
Lung Infection Pseudomonal	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Mastoiditis	0	0	0	1 (0.9)	0	1 (0.7)
Meningitis	0	1 (2 2)	0	0	0	1 (0.7)
Meningitis Cryptococcal	0	0	6 (3.0)	2 (1.9)	6 (2.2)	2 (1.3)
Meningitis Tuberculous	0	0	1 (0.5)	0	1 (0.4)	0
Molluscum Contagiosum	0	0	1 (0.5)	0	1 (0.4)	0
Mucormycosis	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Mycobacterial Infection	0	0	4 (2.0)	1 (0.9)	4 (1.4)	1 (0.7)
Mycobacterium Avium Complex Infection	0	0	1 (0.5)	0	1 (0.4)	0

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Mycobacterium Kansasii Infection	1 (1.3)	0	0	0	1 (0.4)	0
Mycoplasma Infection	0	0	0	1 (0.9)	0	1 (0.7)
Nasopharyngitis	0	0	3 (1.5)	4 (3.8)	3 (1.1)	4 (2.6)
Neurosyphilis	0	0	0	1 (0.9)	0	1 (0.7)
Nocardiosis	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Oesophageal Candidiasis	0	0	3 (1.5)	0	3 (1.1)	0
Onychomycosis	0	0	1 (0.5)	0	1 (0.4)	0
Oral Candidiasis	5 (6.3)	3 (6.7)	2 (1.0)	1 (0.9)	7 (2.5)	4 (2.6)
Oral Fungal Infection	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Oral Hairy Leukoplakia	0	0	1 (0.5)	0	1 (0.4)	0
Oral Herpes	2 (2.5)	2 (4.4)	6 (3.0)	2 (1.9)	8 (2.9)	4 (2.6)
Orchitis	0	0	1 (0.5)	0	1 (0.4)	0
Osteomyelitis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Otitis Media	0	1 (2 2)	0	2 (1.9)	0	3 (2.0)
Parainfluenzae Virus Infection	1 (1.3)	0	0	0	1 (0.4)	0
Paronychia	0	0	2 (1.0)	0	2 (0.7)	0
Pelvic Abscess	0	0	1 (0.5)	0	1 (0.4)	0
Periorbital Infection	0	0	1 (0.5)	0	1 (0.4)	0
Peritonitis	0	0	1 (0.5)	0	1 (0.4)	0
Pharyngitis	1 (1.3)	1 (2 2)	0	1 (0.9)	1 (0.4)	2 (1.3)
Pharyngotonsillitis	0	0	0	1 (0.9)	0	1 (0.7)
Plague	1 (1.3)	0	0	0	1 (0.4)	0

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	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Pleural Infection Bacterial	0	0	1 (0.5)	0	1 (0.4)	0
Pneumococcal Sepsis	0	0	0	1 (0.9)	0	1 (0.7)
Pneumocystis Jirovecii Pneumonia	0	0	5 (2.5)	1 (0.9)	5 (1.8)	1 (0.7)
Pneumonia	8 (10.1)	9 (20.0)	15 (7.6)	17 (16.0)	23 (8.3)	26 (17.2)
Pneumonia Bacterial	2 (2.5)	2 (4.4)	1 (0.5)	0	3 (1.1)	2 (1.3)
Pneumonia Cytomegaloviral	0	0	1 (0.5)	0	1 (0.4)	0
Pneumonia Escherichia	0	0	1 (0.5)	0	1 (0.4)	0
Pneumonia Fungal	3 (3.8)	4 (8.9)	5 (2.5)	2 (1.9)	8 (2.9)	6 (4.0)
Pneumonia Klebsiella	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Pneumonia Pseudomonal	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Pneumonia Staphylococcal	1 (1.3)	1 (2.2)	0	1 (0.9)	1 (0.4)	2 (1.3)
Postoperative Wound Infection	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Proctitis Herpes	0	1 (2.2)	0	0	0	1 (0.7)
Pseudallescheria Infection	0	0	1 (0.5)	0	1 (0.4)	0
Pseudomembranous Colitis	0	1 (2 2)	0	0	0	1 (0.7)
Pseudomonas Infection	2 (2.5)	1 (2.2)	0	2 (1.9)	2 (0.7)	3 (2.0)
Pulmonary Mycosis	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Pulmonary Tuberculosis	0	0	1 (0.5)	0	1 (0.4)	0
Purulent Discharge	0	0	1 (0.5)	0	1 (0.4)	0
Pyelonephritis	1 (1.3)	0	0	0	1 (0.4)	0
Respiratory Syncytial Virus Infection	1 (1.3)	1 (2.2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Respiratory Tract Infection	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Retinitis	0	0	1 (0.5)	0	1 (0.4)	0
Rhinitis	0	1 (2 2)	2 (1.0)	1 (0.9)	2 (0.7)	2 (1.3)
Salmonella Sepsis	0	0	1 (0.5)	0	1 (0.4)	0
Sepsis	5 (6.3)	4 (8 9)	10 (5.1)	2 (1.9)	15 (5.4)	6 (4.0)
Septic Embolus	3 (3.8)	1 (2 2)	0	0	3 (1.1)	1 (0.7)
Septic Shock	3 (3.8)	3 (6.7)	2 (1.0)	0	5 (1.8)	3 (2.0)
Serratia Infection	0	1 (2 2)	0	0	0	1 (0.7)
Sinusitis	4 (5.1)	6 (13.3)	9 (4.5)	6 (5.7)	13 (4.7)	12 (7.9)
Sinusitis Aspergillus	0	0	0	1 (0.9)	0	1 (0.7)
Sinusitis Bacterial	0	0	2 (1.0)	0	2 (0.7)	0
Sinusitis Fungal	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Skin Bacterial Infection	0	0	1 (0.5)	0	1 (0.4)	0
Skin Infection	1 (1.3)	0	0	0	1 (0.4)	0
Staphylococcal Bacteraemia	6 (7.6)	4 (8.9)	5 (2.5)	3 (2.8)	11 (4.0)	7 (4.6)
Staphylococcal Infection	3 (3.8)	4 (8 9)	10 (5.1)	3 (2.8)	13 (4.7)	7 (4.6)
Staphylococcal Sepsis	1 (1.3)	1 (2 2)	3 (1.5)	3 (2.8)	4 (1.4)	4 (2.6)
Staphylococcal Skin Infection	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Stenotrophomonas Infection	2 (2.5)	1 (2.2)	0	0	2 (0.7)	1 (0.7)
Stenotrophomonas Sepsis	0	0	0	1 (0.9)	0	1 (0.7)
Subcutaneous Abscess	0	0	0	1 (0.9)	0	1 (0.7)
Superinfection Fungal	0	0	1 (0.5)	0	1 (0.4)	0
Syphilis	0	0	0	1 (0.9)	0	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Systemic Candida	0	0	0	1 (0.9)	0	1 (0.7)
Tooth Abscess	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Tooth Infection	1 (1.3)	0	0	0	1 (0.4)	0
Torulopsis Infection	0	1 (2.2)	0	0	0	1 (0.7)
Tracheitis	0	0	0	1 (0.9)	0	1 (0.7)
Trichosporon Infection	1 (1.3)	0	0	0	1 (0.4)	0
Tuberculosis	0	0	3 (1.5)	0	3 (1.1)	0
Upper Respiratory Tract Infection	8 (10.1)	0	7 (3.5)	4 (3.8)	15 (5.4)	4 (2.6)
Urinary Tract Infection	2 (2.5)	3 (6.7)	8 (4.0)	6 (5.7)	10 (3.6)	9 (6.0)
Urinary Tract Infection Staphylococcal	0	0	0	2 (1.9)	0	2 (1.3)
Varicella	0	0	0	1 (0.9)	0	1 (0.7)
Varicella Zoster Virus Infection	0	0	1 (0.5)	0	1 (0.4)	0
Viral Infection	3 (3.8)	0	2 (1.0)	1 (0.9)	5 (1.8)	1 (0.7)
Viral Sinusitis	1 (1.3)	0	0	0	1 (0.4)	0
Wound Infection	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Wound Infection Fungal	0	1 (2 2)	0	0	0	1 (0.7)
Injury, Poisoning And Procedural Complications	**16 (20.3)**	**14 (31 1)**	**33 (16.7)**	**20 (18.9)**	**49 (17.7)**	**34 (22.5)**
Arthropod Bite	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Barotitis Media	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Contusion	1 (1.3)	5 (11.1)	1 (0.5)	2 (1.9)	2 (0.7)	7 (4.6)
Corneal Abrasion	1 (1.3)	0	0	0	1 (0.4)	0

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Eschar	0	0	1 (0.5)	0	1 (0.4)	0
Excoriation	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Eye Burns	0	0	2 (1.0)	0	2 (0.7)	0
Eye Contusion	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Fall	3 (3.8)	5 (11.1)	4 (2.0)	4 (3.8)	7 (2.5)	9 (6.0)
Femur Fracture	0	0	0	1 (0.9)	0	1 (0.7)
Foot Fracture	0	0	1 (0.5)	0	1 (0.4)	0
Graft Complication	1 (1.3)	0	0	0	1 (0.4)	0
Haemolytic Transfusion Reaction	0	0	0	1 (0.9)	0	1 (0.7)
Head Injury	0	0	1 (0.5)	0	1 (0.4)	0
Hip Fracture	0	0	1 (0.5)	0	1 (0.4)	0
Hyphaema	0	0	0	1 (0.9)	0	1 (0.7)
Incision Site Haematoma	0	0	1 (0.5)	0	1 (0.4)	0
Incision Site Pain	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Infusion Related Reaction	2 (2.5)	0	3 (1.5)	1 (0.9)	5 (1.8)	1 (0.7)
Injury	2 (2.5)	0	1 (0.5)	0	3 (1.1)	0
Joint Injury	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Laceration	1 (1.3)	1 (2 2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Limb Injury	0	0	1 (0.5)	0	1 (0.4)	0
Muscle Strain	0	0	1 (0.5)	0	1 (0.4)	0
Overdose	0	0	1 (0.5)	0	1 (0.4)	0
Post Lumbar Puncture Syndrome	0	0	1 (0.5)	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Post Procedural Haemorrhage	2 (2.5)	1 (2 2)	2 (1.0)	0	4 (1.4)	1 (0.7)
Procedural Complication	0	0	1 (0.5)	0	1 (0.4)	0
Procedural Pain	2 (2.5)	2 (4.4)	4 (2.0)	3 (2.8)	6 (2.2)	5 (3.3)
Procedural Site Reaction	1 (1.3)	0	0	0	1 (0.4)	0
Scratch	1 (1.3)	0	0	0	1 (0.4)	0
Skin Abrasion	0	1 (2 2)	0	0	0	1 (0.7)
Spinal Compression Fracture	0	1 (2.2)	0	0	0	1 (0.7)
Spinal Cord Injury	1 (1.3)	0	0	0	1 (0.4)	0
Stress Fracture	1 (1.3)	0	0	0	1 (0.4)	0
Subarachnoid Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Sunburn	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Toxicity To Various Agents	0	1 (2 2)	3 (1.5)	2 (1.9)	3 (1.1)	3 (2.0)
Tracheal Haemorrhage	1 (1.3)	0	0	0	1 (0.4)	0
Transfusion Reaction	1 (1.3)	0	5 (2.5)	2 (1.9)	6 (2.2)	2 (1.3)
Wound	0	0	1 (0.5)	0	1 (0.4)	0
Wound Complication	0	0	0	1 (0.9)	0	1 (0.7)
Wound Decomposition	0	1 (2.2)	0	0	0	1 (0.7)
Wound Necrosis	0	1 (2 2)	0	0	0	1 (0.7)
Investigations	**46 (58.2)**	**27 (60.0)**	**86 (43.4)**	**54 (50.9)**	**132 (47.7)**	**81 (53.6)**
Activated Partial Thromboplastin Time Prolonged	0	1 (2.2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Alanine Aminotransferase	1 (1.3)	0	0	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Alanine Aminotransferase Increased	10 (12.7)	0	11 (5.6)	5 (4.7)	21 (7.6)	5 (3.3)
Ammonia Increased	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Amylase	0	0	0	1 (0.9)	0	1 (0.7)
Amylase Increased	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Anticoagulation Drug Level Above Therapeutic	0	0	1 (0.5)	0	1 (0.4)	0
Aspartate Aminotransferase Increased	3 (3.8)	0	10 (5.1)	7 (6.6)	13 (4.7)	7 (4.6)
Aspiration Pleural Cavity	0	1 (2 2)	0	0	0	1 (0.7)
Atrial Pressure Increased	0	0	0	1 (0.9)	0	1 (0.7)
Bacterial Test Positive	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Bilirubin Conjugated Increased	0	1 (2.2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Biopsy Brain	0	0	1 (0.5)	0	1 (0.4)	0
Biopsy Skin	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Biopsy Skin Abnormal	0	0	1 (0.5)	0	1 (0.4)	0
Blast Cell Count Increased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Albumin Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Alkaline Phosphatase Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Blood Alkaline Phosphatase Increased	7 (8.9)	2 (4.4)	10 (5.1)	5 (4.7)	17 (6.1)	7 (4.6)
Blood Bilirubin Increased	5 (6.3)	3 (6.7)	5 (2.5)	3 (2.8)	10 (3.6)	6 (4.0)
Blood Cholesterol Increased	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Blood Creatinine Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Blood Creatinine Increased	11 (13.9)	2 (4.4)	10 (5.1)	3 (2.8)	21 (7.6)	5 (3.3)
Blood Culture Positive	1 (1.3)	0	5 (2.5)	2 (1.9)	6 (2.2)	2 (1.3)

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All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Blood Electrolytes Decreased	1 (1.3)	0	0	0	1 (0.4)	0
Blood Fibrinogen Decreased	0	1 (2 2)	0	0	0	1 (0.7)
Blood Gases Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Blood Glucose Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Glucose Increased	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Blood Immunoglobulin G Decreased	1 (1.3)	0	0	0	1 (0.4)	0
Blood Lactate Dehydrogenase Increased	3 (3.8)	1 (2.2)	3 (1.5)	3 (2.8)	6 (2.2)	4 (2.6)
Blood Lactic Acid Increased	1 (1.3)	0	0	0	1 (0.4)	0
Blood Magnesium Decreased	0	0	1 (0.5)	0	1 (0.4)	0
Blood Phosphorus Increased	2 (2.5)	0	0	0	2 (0.7)	0
Blood Potassium Decreased	0	0	3 (1.5)	1 (0.9)	3 (1.1)	1 (0.7)
Blood Potassium Increased	1 (1.3)	0	0	0	1 (0.4)	0
Blood Pressure Decreased	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Blood Pressure Increased	3 (3.8)	0	4 (2.0)	1 (0.9)	7 (2.5)	1 (0.7)
Blood Pressure Orthostatic	1 (1.3)	1 (2.2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Blood Pressure Systolic Increased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Sodium Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Sodium Increased	1 (1.3)	0	0	0	1 (0.4)	0
Blood Triglycerides Increased	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Blood Urea Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Blood Urea Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Blood Urea Increased	4 (5.1)	3 (6.7)	2 (1.0)	1 (0.9)	6 (2.2)	4 (2.6)

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All Randomized Subjects
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	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Blood Uric Acid	0	0	0	1 (0.9)	0	1 (0.7)
Blood Uric Acid Increased	0	0	2 (1.0)	2 (1.9)	2 (0.7)	2 (1.3)
Blood Urine Present	1 (1.3)	0	0	0	1 (0.4)	0
Body Temperature	0	0	0	1 (0.9)	0	1 (0.7)
Body Temperature Increased	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Breath Sounds Abnormal	3 (3.8)	0	1 (0.5)	3 (2.8)	4 (1.4)	3 (2.0)
Carbon Dioxide Increased	0	0	2 (1.0)	0	2 (0.7)	0
Cardiac Murmur	0	0	2 (1.0)	0	2 (0.7)	0
Cardioactive Drug Level Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Cardioactive Drug Level Increased	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Chest X-Ray Abnormal	0	1 (2 2)	1 (0.5)	2 (1.9)	1 (0.4)	3 (2.0)
Clostridium Test	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Clostridium Test Positive	2 (2.5)	1 (2.2)	3 (1.5)	3 (2.8)	5 (1.8)	4 (2.6)
Computerised Tomogram Abnormal	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Csf Protein Increased	1 (1.3)	0	0	0	1 (0.4)	0
Culture Urine Positive	0	0	0	1 (0.9)	0	1 (0.7)
Cytomegalovirus Test	0	1 (2.2)	2 (1.0)	2 (1.9)	2 (0.7)	3 (2.0)
Cytomegalovirus Test Positive	1 (1.3)	1 (2.2)	1 (0.5)	1 (0.9)	2 (0.7)	2 (1.3)
Drug Level Changed	2 (2.5)	1 (2 2)	1 (0.5)	0	3 (1.1)	1 (0.7)
Drug Level Increased	3 (3.8)	2 (4.4)	1 (0.5)	2 (1.9)	4 (1.4)	4 (2.6)
Ejection Fraction Decreased	1 (1.3)	1 (2.2)	1 (0.5)	1 (0.9)	2 (0.7)	2 (1.3)
Electrocardiogram Abnormal	1 (1.3)	1 (2.2)	2 (1.0)	0	3 (1.1)	1 (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, Sex
Number (%) of Subjects

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Electrocardiogram Change	0	0	1 (0.5)	0	1 (0.4)	0
Electrocardiogram Qrs Complex Prolonged	0	0	1 (0.5)	0	1 (0.4)	0
Electrocardiogram Qt Interval Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Electrocardiogram Qt Prolonged	0	0	7 (3.5)	4 (3.8)	7 (2.5)	4 (2.6)
Electrocardiogram St Segment Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Electrocardiogram St Segment Elevation	0	1 (2 2)	0	0	0	1 (0.7)
Electrocardiogram T Wave Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Electrocardiogram T Wave Inversion	0	0	1 (0.5)	0	1 (0.4)	0
Electrocardiogram T Wave Peaked	0	1 (2.2)	0	0	0	1 (0.7)
Electroencephalogram Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Eosinophil Count Increased	1 (1.3)	0	0	0	1 (0.4)	0
Fundoscopy Abnormal	0	0	1 (0.5)	0	1 (0.4)	0
Fungal Test Positive	1 (1.3)	1 (2.2)	2 (1.0)	2 (1.9)	3 (1.1)	3 (2.0)
Gamma-Glutamyltransferase Increased	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
General Physical Condition Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Glucocorticoids Decreased	0	0	1 (0.5)	0	1 (0.4)	0
Haemoglobin Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Haemoglobin Decreased	2 (2.5)	1 (2.2)	2 (1.0)	1 (0.9)	4 (1.4)	2 (1.3)
Heart Rate Irregular	2 (2.5)	0	2 (1.0)	1 (0.9)	4 (1.4)	1 (0.7)
Hepatic Enzyme Increased	5 (6.3)	0	3 (1.5)	1 (0.9)	8 (2.9)	1 (0.7)
Hepatitis A Antibody Positive	1 (1.3)	0	0	0	1 (0.4)	0
Hepatitis C Virus Test Positive	0	0	1 (0.5)	0	1 (0.4)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Herpes Simplex Test Positive	0	0	0	1 (0.9)	0	1 (0.7)
International Normalised Ratio Decreased	0	0	0	1 (0.9)	0	1 (0.7)
International Normalised Ratio Increased	0	0	0	1 (0.9)	0	1 (0.7)
Laboratory Test Abnormal	0	0	1 (0.5)	0	1 (0.4)	0
Lipase	0	0	0	1 (0.9)	0	1 (0.7)
Lipase Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Lipase Increased	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Liver Function Test Abnormal	0	1 (2 2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Liver Function Test Increased	6 (7.6)	4 (8.9)	5 (2.5)	3 (2.8)	11 (4.0)	7 (4.6)
Medical Observation Normal	0	1 (2 2)	0	0	0	1 (0.7)
Myocardial Necrosis Marker Increased	0	0	1 (0.5)	0	1 (0.4)	0
Neutrophil Count Decreased	1 (1.3)	0	2 (1.0)	1 (0.9)	3 (1.1)	1 (0.7)
Nuclear Magnetic Resonance Imaging Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Nutritional Condition Abnormal	0	1 (2.2)	0	0	0	1 (0.7)
Occult Blood Positive	2 (2.5)	0	3 (1.5)	0	5 (1.8)	0
Oxygen Saturation Decreased	5 (6.3)	2 (4.4)	1 (0.5)	0	6 (2.2)	2 (1.3)
Pancreatic Enzymes Increased	2 (2.5)	0	0	0	2 (0.7)	0
Platelet Count Decreased	1 (1.3)	1 (2 2)	3 (1.5)	0	4 (1.4)	1 (0.7)
Platelet Count Increased	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Prostatic Specific Antigen Increased	1 (1.3)	0	0	0	1 (0.4)	0
Prothrombin Level Increased	0	0	0	1 (0.9)	0	1 (0.7)
Prothrombin Time Prolonged	0	2 (4.4)	3 (1.5)	1 (0.9)	3 (1.1)	3 (2.0)

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Prothrombin Time Shortened	1 (1.3)	2 (4.4)	0	0	1 (0.4)	2 (1.3)
Pulmonary Function Test Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Pupillary Light Reflex Tests Abnormal	0	0	1 (0.5)	0	1 (0.4)	0
Qrs Axis Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Renal Scan	0	1 (2 2)	0	0	0	1 (0.7)
Respiratory Rate Increased	0	0	1 (0.5)	0	1 (0.4)	0
Right Ventricular Systolic Pressure Increased	0	0	1 (0.5)	0	1 (0.4)	0
Serum Ferritin Increased	0	1 (2.2)	0	0	0	1 (0.7)
Spleen Palpable	0	0	1 (0.5)	0	1 (0.4)	0
Sputum Culture Positive	0	0	0	1 (0.9)	0	1 (0.7)
Transaminases Increased	0	0	2 (1.0)	0	2 (0.7)	0
Troponin Increased	0	0	0	2 (1.9)	0	2 (1.3)
Urine Output Decreased	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Viral Load Increased	0	0	1 (0.5)	0	1 (0.4)	0
Weight Decreased	5 (6.3)	2 (4.4)	11 (5.6)	8 (7.5)	16 (5.8)	10 (6.6)
Weight Increased	0	0	2 (1.0)	0	2 (0.7)	0
White Blood Cell Count Decreased	0	2 (4.4)	0	1 (0.9)	0	3 (2.0)
White Blood Cell Count Increased	1 (1.3)	1 (2.2)	2 (1.0)	4 (3.8)	3 (1.1)	5 (3.3)
White Blood Cells Urine Positive	0	1 (2.2)	0	0	0	1 (0.7)
X-Ray Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Metabolism And Nutrition Disorders	**55 (69.6)**	**26 (57 8)**	**83 (41.9)**	**43 (40.6)**	**138 (49.8)**	**69 (45.7)**

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Acidosis	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Cachexia	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Decreased Appetite	18 (22.8)	5 (11.1)	27 (13.6)	16 (15.1)	45 (16.2)	21 (13.9)
Dehydration	9 (11.4)	2 (4.4)	13 (6.6)	6 (5.7)	22 (7.9)	8 (5.3)
Diabetes Mellitus	1 (1.3)	1 (2.2)	2 (1.0)	0	3 (1.1)	1 (0.7)
Diabetes Mellitus Inadequate Control	0	0	0	1 (0.9)	0	1 (0.7)
Electrolyte Imbalance	0	2 (4.4)	1 (0.5)	3 (2.8)	1 (0.4)	5 (3.3)
Failure To Thrive	3 (3.8)	1 (2.2)	2 (1.0)	1 (0.9)	5 (1.8)	2 (1.3)
Fluid Overload	3 (3.8)	4 (8 9)	4 (2.0)	4 (3.8)	7 (2.5)	8 (5.3)
Fluid Retention	1 (1.3)	2 (4.4)	2 (1.0)	0	3 (1.1)	2 (1.3)
Hypercalcaemia	3 (3.8)	4 (8 9)	2 (1.0)	1 (0.9)	5 (1.8)	5 (3.3)
Hypercholesterolaemia	0	0	2 (1.0)	0	2 (0.7)	0
Hypercreatininaemia	1 (1.3)	0	0	0	1 (0.4)	0
Hyperglycaemia	14 (17.7)	7 (15.6)	6 (3.0)	8 (7 5)	20 (7.2)	15 (9.9)
Hyperkalaemia	9 (11.4)	4 (8.9)	7 (3.5)	8 (7.5)	16 (5.8)	12 (7.9)
Hyperlipidaemia	0	0	1 (0.5)	0	1 (0.4)	0
Hypernatraemia	3 (3.8)	1 (2 2)	1 (0.5)	0	4 (1.4)	1 (0.7)
Hyperphosphataemia	0	1 (2 2)	0	2 (1.9)	0	3 (2.0)
Hypertriglyceridaemia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Hyperuricaemia	3 (3.8)	1 (2.2)	3 (1.5)	0	6 (2.2)	1 (0.7)
Hypervolaemia	0	0	3 (1.5)	0	3 (1.1)	0
Hypoalbuminaemia	2 (2.5)	1 (2 2)	2 (1.0)	0	4 (1.4)	1 (0.7)

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Hypocalcaemia	8 (10.1)	6 (13.3)	6 (3.0)	8 (7.5)	14 (5.1)	14 (9.3)
Hypoglycaemia	1 (1.3)	0	5 (2.5)	1 (0.9)	6 (2.2)	1 (0.7)
Hypokalaemia	13 (16.5)	5 (11.1)	27 (13.6)	11 (10.4)	40 (14.4)	16 (10.6)
Hypomagnesaemia	7 (8.9)	4 (8 9)	13 (6.6)	5 (4.7)	20 (7.2)	9 (6.0)
Hyponatraemia	1 (1.3)	5 (11.1)	5 (2.5)	3 (2.8)	6 (2.2)	8 (5.3)
Hypophagia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Hypophosphataemia	0	4 (8 9)	5 (2.5)	1 (0.9)	5 (1.8)	5 (3.3)
Hypoproteinaemia	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Hypovolaemia	0	0	4 (2.0)	3 (2.8)	4 (1.4)	3 (2.0)
Iron Overload	3 (3.8)	0	0	0	3 (1.1)	0
Lactic Acidosis	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Malnutrition	1 (1.3)	2 (4.4)	6 (3.0)	2 (1.9)	7 (2.5)	4 (2.6)
Metabolic Acidosis	7 (8.9)	4 (8 9)	6 (3.0)	3 (2.8)	13 (4.7)	7 (4.6)
Metabolic Alkalosis	0	2 (4.4)	0	0	0	2 (1.3)
Metabolic Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Polydipsia	0	0	3 (1.5)	0	3 (1.1)	0
Tumour Lysis Syndrome	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Vitamin K Deficiency	1 (1.3)	0	0	0	1 (0.4)	0
Musculoskeletal And Connective Tissue Disorders	**33 (41.8)**	**22 (48 9)**	**73 (36.9)**	**45 (42.5)**	**106 (38.3)**	**67 (44.4)**
Amyotrophy	1 (1.3)	0	0	0	1 (0.4)	0
Arthralgia	8 (10.1)	4 (8 9)	14 (7.1)	5 (4.7)	22 (7.9)	9 (6.0)

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Arthritis	0	0	2 (1.0)	0	2 (0.7)	0
Back Pain	9 (11.4)	9 (20.0)	9 (4.5)	13 (12.3)	18 (6.5)	22 (14.6)
Bone Lesion	1 (1.3)	0	0	0	1 (0.4)	0
Bone Pain	2 (2.5)	2 (4.4)	6 (3.0)	2 (1.9)	8 (2.9)	4 (2.6)
Bursitis	0	0	1 (0.5)	0	1 (0.4)	0
Chest Wall Mass	0	0	1 (0.5)	0	1 (0.4)	0
Compartment Syndrome	0	1 (2.2)	0	0	0	1 (0.7)
Dactylitis	0	0	0	1 (0.9)	0	1 (0.7)
Fistula	0	0	2 (1.0)	0	2 (0.7)	0
Fistula Discharge	0	0	1 (0.5)	0	1 (0.4)	0
Flank Pain	1 (1.3)	2 (4.4)	4 (2.0)	3 (2.8)	5 (1.8)	5 (3.3)
Groin Pain	0	0	2 (1.0)	0	2 (0.7)	0
Haemarthrosis	0	1 (2 2)	0	0	0	1 (0.7)
Hypercreatinaemia	0	0	0	1 (0.9)	0	1 (0.7)
Joint Range Of Motion Decreased	1 (1.3)	0	0	0	1 (0.4)	0
Joint Stiffness	0	0	1 (0.5)	0	1 (0.4)	0
Joint Swelling	2 (2.5)	0	2 (1.0)	2 (1.9)	4 (1.4)	2 (1.3)
Mobility Decreased	2 (2.5)	0	1 (0.5)	1 (0.9)	3 (1.1)	1 (0.7)
Muscle Atrophy	3 (3.8)	0	2 (1.0)	0	5 (1.8)	0
Muscle Contracture	0	0	1 (0.5)	0	1 (0.4)	0
Muscle Rigidity	1 (1.3)	0	0	0	1 (0.4)	0
Muscle Spasms	1 (1.3)	1 (2 2)	11 (5.6)	2 (1.9)	12 (4.3)	3 (2.0)

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All Randomized Subjects
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Number (%) of Subjects

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Muscle Twitching	0	0	0	2 (1.9)	0	2 (1.3)
Muscular Weakness	8 (10.1)	2 (4.4)	9 (4.5)	5 (4.7)	17 (6.1)	7 (4.6)
Musculoskeletal Chest Pain	1 (1.3)	2 (4.4)	2 (1.0)	3 (2.8)	3 (1.1)	5 (3.3)
Musculoskeletal Discomfort	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Musculoskeletal Pain	5 (6.3)	2 (4.4)	12 (6.1)	6 (5.7)	17 (6.1)	8 (5.3)
Musculoskeletal Stiffness	3 (3.8)	0	1 (0.5)	2 (1.9)	4 (1.4)	2 (1.3)
Myalgia	3 (3.8)	0	8 (4.0)	5 (4.7)	11 (4.0)	5 (3.3)
Myopathy	4 (5.1)	1 (2 2)	0	1 (0.9)	4 (1.4)	2 (1.3)
Myositis	1 (1.3)	0	0	0	1 (0.4)	0
Neck Pain	0	2 (4.4)	4 (2.0)	5 (4.7)	4 (1.4)	7 (4.6)
Nuchal Rigidity	0	0	5 (2.5)	2 (1.9)	5 (1.8)	2 (1.3)
Osteoarthritis	0	0	1 (0.5)	0	1 (0.4)	0
Osteonecrosis	0	0	2 (1.0)	0	2 (0.7)	0
Pain In Extremity	14 (17.7)	9 (20.0)	18 (9.1)	12 (11.3)	32 (11.6)	21 (13.9)
Pain In Jaw	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Pathological Fracture	0	1 (2 2)	0	0	0	1 (0.7)
Psoriatic Arthropathy	0	0	0	1 (0.9)	0	1 (0.7)
Rhabdomyolysis	1 (1.3)	0	0	0	1 (0.4)	0
Rheumatoid Arthritis	0	0	0	1 (0.9)	0	1 (0.7)
Rotator Cuff Syndrome	1 (1.3)	0	0	0	1 (0.4)	0
Soft Tissue Mass	0	0	1 (0.5)	0	1 (0.4)	0
Spinal Osteoarthritis	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)

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All Randomized Subjects
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Number (%) of Subjects

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Synovitis	0	0	0	1 (0.9)	0	1 (0.7)
Systemic Lupus Erythematosus	0	0	1 (0.5)	0	1 (0.4)	0
Tendon Pain	0	0	1 (0.5)	0	1 (0.4)	0
Vertebral Lesion	0	1 (2 2)	0	0	0	1 (0.7)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**17 (21.5)**	**11 (24.4)**	**34 (17.2)**	**15 (14.2)**	**51 (18.4)**	**26 (17.2)**
Acute Lymphocytic Leukaemia Recurrent	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Acute Myeloid Leukaemia	6 (7.6)	4 (8.9)	14 (7.1)	7 (6.6)	20 (7.2)	11 (7.3)
Acute Myeloid Leukaemia Recurrent	1 (1.3)	1 (2.2)	8 (4.0)	1 (0.9)	9 (3.2)	2 (1.3)
Anogenital Warts	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Blast Cell Crisis	0	0	1 (0.5)	0	1 (0.4)	0
Blast Crisis In Myelogenous Leukaemia	0	0	1 (0.5)	0	1 (0.4)	0
Central Nervous System Lymphoma	0	0	0	1 (0.9)	0	1 (0.7)
Chloroma	0	0	1 (0.5)	0	1 (0.4)	0
Chronic Lymphocytic Leukaemia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Chronic Lymphocytic Leukaemia Recurrent	1 (1.3)	0	0	0	1 (0.4)	0
Chronic Myeloid Leukaemia	2 (2.5)	2 (4.4)	1 (0.5)	3 (2.8)	3 (1.1)	5 (3.3)
Fibroadenoma Of Breast	0	0	0	1 (0.9)	0	1 (0.7)
Hepatic Cancer	0	0	1 (0.5)	0	1 (0.4)	0
Hepatic Neoplasm	0	1 (2 2)	0	0	0	1 (0.7)
Kaposi's Sarcoma	0	0	3 (1.5)	0	3 (1.1)	0

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Leukaemia	0	1 (2 2)	2 (1.0)	1 (0.9)	2 (0.7)	2 (1.3)
Leukaemia Cutis	0	0	1 (0.5)	0	1 (0.4)	0
Leukaemic Retinopathy	0	0	1 (0.5)	0	1 (0.4)	0
Lipoma Of Breast	1 (1.3)	0	0	0	1 (0.4)	0
Lung Neoplasm	1 (1.3)	0	0	0	1 (0.4)	0
Lymphocytic Leukaemia	1 (1.3)	0	0	0	1 (0.4)	0
Lymphoma	0	1 (2 2)	2 (1.0)	1 (0.9)	2 (0.7)	2 (1.3)
Metastases To Bone	1 (1.3)	0	0	0	1 (0.4)	0
Metastases To Meninges	0	0	0	1 (0.9)	0	1 (0.7)
Myelodysplastic Syndrome	1 (1.3)	0	0	0	1 (0.4)	0
Neoplasm	0	0	1 (0.5)	0	1 (0.4)	0
Neoplasm Malignant	0	0	1 (0.5)	0	1 (0.4)	0
Non-Hodgkin's Lymphoma	1 (1.3)	2 (4.4)	0	0	1 (0.4)	2 (1.3)
Plasma Cell Myeloma	0	1 (2.2)	0	0	0	1 (0.7)
Respiratory Tract Neoplasm	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
T-Cell Lymphoma	0	0	1 (0.5)	0	1 (0.4)	0
Nervous System Disorders	**43 (54.4)**	**31 (68 9)**	**104 (52.5)**	**59 (55.7)**	**147 (53.1)**	**90 (59.6)**
Ageusia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Amnesia	0	1 (2 2)	2 (1.0)	1 (0.9)	2 (0.7)	2 (1.3)
Aphasia	2 (2.5)	1 (2 2)	0	0	2 (0.7)	1 (0.7)
Arachnoiditis	1 (1.3)	0	0	0	1 (0.4)	0

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Asterixis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Ataxia	0	0	3 (1.5)	1 (0.9)	3 (1.1)	1 (0.7)
Balance Disorder	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Brain Oedema	0	2 (4.4)	1 (0.5)	0	1 (0.4)	2 (1.3)
Brain Stem Syndrome	0	0	1 (0.5)	0	1 (0.4)	0
Cauda Equina Syndrome	0	1 (2 2)	0	0	0	1 (0.7)
Central Nervous System Inflammation	1 (1.3)	0	0	0	1 (0.4)	0
Central Nervous System Lesion	0	0	3 (1.5)	0	3 (1.1)	0
Cerebral Atrophy	1 (1.3)	1 (2 2)	1 (0.5)	0	2 (0.7)	1 (0.7)
Cerebral Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Cerebral Haematoma	0	0	0	1 (0.9)	0	1 (0.7)
Cerebral Haemorrhage	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Cerebral Infarction	0	2 (4.4)	2 (1.0)	0	2 (0.7)	2 (1.3)
Cerebrovascular Accident	1 (1.3)	1 (2 2)	2 (1.0)	0	3 (1.1)	1 (0.7)
Choreoathetosis	0	0	1 (0.5)	0	1 (0.4)	0
Cognitive Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Coma	1 (1.3)	6 (13.3)	1 (0.5)	0	2 (0.7)	6 (4.0)
Coordination Abnormal	1 (1.3)	0	3 (1.5)	0	4 (1.4)	0
Cranial Nerve Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Demyelination	0	0	1 (0.5)	0	1 (0.4)	0
Depressed Level Of Consciousness	2 (2.5)	1 (2.2)	2 (1.0)	0	4 (1.4)	1 (0.7)
Dizziness	12 (15.2)	6 (13.3)	18 (9.1)	12 (11.3)	30 (10.8)	18 (11.9)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Dizziness Postural	0	0	1 (0.5)	0	1 (0.4)	0
Dysarthria	2 (2.5)	0	2 (1.0)	3 (2.8)	4 (1.4)	3 (2.0)
Dysgeusia	0	1 (2.2)	1 (0.5)	1 (0.9)	1 (0.4)	2 (1.3)
Dyskinesia	0	0	0	1 (0.9)	0	1 (0.7)
Dystonia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Embolic Stroke	1 (1.3)	0	0	0	1 (0.4)	0
Encephalomalacia	0	1 (2 2)	0	0	0	1 (0.7)
Encephalopathy	2 (2.5)	0	1 (0.5)	1 (0.9)	3 (1.1)	1 (0.7)
Facial Paralysis	0	0	3 (1.5)	0	3 (1.1)	0
Facial Paresis	0	1 (2 2)	0	0	0	1 (0.7)
Haemorrhage Intracranial	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Haemorrhagic Cerebral Infarction	0	1 (2 2)	0	0	0	1 (0.7)
Head Titubation	0	1 (2 2)	0	0	0	1 (0.7)
Headache	15 (19.0)	9 (20.0)	56 (28.3)	32 (30.2)	71 (25.6)	41 (27.2)
Hemianopia	0	0	1 (0.5)	0	1 (0.4)	0
Hemianopia Homonymous	0	0	1 (0.5)	0	1 (0.4)	0
Hemiparesis	3 (3.8)	1 (2 2)	3 (1.5)	0	6 (2.2)	1 (0.7)
Hemiplegia	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Hyperreflexia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Hypoaesthesia	1 (1.3)	6 (13.3)	7 (3.5)	3 (2.8)	8 (2.9)	9 (6.0)
Hypokinesia	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Hyporeflexia	0	1 (2 2)	3 (1.5)	0	3 (1.1)	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Hypotonia	0	0	2 (1.0)	2 (1.9)	2 (0.7)	2 (1.3)
IIIrd Nerve Paralysis	0	0	0	1 (0.9)	0	1 (0.7)
Intellectual Disability	1 (1.3)	0	0	0	1 (0.4)	0
Intention Tremor	1 (1.3)	0	0	0	1 (0.4)	0
Intracranial Pressure Increased	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Intraventricular Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Ischaemic Stroke	2 (2.5)	0	0	0	2 (0.7)	0
Lethargy	7 (8.9)	5 (11.1)	4 (2.0)	3 (2.8)	11 (4.0)	8 (5.3)
Loss Of Consciousness	2 (2.5)	1 (2.2)	2 (1.0)	0	4 (1.4)	1 (0.7)
Memory Impairment	2 (2.5)	0	3 (1.5)	2 (1.9)	5 (1.8)	2 (1.3)
Mental Impairment	0	0	2 (1.0)	2 (1.9)	2 (0.7)	2 (1.3)
Metabolic Encephalopathy	0	1 (2 2)	0	0	0	1 (0.7)
Migraine	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Mononeuropathy Multiplex	0	0	0	1 (0.9)	0	1 (0.7)
Motor Dysfunction	0	0	0	1 (0.9)	0	1 (0.7)
Myoclonus	0	1 (2 2)	0	1 (0.9)	0	2 (1.3)
Nervous System Disorder	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Neurological Decompensation	0	1 (2.2)	0	0	0	1 (0.7)
Neuropathy Peripheral	1 (1.3)	0	4 (2.0)	0	5 (1.8)	0
Nystagmus	1 (1.3)	0	0	0	1 (0.4)	0
Occipital Neuralgia	0	0	0	1 (0.9)	0	1 (0.7)
Paraesthesia	3 (3.8)	3 (6.7)	9 (4.5)	4 (3.8)	12 (4.3)	7 (4.6)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Parkinsonism	1 (1.3)	0	0	0	1 (0.4)	0
Peroneal Nerve Palsy	0	1 (2 2)	0	0	0	1 (0.7)
Post Herpetic Neuralgia	0	0	1 (0.5)	0	1 (0.4)	0
Postural Tremor	0	1 (2.2)	0	0	0	1 (0.7)
Presyncope	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Psychomotor Skills Impaired	1 (1.3)	0	0	0	1 (0.4)	0
Restless Legs Syndrome	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Sciatica	0	0	2 (1.0)	0	2 (0.7)	0
Sedation	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Seizure	5 (6.3)	2 (4.4)	8 (4.0)	2 (1.9)	13 (4.7)	4 (2.6)
Sensory Loss	1 (1.3)	0	2 (1.0)	3 (2.8)	3 (1.1)	3 (2.0)
Sinus Headache	0	2 (4.4)	0	0	0	2 (1.3)
Slow Response To Stimuli	1 (1.3)	0	0	0	1 (0.4)	0
Somnolence	5 (6.3)	4 (8.9)	8 (4.0)	4 (3.8)	13 (4.7)	8 (5.3)
Speech Disorder	2 (2.5)	0	3 (1.5)	2 (1.9)	5 (1.8)	2 (1.3)
Syncope	0	0	4 (2.0)	0	4 (1.4)	0
Tension Headache	0	0	4 (2.0)	0	4 (1.4)	0
Toxic Encephalopathy	0	0	0	1 (0.9)	0	1 (0.7)
Tremor	7 (8.9)	4 (8 9)	11 (5.6)	9 (8.5)	18 (6.5)	13 (8.6)
Unresponsive To Stimuli	4 (5.1)	6 (13.3)	1 (0.5)	4 (3.8)	5 (1.8)	10 (6.6)
Visual Field Defect	0	0	1 (0.5)	0	1 (0.4)	0
Vocal Cord Paralysis	0	0	1 (0.5)	0	1 (0.4)	0

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Product Issues	**0**	**0**	**1 (0.5)**	**1 (0 9)**	**1 (0.4)**	**1 (0.7)**
Device Occlusion	0	0	0	1 (0.9)	0	1 (0.7)
Thrombosis In Device	0	0	1 (0.5)	0	1 (0.4)	0
Psychiatric Disorders	**42 (53.2)**	**24 (53 3)**	**58 (29.3)**	**36 (34.0)**	**100 (36.1)**	**60 (39.7)**
Adjustment Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Aggression	0	0	1 (0.5)	0	1 (0.4)	0
Agitation	5 (6.3)	2 (4.4)	4 (2.0)	6 (5.7)	9 (3.2)	8 (5.3)
Anxiety	10 (12.7)	7 (15.6)	17 (8.6)	15 (14.2)	27 (9.7)	22 (14.6)
Belligerence	1 (1.3)	0	0	0	1 (0.4)	0
Blunted Affect	1 (1.3)	0	0	0	1 (0.4)	0
Confusional State	11 (13.9)	7 (15.6)	10 (5.1)	7 (6.6)	21 (7.6)	14 (9.3)
Delirium	1 (1.3)	0	2 (1.0)	1 (0.9)	3 (1.1)	1 (0.7)
Delusion	0	0	0	1 (0.9)	0	1 (0.7)
Depressed Mood	0	0	2 (1.0)	0	2 (0.7)	0
Depression	13 (16.5)	10 (22 2)	17 (8.6)	10 (9.4)	30 (10.8)	20 (13.2)
Disorientation	2 (2.5)	0	1 (0.5)	2 (1.9)	3 (1.1)	2 (1.3)
Eating Disorder	0	0	0	1 (0.9)	0	1 (0.7)
Echolalia	0	0	0	1 (0.9)	0	1 (0.7)
Flat Affect	2 (2.5)	0	1 (0.5)	0	3 (1.1)	0
Hallucination	1 (1.3)	2 (4.4)	1 (0.5)	1 (0.9)	2 (0.7)	3 (2.0)

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Hallucination, Auditory	0	1 (2 2)	0	0	0	1 (0.7)
Hallucination, Visual	0	2 (4.4)	1 (0.5)	0	1 (0.4)	2 (1.3)
Insomnia	13 (16.5)	9 (20.0)	22 (11.1)	9 (8 5)	35 (12.6)	18 (11.9)
Irritability	0	1 (2.2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Libido Decreased	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Mental Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Mental Status Changes	9 (11.4)	6 (13.3)	13 (6.6)	4 (3.8)	22 (7.9)	10 (6.6)
Mood Altered	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Mood Swings	0	1 (2.2)	0	1 (0.9)	0	2 (1.3)
Nervousness	0	0	1 (0.5)	0	1 (0.4)	0
Nightmare	0	0	2 (1.0)	0	2 (0.7)	0
Organic Brain Syndrome	0	0	0	1 (0.9)	0	1 (0.7)
Paranoia	1 (1.3)	0	0	0	1 (0.4)	0
Perseveration	0	0	0	1 (0.9)	0	1 (0.7)
Posturing	0	1 (2 2)	0	0	0	1 (0.7)
Psychomotor Retardation	0	0	0	1 (0.9)	0	1 (0.7)
Psychotic Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Restlessness	2 (2.5)	4 (8 9)	1 (0.5)	1 (0.9)	3 (1.1)	5 (3.3)
Sleep Disorder	0	0	2 (1.0)	0	2 (0.7)	0
Staring	1 (1.3)	0	0	0	1 (0.4)	0
Substance-Induced Psychotic Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Tearfulness	1 (1.3)	0	0	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Renal And Urinary Disorders	**41 (51.9)**	**22 (48 9)**	**38 (19.2)**	**22 (20.8)**	**79 (28.5)**	**44 (29.1)**
Acute Kidney Injury	4 (5.1)	5 (11.1)	3 (1.5)	2 (1.9)	7 (2.5)	7 (4.6)
Anuria	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Azotaemia	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Bladder Pain	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Bladder Spasm	0	1 (2.2)	1 (0.5)	2 (1.9)	1 (0.4)	3 (2.0)
Choluria	0	0	1 (0.5)	0	1 (0.4)	0
Chronic Kidney Disease	2 (2.5)	0	1 (0.5)	0	3 (1.1)	0
Cystitis Haemorrhagic	2 (2.5)	1 (2.2)	1 (0.5)	2 (1.9)	3 (1.1)	3 (2.0)
Dysuria	8 (10.1)	2 (4.4)	4 (2.0)	1 (0.9)	12 (4.3)	3 (2.0)
End Stage Renal Disease	1 (1.3)	0	0	0	1 (0.4)	0
Haematuria	2 (2.5)	2 (4.4)	5 (2.5)	1 (0.9)	7 (2.5)	3 (2.0)
Hydronephrosis	1 (1.3)	0	0	0	1 (0.4)	0
Incontinence	3 (3.8)	0	1 (0.5)	0	4 (1.4)	0
Micturition Urgency	2 (2.5)	1 (2 2)	0	0	2 (0.7)	1 (0.7)
Nephritis	0	1 (2 2)	0	0	0	1 (0.7)
Nephrolithiasis	1 (1.3)	1 (2 2)	0	0	1 (0.4)	1 (0.7)
Nephropathy Toxic	2 (2.5)	0	2 (1.0)	1 (0.9)	4 (1.4)	1 (0.7)
Nocturia	2 (2.5)	0	3 (1.5)	0	5 (1.8)	0
Oliguria	1 (1.3)	2 (4.4)	0	0	1 (0.4)	2 (1.3)
Pollakiuria	4 (5.1)	1 (2 2)	3 (1.5)	0	7 (2.5)	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Polyuria	0	0	4 (2.0)	0	4 (1.4)	0
Renal Colic	1 (1.3)	0	0	0	1 (0.4)	0
Renal Cyst	1 (1.3)	0	0	0	1 (0.4)	0
Renal Disorder	0	1 (2 2)	1 (0.5)	3 (2.8)	1 (0.4)	4 (2.6)
Renal Failure	21 (26.6)	13 (28 9)	12 (6.1)	9 (8 5)	33 (11.9)	22 (14.6)
Renal Impairment	4 (5.1)	1 (2 2)	1 (0.5)	2 (1.9)	5 (1.8)	3 (2.0)
Renal Mass	0	1 (2 2)	0	0	0	1 (0.7)
Renal Tubular Acidosis	0	0	0	2 (1.9)	0	2 (1.3)
Renal Tubular Necrosis	0	0	0	1 (0.9)	0	1 (0.7)
Urinary Hesitation	0	0	3 (1.5)	0	3 (1.1)	0
Urinary Incontinence	1 (1.3)	2 (4.4)	4 (2.0)	1 (0.9)	5 (1.8)	3 (2.0)
Urinary Retention	0	1 (2 2)	0	2 (1.9)	0	3 (2.0)
Urine Flow Decreased	1 (1.3)	0	0	0	1 (0.4)	0
Reproductive System And Breast Disorders	**1 (1.3)**	**10 (22 2)**	**9 (4.5)**	**14 (13.2)**	**10 (3.6)**	**24 (15.9)**
Amenorrhoea	0	0	0	1 (0.9)	0	1 (0.7)
Benign Prostatic Hyperplasia	0	0	1 (0.5)	0	1 (0.4)	0
Breast Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Breast Swelling	0	0	1 (0.5)	0	1 (0.4)	0
Breast Tenderness	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Dysmenorrhoea	0	0	0	1 (0.9)	0	1 (0.7)
Erectile Dysfunction	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Hypomenorrhoea	0	0	0	1 (0.9)	0	1 (0.7)
Menstruation Delayed	0	0	0	1 (0.9)	0	1 (0.7)
Nipple Exudate Bloody	0	1 (2.2)	0	0	0	1 (0.7)
Ovarian Cyst	0	0	0	1 (0.9)	0	1 (0.7)
Pelvic Fluid Collection	0	0	1 (0.5)	0	1 (0.4)	0
Premature Menopause	0	1 (2 2)	0	0	0	1 (0.7)
Prostatitis	0	0	1 (0.5)	0	1 (0.4)	0
Pruritus Genital	0	1 (2.2)	0	0	0	1 (0.7)
Scrotal Mass	0	0	1 (0.5)	0	1 (0.4)	0
Scrotal Oedema	0	0	1 (0.5)	0	1 (0.4)	0
Scrotal Pain	0	0	1 (0.5)	0	1 (0.4)	0
Scrotal Ulcer	0	0	1 (0.5)	0	1 (0.4)	0
Testicular Pain	0	0	1 (0.5)	0	1 (0.4)	0
Uterine Haemorrhage	0	1 (2.2)	0	0	0	1 (0.7)
Vaginal Discharge	0	0	0	1 (0.9)	0	1 (0.7)
Vaginal Haemorrhage	0	5 (11.1)	0	6 (5.7)	0	11 (7.3)
Vulvovaginal Pain	0	0	0	1 (0.9)	0	1 (0.7)
Vulvovaginal Pruritus	0	1 (2 2)	0	0	0	1 (0.7)
Respiratory, Thoracic And Mediastinal Disorders	**57 (72.2)**	**36 (80.0)**	**106 (53.5)**	**58 (54.7)**	**163 (58.8)**	**94 (62.3)**
Acute Respiratory Distress Syndrome	3 (3.8)	3 (6.7)	1 (0.5)	0	4 (1.4)	3 (2.0)
Acute Respiratory Failure	1 (1.3)	0	0	2 (1.9)	1 (0.4)	2 (1.3)

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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, Sex
Number (%) of Subjects

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Allergic Sinusitis	1 (1.3)	0	0	0	1 (0.4)	0
Apnoea	0	1 (2 2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Asthma	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Atelectasis	4 (5.1)	0	1 (0.5)	1 (0.9)	5 (1.8)	1 (0.7)
Bronchial Obstruction	0	0	0	1 (0.9)	0	1 (0.7)
Bronchial Wall Thickening	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Bronchiectasis	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Bronchospasm	3 (3.8)	0	2 (1.0)	0	5 (1.8)	0
Cheyne-Stokes Respiration	1 (1.3)	0	0	0	1 (0.4)	0
Chronic Obstructive Pulmonary Disease	0	0	2 (1.0)	4 (3.8)	2 (0.7)	4 (2.6)
Cough	20 (25.3)	7 (15.6)	41 (20.7)	17 (16.0)	61 (22.0)	24 (15.9)
Dysphonia	1 (1.3)	0	2 (1.0)	2 (1.9)	3 (1.1)	2 (1.3)
Dyspnoea	22 (27.8)	11 (24.4)	38 (19.2)	28 (26.4)	60 (21.7)	39 (25.8)
Dyspnoea Exertional	4 (5.1)	1 (2.2)	3 (1.5)	1 (0.9)	7 (2.5)	2 (1.3)
Emphysema	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Epistaxis	13 (16.5)	11 (24.4)	18 (9.1)	6 (5.7)	31 (11.2)	17 (11.3)
Haemoptysis	13 (16.5)	8 (17.8)	12 (6.1)	6 (5.7)	25 (9.0)	14 (9.3)
Haemothorax	0	3 (6.7)	1 (0.5)	0	1 (0.4)	3 (2.0)
Hiccups	2 (2.5)	0	3 (1.5)	0	5 (1.8)	0
Hypercapnia	1 (1.3)	0	0	0	1 (0.4)	0
Hypopnoea	0	0	0	1 (0.9)	0	1 (0.7)
Hypoxia	7 (8.9)	4 (8 9)	6 (3.0)	4 (3.8)	13 (4.7)	8 (5.3)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Interstitial Lung Disease	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Lower Respiratory Tract Congestion	0	0	0	1 (0.9)	0	1 (0.7)
Lung Consolidation	0	0	1 (0.5)	0	1 (0.4)	0
Lung Disorder	0	2 (4.4)	1 (0.5)	1 (0.9)	1 (0.4)	3 (2.0)
Lung Infiltration	6 (7.6)	3 (6.7)	9 (4.5)	3 (2.8)	15 (5.4)	6 (4.0)
Mediastinal Haematoma	0	1 (2 2)	0	0	0	1 (0.7)
Nasal Congestion	6 (7.6)	1 (2.2)	7 (3.5)	2 (1.9)	13 (4.7)	3 (2.0)
Nasal Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Nasal Dryness	1 (1.3)	0	0	4 (3.8)	1 (0.4)	4 (2.6)
Nasal Obstruction	0	0	1 (0.5)	0	1 (0.4)	0
Nasal Oedema	0	0	1 (0.5)	0	1 (0.4)	0
Nasal Septum Perforation	0	0	1 (0.5)	0	1 (0.4)	0
Nasal Ulcer	0	0	1 (0.5)	0	1 (0.4)	0
Obliterative Bronchiolitis	0	1 (2 2)	0	0	0	1 (0.7)
Obstructive Airways Disorder	0	1 (2 2)	0	0	0	1 (0.7)
Organising Pneumonia	3 (3.8)	0	0	0	3 (1.1)	0
Oropharyngeal Pain	6 (7.6)	4 (8 9)	12 (6.1)	10 (9.4)	18 (6.5)	14 (9.3)
Oropharyngeal Plaque	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Orthopnoea	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Painful Respiration	0	1 (2 2)	0	0	0	1 (0.7)
Paranasal Sinus Hypersecretion	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Pharyngeal Disorder	0	1 (2 2)	0	0	0	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Pharyngeal Erythema	0	0	1 (0.5)	0	1 (0.4)	0
Pharyngeal Ulceration	0	1 (2 2)	0	0	0	1 (0.7)
Pleural Effusion	8 (10.1)	9 (20.0)	12 (6.1)	8 (7 5)	20 (7.2)	17 (11.3)
Pleural Fibrosis	1 (1.3)	0	0	0	1 (0.4)	0
Pleuritic Pain	5 (6.3)	2 (4.4)	4 (2.0)	5 (4.7)	9 (3.2)	7 (4.6)
Pneumomediastinum	1 (1.3)	0	0	0	1 (0.4)	0
Pneumonia Aspiration	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Pneumonitis	0	1 (2.2)	0	0	0	1 (0.7)
Pneumothorax	3 (3.8)	0	2 (1.0)	1 (0.9)	5 (1.8)	1 (0.7)
Productive Cough	4 (5.1)	1 (2 2)	7 (3.5)	2 (1.9)	11 (4.0)	3 (2.0)
Pulmonary Alveolar Haemorrhage	1 (1.3)	1 (2 2)	0	1 (0.9)	1 (0.4)	2 (1.3)
Pulmonary Congestion	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Pulmonary Fibrosis	0	2 (4.4)	0	0	0	2 (1.3)
Pulmonary Haemorrhage	2 (2.5)	2 (4.4)	2 (1.0)	1 (0.9)	4 (1.4)	3 (2.0)
Pulmonary Hypertension	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Pulmonary Infarction	0	0	0	1 (0.9)	0	1 (0.7)
Pulmonary Mass	1 (1.3)	1 (2 2)	0	0	1 (0.4)	1 (0.7)
Pulmonary Oedema	2 (2.5)	3 (6.7)	6 (3.0)	4 (3.8)	8 (2.9)	7 (4.6)
Rales	4 (5.1)	1 (2 2)	6 (3.0)	2 (1.9)	10 (3.6)	3 (2.0)
Respiratory Acidosis	2 (2.5)	0	1 (0.5)	1 (0.9)	3 (1.1)	1 (0.7)
Respiratory Alkalosis	0	1 (2 2)	0	2 (1.9)	0	3 (2.0)
Respiratory Arrest	1 (1.3)	0	0	2 (1.9)	1 (0.4)	2 (1.3)

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All Randomized Subjects
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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Respiratory Disorder	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Respiratory Distress	6 (7.6)	3 (6.7)	5 (2.5)	7 (6.6)	11 (4.0)	10 (6.6)
Respiratory Failure	12 (15.2)	11 (24.4)	13 (6.6)	8 (7 5)	25 (9.0)	19 (12.6)
Respiratory Tract Congestion	2 (2.5)	0	3 (1.5)	1 (0.9)	5 (1.8)	1 (0.7)
Rhinitis Allergic	1 (1.3)	0	4 (2.0)	2 (1.9)	5 (1.8)	2 (1.3)
Rhinorrhoea	8 (10.1)	2 (4.4)	4 (2.0)	5 (4.7)	12 (4.3)	7 (4.6)
Rhonchi	1 (1.3)	0	3 (1.5)	2 (1.9)	4 (1.4)	2 (1.3)
Sinus Congestion	5 (6.3)	2 (4.4)	3 (1.5)	2 (1.9)	8 (2.9)	4 (2.6)
Sinus Pain	0	0	1 (0.5)	0	1 (0.4)	0
Sneezing	1 (1.3)	0	0	0	1 (0.4)	0
Sputum Increased	0	0	2 (1.0)	0	2 (0.7)	0
Tachypnoea	4 (5.1)	2 (4.4)	7 (3.5)	5 (4.7)	11 (4.0)	7 (4.6)
Throat Irritation	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Throat Tightness	0	1 (2 2)	0	0	0	1 (0.7)
Upper-Airway Cough Syndrome	3 (3.8)	1 (2 2)	0	2 (1.9)	3 (1.1)	3 (2.0)
Vocal Cord Disorder	0	0	1 (0.5)	0	1 (0.4)	0
Wheezing	6 (7.6)	0	10 (5.1)	3 (2.8)	16 (5.8)	3 (2.0)
Skin And Subcutaneous Tissue Disorders	**34 (43.0)**	**25 (55.6)**	**80 (40.4)**	**45 (42.5)**	**114 (41.2)**	**70 (46.4)**
Acne	0	0	1 (0.5)	0	1 (0.4)	0
Alopecia	0	1 (2 2)	7 (3.5)	7 (6.6)	7 (2.5)	8 (5.3)
Blister	2 (2.5)	0	1 (0.5)	1 (0.9)	3 (1.1)	1 (0.7)

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	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Blood Blister	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Cold Sweat	0	0	1 (0.5)	0	1 (0.4)	0
Cutaneous Lupus Erythematosus	0	0	1 (0.5)	0	1 (0.4)	0
Decubitus Ulcer	3 (3.8)	0	2 (1.0)	4 (3.8)	5 (1.8)	4 (2.6)
Dermal Cyst	0	0	1 (0.5)	0	1 (0.4)	0
Dermatitis Allergic	1 (1.3)	0	3 (1.5)	0	4 (1.4)	0
Dermatitis Atopic	1 (1.3)	0	0	0	1 (0.4)	0
Dermatosis	0	0	1 (0.5)	0	1 (0.4)	0
Drug Eruption	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Dry Skin	2 (2.5)	2 (4.4)	7 (3.5)	1 (0.9)	9 (3.2)	3 (2.0)
Ecchymosis	4 (5.1)	3 (6.7)	4 (2.0)	2 (1.9)	8 (2.9)	5 (3.3)
Erythema	4 (5.1)	4 (8 9)	3 (1.5)	6 (5.7)	7 (2.5)	10 (6.6)
Hyperhidrosis	0	2 (4.4)	3 (1.5)	5 (4.7)	3 (1.1)	7 (4.6)
Ingrowing Nail	1 (1.3)	0	4 (2.0)	0	5 (1.8)	0
Lipodystrophy Acquired	0	0	2 (1.0)	0	2 (0.7)	0
Livedo Reticularis	0	0	2 (1.0)	0	2 (0.7)	0
Macule	0	0	1 (0.5)	0	1 (0.4)	0
Miliaria	0	0	1 (0.5)	0	1 (0.4)	0
Neutrophilic Dermatosis	0	0	0	1 (0.9)	0	1 (0.7)
Night Sweats	1 (1.3)	2 (4.4)	9 (4.5)	1 (0.9)	10 (3.6)	3 (2.0)
Onychoclasis	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Palmar Erythema	2 (2.5)	0	0	0	2 (0.7)	0

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Petechiae	4 (5.1)	2 (4.4)	4 (2.0)	4 (3.8)	8 (2.9)	6 (4.0)
Photosensitivity Reaction	1 (1.3)	0	0	0	1 (0.4)	0
Pigmentation Disorder	1 (1.3)	0	0	0	1 (0.4)	0
Prurigo	0	0	0	1 (0.9)	0	1 (0.7)
Pruritus	7 (8.9)	8 (17.8)	8 (4.0)	6 (5.7)	15 (5.4)	14 (9.3)
Pruritus Allergic	0	0	1 (0.5)	0	1 (0.4)	0
Pruritus Generalised	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Psoriasis	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Purpura	0	0	1 (0.5)	0	1 (0.4)	0
Rash	12 (15.2)	5 (11.1)	18 (9.1)	11 (10.4)	30 (10.8)	16 (10.6)
Rash Erythematous	3 (3.8)	0	2 (1.0)	1 (0.9)	5 (1.8)	1 (0.7)
Rash Generalised	1 (1.3)	1 (2.2)	3 (1.5)	3 (2.8)	4 (1.4)	4 (2.6)
Rash Macular	1 (1.3)	2 (4.4)	0	2 (1.9)	1 (0.4)	4 (2.6)
Rash Maculo-Papular	0	2 (4.4)	3 (1.5)	3 (2.8)	3 (1.1)	5 (3.3)
Rash Papular	0	0	2 (1.0)	0	2 (0.7)	0
Rash Pruritic	0	0	5 (2.5)	3 (2.8)	5 (1.8)	3 (2.0)
Rash Vesicular	0	1 (2 2)	1 (0.5)	1 (0.9)	1 (0.4)	2 (1.3)
Scab	0	0	1 (0.5)	0	1 (0.4)	0
Skin Burning Sensation	1 (1.3)	0	0	0	1 (0.4)	0
Skin Discolouration	1 (1.3)	0	0	0	1 (0.4)	0
Skin Disorder	2 (2.5)	1 (2 2)	1 (0.5)	0	3 (1.1)	1 (0.7)
Skin Exfoliation	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Skin Haemorrhage	0	0	2 (1.0)	0	2 (0.7)	0
Skin Hyperpigmentation	0	1 (2 2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Skin Irritation	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Skin Lesion	5 (6.3)	3 (6.7)	9 (4.5)	2 (1.9)	14 (5.1)	5 (3.3)
Skin Mass	3 (3.8)	2 (4.4)	2 (1.0)	1 (0.9)	5 (1.8)	3 (2.0)
Skin Ulcer	0	1 (2 2)	1 (0.5)	2 (1.9)	1 (0.4)	3 (2.0)
Skin Ulcer Haemorrhage	0	1 (2 2)	0	0	0	1 (0.7)
Stevens-Johnson Syndrome	0	0	2 (1.0)	0	2 (0.7)	0
Subcutaneous Emphysema	1 (1.3)	1 (2.2)	0	0	1 (0.4)	1 (0.7)
Swelling Face	2 (2.5)	1 (2 2)	2 (1.0)	1 (0.9)	4 (1.4)	2 (1.3)
Urticaria	0	2 (4.4)	5 (2.5)	2 (1.9)	5 (1.8)	4 (2.6)
Urticaria Papular	0	0	3 (1.5)	1 (0.9)	3 (1.1)	1 (0.7)
Social Circumstances	**0**	**0**	**1 (0.5)**	**0**	**1 (0.4)**	**0**
Treatment Noncompliance	0	0	1 (0.5)	0	1 (0.4)	0
Surgical And Medical Procedures	**10 (12.7)**	**9 (20.0)**	**27 (13.6)**	**14 (13.2)**	**37 (13.4)**	**23 (15.2)**
Abdominal Cavity Drainage	0	1 (2 2)	0	0	0	1 (0.7)
Autologous Bone Marrow Transplantation Therapy	0	0	0	1 (0.9)	0	1 (0.7)
Bone Marrow Transplant	0	0	0	1 (0.9)	0	1 (0.7)
Cataract Operation	1 (1.3)	1 (2.2)	2 (1.0)	1 (0.9)	3 (1.1)	2 (1.3)
Catheter Removal	0	0	1 (0.5)	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Central Venous Catheter Removal	0	0	1 (0.5)	0	1 (0.4)	0
Chemotherapy	0	0	4 (2.0)	1 (0.9)	4 (1.4)	1 (0.7)
Choledocholithotomy	0	0	1 (0.5)	0	1 (0.4)	0
Corneal Transplant	0	0	0	1 (0.9)	0	1 (0.7)
Debridement	0	0	2 (1.0)	2 (1.9)	2 (0.7)	2 (1.3)
Endotracheal Intubation	0	0	2 (1.0)	0	2 (0.7)	0
Exploratory Operation	0	0	1 (0.5)	0	1 (0.4)	0
Eye Laser Surgery	0	0	0	1 (0.9)	0	1 (0.7)
Eye Operation	0	0	0	1 (0.9)	0	1 (0.7)
Gastrostomy	0	0	1 (0.5)	0	1 (0.4)	0
Haemofiltration	0	0	1 (0.5)	0	1 (0.4)	0
Laparotomy	0	1 (2 2)	0	0	0	1 (0.7)
Lung Lobectomy	2 (2.5)	0	0	0	2 (0.7)	0
Lung Operation	0	0	0	1 (0.9)	0	1 (0.7)
Lung Transplant	0	0	0	1 (0.9)	0	1 (0.7)
Maxillofacial Operation	0	0	0	1 (0.9)	0	1 (0.7)
Medical Device Implantation	0	1 (2 2)	0	0	0	1 (0.7)
Metabolic Abnormality Management	0	1 (2 2)	0	0	0	1 (0.7)
Nail Operation	0	0	2 (1.0)	0	2 (0.7)	0
Omentectomy	0	0	1 (0.5)	0	1 (0.4)	0
Orthopaedic Procedure	0	0	1 (0.5)	0	1 (0.4)	0
Photopheresis	0	1 (2 2)	0	0	0	1 (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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Plastic Surgery To The Face	1 (1.3)	0	0	0	1 (0.4)	0
Pneumonectomy	0	1 (2.2)	0	0	0	1 (0.7)
Polypectomy	0	0	1 (0.5)	0	1 (0.4)	0
Pulmonary Resection	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Sinus Operation	3 (3.8)	1 (2.2)	6 (3.0)	1 (0.9)	9 (3.2)	2 (1.3)
Skin Graft	1 (1.3)	0	0	0	1 (0.4)	0
Splenectomy	0	0	0	1 (0.9)	0	1 (0.7)
Stem Cell Transplant	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Surgery	0	0	1 (0.5)	0	1 (0.4)	0
Therapeutic Procedure	0	0	2 (1.0)	0	2 (0.7)	0
Thoracotomy	1 (1.3)	0	0	0	1 (0.4)	0
Tooth Extraction	1 (1.3)	0	1 (0.5)	2 (1.9)	2 (0.7)	2 (1.3)
Transfusion	0	1 (2 2)	0	0	0	1 (0.7)
Transplant	1 (1.3)	0	0	0	1 (0.4)	0
Wisdom Teeth Removal	0	0	1 (0.5)	0	1 (0.4)	0
Wound Drainage	0	0	0	1 (0.9)	0	1 (0.7)
Vascular Disorders	**36 (45.6)**	**24 (53 3)**	**58 (29.3)**	**28 (26.4)**	**94 (33.9)**	**52 (34.4)**
Aneurysm	0	0	1 (0.5)	0	1 (0.4)	0
Angiopathy	0	1 (2 2)	0	0	0	1 (0.7)
Aortic Aneurysm	0	0	0	2 (1.9)	0	2 (1.3)
Arterial Insufficiency	1 (1.3)	0	0	0	1 (0.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Arteriosclerosis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Circulatory Collapse	0	1 (2 2)	0	0	0	1 (0.7)
Deep Vein Thrombosis	3 (3.8)	1 (2.2)	1 (0.5)	1 (0.9)	4 (1.4)	2 (1.3)
Flushing	4 (5.1)	1 (2 2)	2 (1.0)	1 (0.9)	6 (2.2)	2 (1.3)
Haematoma	2 (2.5)	2 (4.4)	4 (2.0)	3 (2.8)	6 (2.2)	5 (3.3)
Haemodynamic Instability	0	1 (2 2)	0	0	0	1 (0.7)
Haemorrhage	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Hot Flush	0	0	1 (0.5)	0	1 (0.4)	0
Hypertension	15 (19.0)	9 (20.0)	22 (11.1)	9 (8 5)	37 (13.4)	18 (11.9)
Hypoperfusion	0	1 (2.2)	0	0	0	1 (0.7)
Hypotension	17 (21.5)	12 (26.7)	21 (10.6)	13 (12.3)	38 (13.7)	25 (16.6)
Hypovolaemic Shock	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Infarction	0	0	0	1 (0.9)	0	1 (0.7)
Intermittent Claudication	0	0	1 (0.5)	0	1 (0.4)	0
Ischaemia	2 (2.5)	0	0	2 (1.9)	2 (0.7)	2 (1.3)
Orthostatic Hypertension	0	1 (2.2)	0	0	0	1 (0.7)
Orthostatic Hypotension	2 (2.5)	2 (4.4)	3 (1.5)	0	5 (1.8)	2 (1.3)
Pallor	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Peripheral Artery Thrombosis	0	0	1 (0.5)	0	1 (0.4)	0
Peripheral Ischaemia	1 (1.3)	0	0	0	1 (0.4)	0
Peripheral Venous Disease	0	0	1 (0.5)	0	1 (0.4)	0
Phlebitis	0	1 (2 2)	2 (1.0)	2 (1.9)	2 (0.7)	3 (2.0)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Poor Peripheral Circulation	0	0	0	1 (0.9)	0	1 (0.7)
Raynaud's Phenomenon	0	0	0	1 (0.9)	0	1 (0.7)
Shock Haemorrhagic	0	1 (2 2)	0	0	0	1 (0.7)
Thrombophlebitis	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Thrombophlebitis Superficial	0	0	1 (0.5)	0	1 (0.4)	0
Thrombosis	0	0	1 (0.5)	0	1 (0.4)	0
Vasodilatation	1 (1.3)	0	0	0	1 (0.4)	0
Venous Thrombosis	0	1 (2.2)	0	0	0	1 (0.7)

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

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付録 2.7.4-169　　性別ごとの副作用の発現例数（%）（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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Subjects Reporting Any Adverse Event	**22 (27.8)**	**15 (33 3)**	**82 (41.4)**	**45 (42.5)**	**104 (37.5)**	**60 (39.7)**
Blood And Lymphatic System Disorders	**0**	**0**	**6 (3.0)**	**2 (1 9)**	**6 (2.2)**	**2 (1.3)**
Anaemia	0	0	3 (1.5)	1 (0.9)	3 (1.1)	1 (0.7)
Eosinophilia	0	0	1 (0.5)	0	1 (0.4)	0
Pancytopenia	0	0	0	1 (0.9)	0	1 (0.7)
Thrombocytopenia	0	0	2 (1.0)	0	2 (0.7)	0
Cardiac Disorders	**1 (1.3)**	**3 (6.7)**	**8 (4.0)**	**2 (1.9)**	**9 (3.2)**	**5 (3.3)**
Aortic Valve Sclerosis	0	0	0	1 (0.9)	0	1 (0.7)
Arteriosclerosis Coronary Artery	0	0	0	1 (0.9)	0	1 (0.7)
Atrial Fibrillation	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Atrial Flutter	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Bundle Branch Block	0	0	1 (0.5)	0	1 (0.4)	0
Cardio-Respiratory Arrest	0	1 (2 2)	1 (0.5)	0	1 (0.4)	1 (0.7)
Extrasystoles	0	0	1 (0.5)	0	1 (0.4)	0
Left Ventricular Hypertrophy	0	0	1 (0.5)	0	1 (0.4)	0
Mitral Valve Stenosis	0	0	0	1 (0.9)	0	1 (0.7)
Myocardial Infarction	0	0	1 (0.5)	0	1 (0.4)	0
Supraventricular Tachycardia	0	1 (2 2)	2 (1.0)	0	2 (0.7)	1 (0.7)
Tachycardia	0	0	0	1 (0.9)	0	1 (0.7)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Ventricular Extrasystoles	0	0	2 (1.0)	0	2 (0.7)	0
Ventricular Hypertrophy	0	0	1 (0.5)	0	1 (0.4)	0
Ventricular Tachycardia	0	1 (2 2)	0	0	0	1 (0.7)
Ear And Labyrinth Disorders	**0**	**1 (2.2)**	**0**	**1 (0 9)**	**0**	**2 (1.3)**
Ear Pain	0	0	0	1 (0.9)	0	1 (0.7)
Hypoacusis	0	1 (2 2)	0	0	0	1 (0.7)
Tinnitus	0	1 (2 2)	0	0	0	1 (0.7)
Endocrine Disorders	**0**	**0**	**1 (0.5)**	**0**	**1 (0.4)**	**0**
Adrenal Insufficiency	0	0	1 (0.5)	0	1 (0.4)	0
Adrenocortical Insufficiency Acute	0	0	1 (0.5)	0	1 (0.4)	0
Hypogonadism	0	0	1 (0.5)	0	1 (0.4)	0
Eye Disorders	**1 (1.3)**	**0**	**5 (2.5)**	**1 (0 9)**	**6 (2.2)**	**1 (0.7)**
Conjunctival Hyperaemia	0	0	1 (0.5)	0	1 (0.4)	0
Erythema Of Eyelid	0	0	1 (0.5)	0	1 (0.4)	0
Eye Irritation	0	0	1 (0.5)	0	1 (0.4)	0
Eye Pain	0	0	1 (0.5)	0	1 (0.4)	0
Vision Blurred	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Gastrointestinal Disorders	**11 (13.9)**	**8 (17.8)**	**37 (18.7)**	**25 (23.6)**	**48 (17.3)**	**33 (21.9)**

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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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Abdominal Discomfort	1 (1.3)	0	0	0	1 (0.4)	0
Abdominal Distension	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Abdominal Pain	2 (2.5)	0	1 (0.5)	4 (3.8)	3 (1.1)	4 (2.6)
Abdominal Pain Upper	1 (1.3)	0	8 (4.0)	3 (2.8)	9 (3.2)	3 (2.0)
Abdominal Tenderness	0	0	0	1 (0.9)	0	1 (0.7)
Abnormal Faeces	1 (1.3)	0	0	0	1 (0.4)	0
Constipation	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Diarrhoea	1 (1.3)	2 (4.4)	5 (2.5)	7 (6.6)	6 (2.2)	9 (6.0)
Dry Mouth	0	0	4 (2.0)	0	4 (1.4)	0
Dyspepsia	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Dysphagia	0	0	0	1 (0.9)	0	1 (0.7)
Eructation	0	0	0	1 (0.9)	0	1 (0.7)
Faeces Soft	0	0	1 (0.5)	0	1 (0.4)	0
Flatulence	0	0	1 (0.5)	2 (1.9)	1 (0.4)	2 (1.3)
Gastrointestinal Haemorrhage	1 (1.3)	0	0	0	1 (0.4)	0
Gastrooesophageal Reflux Disease	0	0	0	1 (0.9)	0	1 (0.7)
Hypoaesthesia Oral	0	1 (2 2)	0	0	0	1 (0.7)
Ileus	0	0	0	1 (0.9)	0	1 (0.7)
Lip Dry	0	0	2 (1.0)	0	2 (0.7)	0
Lip Swelling	0	0	1 (0.5)	0	1 (0.4)	0
Nausea	5 (6.3)	5 (11.1)	13 (6.6)	12 (11.3)	18 (6.5)	17 (11.3)
Oesophageal Ulcer	0	0	0	1 (0.9)	0	1 (0.7)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Oral Disorder	0	0	0	1 (0.9)	0	1 (0.7)
Pancreatitis	0	0	0	1 (0.9)	0	1 (0.7)
Retching	0	1 (2 2)	0	0	0	1 (0.7)
Vomiting	2 (2.5)	6 (13.3)	11 (5.6)	7 (6.6)	13 (4.7)	13 (8.6)
General Disorders And Administration Site Conditions	**4 (5.1)**	**0**	**9 (4.5)**	**6 (5.7)**	**13 (4.7)**	**6 (4.0)**
Asthenia	1 (1.3)	0	2 (1.0)	2 (1.9)	3 (1.1)	2 (1.3)
Chest Pain	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Chills	0	0	1 (0.5)	0	1 (0.4)	0
Death	0	0	1 (0.5)	0	1 (0.4)	0
Fatigue	4 (5.1)	0	1 (0.5)	2 (1.9)	5 (1.8)	2 (1.3)
Malaise	0	0	0	1 (0.9)	0	1 (0.7)
Mucosal Inflammation	0	0	1 (0.5)	0	1 (0.4)	0
Oedema Peripheral	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Pyrexia	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Hepatobiliary Disorders	**1 (1.3)**	**1 (2.2)**	**3 (1.5)**	**2 (1.9)**	**4 (1.4)**	**3 (2.0)**
Cholestasis	0	1 (2 2)	0	0	0	1 (0.7)
Hepatic Failure	0	0	1 (0.5)	0	1 (0.4)	0
Hepatic Function Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Hepatocellular Injury	0	1 (2 2)	0	0	0	1 (0.7)
Hepatomegaly	0	0	1 (0.5)	0	1 (0.4)	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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Hepatosplenomegaly	0	0	0	1 (0.9)	0	1 (0.7)
Hyperbilirubinaemia	0	0	1 (0.5)	0	1 (0.4)	0
Jaundice	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Immune System Disorders	**0**	**0**	**0**	**1 (0.9)**	**0**	**1 (0.7)**
Drug Hypersensitivity	0	0	0	1 (0.9)	0	1 (0.7)
Infections And Infestations	**0**	**0**	**4 (2.0)**	**0**	**4 (1.4)**	**0**
Conjunctivitis	0	0	2 (1.0)	0	2 (0.7)	0
Meningitis Cryptococcal	0	0	1 (0.5)	0	1 (0.4)	0
Oesophageal Candidiasis	0	0	1 (0.5)	0	1 (0.4)	0
Injury, Poisoning And Procedural Complications	**1 (1.3)**	**0**	**2 (1.0)**	**2 (1.9)**	**3 (1.1)**	**2 (1.3)**
Excoriation	0	0	0	1 (0.9)	0	1 (0.7)
Overdose	0	0	1 (0.5)	0	1 (0.4)	0
Toxicity To Various Agents	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Transfusion Reaction	1 (1.3)	0	0	0	1 (0.4)	0
Investigations	**8 (10.1)**	**1 (2.2)**	**27 (13.6)**	**16 (15.1)**	**35 (12.6)**	**17 (11.3)**
Alanine Aminotransferase Increased	2 (2.5)	0	6 (3.0)	3 (2.8)	8 (2.9)	3 (2.0)
Amylase	0	0	0	1 (0.9)	0	1 (0.7)
Aspartate Aminotransferase Increased	1 (1.3)	0	5 (2.5)	3 (2.8)	6 (2.2)	3 (2.0)

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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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Bilirubin Conjugated Increased	0	0	1 (0.5)	0	1 (0.4)	0
Blood Alkaline Phosphatase Abnormal	1 (1.3)	0	0	0	1 (0.4)	0
Blood Alkaline Phosphatase Increased	0	0	5 (2.5)	0	5 (1.8)	0
Blood Bilirubin Increased	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Blood Creatinine Increased	0	0	3 (1.5)	2 (1.9)	3 (1.1)	2 (1.3)
Blood Gases Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Blood Triglycerides Increased	0	0	1 (0.5)	0	1 (0.4)	0
Blood Urea Increased	0	0	0	1 (0.9)	0	1 (0.7)
Cardioactive Drug Level Decreased	0	0	0	1 (0.9)	0	1 (0.7)
Cardioactive Drug Level Increased	0	0	0	1 (0.9)	0	1 (0.7)
Drug Level Changed	0	0	1 (0.5)	0	1 (0.4)	0
Drug Level Increased	1 (1.3)	1 (2.2)	1 (0.5)	1 (0.9)	2 (0.7)	2 (1.3)
Electrocardiogram Change	0	0	1 (0.5)	0	1 (0.4)	0
Electrocardiogram Qrs Complex Prolonged	0	0	1 (0.5)	0	1 (0.4)	0
Electrocardiogram Qt Prolonged	0	0	4 (2.0)	2 (1.9)	4 (1.4)	2 (1.3)
Gamma-Glutamyltransferase Increased	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Glucocorticoids Decreased	0	0	1 (0.5)	0	1 (0.4)	0
Hepatic Enzyme Increased	1 (1.3)	0	0	1 (0.9)	1 (0.4)	1 (0.7)
Laboratory Test Abnormal	0	0	1 (0.5)	0	1 (0.4)	0
Lipase	0	0	0	1 (0.9)	0	1 (0.7)
Lipase Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Liver Function Test Abnormal	0	0	1 (0.5)	0	1 (0.4)	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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Liver Function Test Increased	2 (2.5)	0	2 (1.0)	1 (0.9)	4 (1.4)	1 (0.7)
Pancreatic Enzymes Increased	1 (1.3)	0	0	0	1 (0.4)	0
Platelet Count Decreased	0	0	1 (0.5)	0	1 (0.4)	0
Qrs Axis Abnormal	0	0	0	1 (0.9)	0	1 (0.7)
Weight Decreased	0	0	1 (0.5)	0	1 (0.4)	0
Weight Increased	0	0	1 (0.5)	0	1 (0.4)	0
Metabolism And Nutrition Disorders	**1 (1.3)**	**2 (4.4)**	**6 (3.0)**	**5 (4.7)**	**7 (2.5)**	**7 (4.6)**
Decreased Appetite	1 (1.3)	1 (2 2)	3 (1.5)	3 (2.8)	4 (1.4)	4 (2.6)
Electrolyte Imbalance	0	0	0	1 (0.9)	0	1 (0.7)
Hyperkalaemia	0	0	0	1 (0.9)	0	1 (0.7)
Hyperphosphataemia	0	0	0	1 (0.9)	0	1 (0.7)
Hyperuricaemia	0	0	1 (0.5)	0	1 (0.4)	0
Hypokalaemia	0	0	1 (0.5)	0	1 (0.4)	0
Metabolic Acidosis	0	1 (2 2)	0	0	0	1 (0.7)
Polydipsia	0	0	2 (1.0)	0	2 (0.7)	0
Musculoskeletal And Connective Tissue Disorders	**3 (3.8)**	**1 (2.2)**	**5 (2.5)**	**3 (2.8)**	**8 (2.9)**	**4 (2.6)**
Arthralgia	1 (1.3)	1 (2 2)	0	0	1 (0.4)	1 (0.7)
Back Pain	0	0	0	1 (0.9)	0	1 (0.7)
Bone Pain	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Fistula	0	0	1 (0.5)	0	1 (0.4)	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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Mobility Decreased	1 (1.3)	0	0	0	1 (0.4)	0
Muscular Weakness	1 (1.3)	0	0	0	1 (0.4)	0
Musculoskeletal Chest Pain	0	0	0	1 (0.9)	0	1 (0.7)
Myalgia	0	0	1 (0.5)	0	1 (0.4)	0
Nuchal Rigidity	0	0	1 (0.5)	0	1 (0.4)	0
Pain In Extremity	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Pain In Jaw	0	0	0	1 (0.9)	0	1 (0.7)
Nervous System Disorders	**2 (2.5)**	**5 (11.1)**	**15 (7.6)**	**17 (16.0)**	**17 (6.1)**	**22 (14.6)**
Balance Disorder	0	0	0	1 (0.9)	0	1 (0.7)
Dizziness	1 (1.3)	0	2 (1.0)	4 (3.8)	3 (1.1)	4 (2.6)
Dysgeusia	0	0	0	1 (0.9)	0	1 (0.7)
Headache	1 (1.3)	2 (4.4)	10 (5.1)	7 (6.6)	11 (4.0)	9 (6.0)
Hyperreflexia	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Hypoaesthesia	0	0	0	1 (0.9)	0	1 (0.7)
Hypotonia	0	0	0	1 (0.9)	0	1 (0.7)
Memory Impairment	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Mental Impairment	0	0	0	1 (0.9)	0	1 (0.7)
Mononeuropathy Multiplex	0	0	0	1 (0.9)	0	1 (0.7)
Neuropathy Peripheral	0	0	1 (0.5)	0	1 (0.4)	0
Paraesthesia	0	1 (2 2)	2 (1.0)	3 (2.8)	2 (0.7)	4 (2.6)
Seizure	0	2 (4.4)	0	0	0	2 (1.3)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Somnolence	0	0	0	3 (2.8)	0	3 (2.0)
Speech Disorder	0	0	0	1 (0.9)	0	1 (0.7)
Tremor	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Psychiatric Disorders	**0**	**0**	**3 (1.5)**	**3 (2.8)**	**3 (1.1)**	**3 (2.0)**
Anxiety	0	0	0	1 (0.9)	0	1 (0.7)
Confusional State	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Delirium	0	0	0	1 (0.9)	0	1 (0.7)
Mental Status Changes	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Renal And Urinary Disorders	**2 (2.5)**	**0**	**5 (2.5)**	**2 (1 9)**	**7 (2.5)**	**2 (1.3)**
Acute Kidney Injury	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Choluria	0	0	1 (0.5)	0	1 (0.4)	0
Chronic Kidney Disease	1 (1.3)	0	0	0	1 (0.4)	0
Nephropathy Toxic	1 (1.3)	0	0	0	1 (0.4)	0
Nocturia	0	0	2 (1.0)	0	2 (0.7)	0
Renal Failure	1 (1.3)	0	1 (0.5)	1 (0.9)	2 (0.7)	1 (0.7)
Renal Tubular Acidosis	0	0	0	1 (0.9)	0	1 (0.7)
Urinary Hesitation	0	0	1 (0.5)	0	1 (0.4)	0
Reproductive System And Breast Disorders	**0**	**0**	**1 (0.5)**	**2 (1.9)**	**1 (0.4)**	**2 (1.3)**
Breast Swelling	0	0	1 (0.5)	0	1 (0.4)	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 by Risk Group, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Breast Tenderness	0	0	1 (0.5)	0	1 (0.4)	0
Hypomenorrhoea	0	0	0	1 (0.9)	0	1 (0.7)
Menstruation Delayed	0	0	0	1 (0.9)	0	1 (0.7)
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**2 (1.0)**	**2 (1.9)**	**2 (0.7)**	**2 (1.3)**
Dyspnoea	0	0	1 (0.5)	1 (0.9)	1 (0.4)	1 (0.7)
Epistaxis	0	0	0	1 (0.9)	0	1 (0.7)
Lung Infiltration	0	0	1 (0.5)	0	1 (0.4)	0
Skin And Subcutaneous Tissue Disorders	**3 (3.8)**	**2 (4.4)**	**12 (6.1)**	**12 (11.3)**	**15 (5.4)**	**14 (9.3)**
Alopecia	0	0	1 (0.5)	3 (2.8)	1 (0.4)	3 (2.0)
Dermatitis Atopic	1 (1.3)	0	0	0	1 (0.4)	0
Dermatosis	0	0	1 (0.5)	0	1 (0.4)	0
Dry Skin	1 (1.3)	0	2 (1.0)	0	3 (1.1)	0
Hyperhidrosis	0	0	1 (0.5)	0	1 (0.4)	0
Pruritus	0	1 (2.2)	1 (0.5)	2 (1.9)	1 (0.4)	3 (2.0)
Rash	1 (1.3)	1 (2.2)	2 (1.0)	3 (2.8)	3 (1.1)	4 (2.6)
Rash Macular	0	0	0	1 (0.9)	0	1 (0.7)
Rash Maculo-Papular	0	0	0	1 (0.9)	0	1 (0.7)
Rash Papular	0	0	1 (0.5)	0	1 (0.4)	0
Rash Pruritic	0	0	2 (1.0)	1 (0.9)	2 (0.7)	1 (0.7)
Rash Vesicular	0	0	0	1 (0.9)	0	1 (0.7)

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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, Sex
Number (%) of Subjects

	BMT		Non-BMT		Overall rIFI Pool	
	Male n = 79	Female n = 45	Male n = 198	Female n = 106	Male n = 277	Female n = 151
Urticaria	0	0	1 (0.5)	0	1 (0.4)	0
Urticaria Papular	0	0	1 (0.5)	0	1 (0.4)	0
Surgical And Medical Procedures	**0**	**0**	**1 (0.5)**	**0**	**1 (0.4)**	**0**
Therapeutic Procedure	0	0	1 (0.5)	0	1 (0.4)	0
Vascular Disorders	**3 (3.8)**	**0**	**2 (1.0)**	**1 (0 9)**	**5 (1.8)**	**1 (0.7)**
Haematoma	1 (1.3)	0	0	0	1 (0.4)	0
Hypertension	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Hypotension	1 (1.3)	0	1 (0.5)	0	2 (0.7)	0
Ischaemia	0	0	0	1 (0.9)	0	1 (0.7)

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

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付録 2.7.4-170　　性別ごと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 by Gender (Incidence > 0% in Any Column)
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 events	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Blood and lymphatic system disorders	**7**	**(9.9)**	**1**	**(16.7)**	**4**	**(12 1)**	**0**	**(0.0)**
Anaemia	2	(2.8)	0	(0.0)	2	(6 1)	0	(0.0)
Eosinophilia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	3	(4.2)	1	(16.7)	1	(3.0)	0	(0.0)
Hypochromic anaemia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Iron deficiency anaemia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Thrombocytopenia	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**8**	**(11.3)**	**0**	**(0.0)**	**4**	**(12 1)**	**0**	**(0.0)**
Atrioventricular block first degree	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Bundle branch block right	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Cardiac failure	4	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure congestive	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cor pulmonale	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Supraventricular extrasystoles	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.0)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Eye disorders	**12**	**(16.9)**	**0**	**(0.0)**	**21**	**(63.6)**	**2**	**(40.0)**

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**12**	**(16.9)**	**0**	**(0.0)**	**21**	**(63.6)**	**2**	**(40.0)**
Blepharitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Colour blindness acquired	0	(0.0)	0	(0.0)	4	(12 1)	1	(20.0)
Conjunctival hyperaemia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Diplopia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Dyschromatopsia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Ocular hyperaemia	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Ocular hypertension	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Photophobia	5	(7.0)	0	(0.0)	9	(27 3)	2	(40.0)
Vision blurred	1	(1.4)	0	(0.0)	4	(12 1)	0	(0.0)
Visual impairment	0	(0.0)	0	(0.0)	5	(15 2)	0	(0.0)
Gastrointestinal disorders	**28**	**(39.4)**	**2**	**(33.3)**	**17**	**(51 5)**	**0**	**(0.0)**
Abdominal discomfort	3	(4.2)	0	(0.0)	1	(3.0)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Cheilitis	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Constipation	12	(16.9)	1	(16.7)	6	(18 2)	0	(0.0)
Dental caries	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Diarrhoea	6	(8.5)	0	(0.0)	4	(12 1)	0	(0.0)
Enterocolitis	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Faeces hard	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Faeces soft	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorder	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Gastrointestinal pain	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Haemorrhoidal haemorrhage	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**28**	**(39.4)**	**2**	**(33.3)**	**17**	**(51 5)**	**0**	**(0.0)**
Haemorrhoids	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Hypoaesthesia oral	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lip dry	2	(2.8)	0	(0.0)	2	(6 1)	0	(0.0)
Melaena	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	5	(7.0)	2	(33.3)	1	(3.0)	0	(0.0)
Oral discomfort	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Oral dysaesthesia	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Stomatitis	5	(7.0)	0	(0.0)	0	(0.0)	0	(0.0)
Trichoglossia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	3	(4.2)	0	(0.0)	2	(6 1)	0	(0.0)
General disorders and administration site conditions	**34**	**(47.9)**	**4**	**(66.7)**	**9**	**(27 3)**	**0**	**(0.0)**
Catheter site erythema	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Chest discomfort	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Chest pain	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Chills	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Malaise	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Mucosal inflammation	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	5	(7.0)	2	(33.3)	1	(3.0)	0	(0.0)
Peripheral swelling	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**34**	**(47.9)**	**4**	**(66.7)**	**9**	**(27 3)**	**0**	**(0.0)**
Pyrexia	25	(35.2)	0	(0.0)	2	(6 1)	0	(0.0)
Thirst	2	(2.8)	1	(16.7)	1	(3.0)	0	(0.0)
Hepatobiliary disorders	**14**	**(19.7)**	**0**	**(0.0)**	**8**	**(24 2)**	**0**	**(0.0)**
Hepatic function abnormal	14	(19.7)	0	(0.0)	6	(18 2)	0	(0.0)
Hepatobiliary disease	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Immune system disorders	**2**	**(2.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cytokine release syndrome	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Graft versus host disease in gastrointestinal tract	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**40**	**(56.3)**	**4**	**(66.7)**	**11**	**(33 3)**	**1**	**(20.0)**
Angular cheilitis	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Bacterial sepsis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Blister infected	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Bronchiolitis	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchitis	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Bronchopulmonary aspergillosis	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Cellulitis	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	2	(2.8)	1	(16.7)	1	(3.0)	0	(0.0)
Conjunctivitis bacterial	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis viral	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cytomegalovirus infection	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Device related infection	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Enterocolitis viral	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**40**	**(56.3)**	**4**	**(66.7)**	**11**	**(33 3)**	**1**	**(20.0)**
Gastroenteritis bacterial	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gingivitis	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Infected dermal cyst	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	3	(4.2)	0	(0.0)	6	(18 2)	1	(20.0)
Oral herpes	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Osteomyelitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Paronychia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Periodontitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Pneumonia	12	(16.9)	0	(0.0)	2	(6 1)	0	(0.0)
Pneumonia bacterial	5	(7.0)	1	(16.7)	1	(3.0)	0	(0.0)
Pneumonia fungal	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Pyelonephritis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sepsis	2	(2.8)	1	(16.7)	0	(0.0)	0	(0.0)
Staphylococcal bacteraemia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Upper respiratory tract infection	2	(2.8)	2	(33.3)	0	(0.0)	0	(0.0)
Urinary tract infection	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**12**	**(16.9)**	**1**	**(16.7)**	**3**	**(9 1)**	**0**	**(0.0)**
Accidental overdose	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Allergic transfusion reaction	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Arthropod bite	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**12**	**(16.9)**	**1**	**(16.7)**	**3**	**(9 1)**	**0**	**(0.0)**
Complications of bone marrow transplant	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Fall	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Laceration	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Ligament sprain	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Limb injury	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Post procedural complication	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Postoperative fever	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Skin abrasion	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal compression fracture	0	(0.0)	1	(16.7)	1	(3.0)	0	(0.0)
Thermal burn	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Transplantation complication	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Wound	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**26**	**(36.6)**	**4**	**(66.7)**	**12**	**(36.4)**	**3**	**(60.0)**
Alanine aminotransferase increased	7	(9.9)	2	(33.3)	2	(6 1)	0	(0.0)
Aspartate aminotransferase increased	8	(11.3)	2	(33.3)	4	(12 1)	0	(0.0)
Blood alkaline phosphatase increased	2	(2.8)	1	(16.7)	4	(12 1)	1	(20.0)
Blood creatinine increased	3	(4.2)	0	(0.0)	3	(9 1)	0	(0.0)
Blood glucose increased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Blood lactate dehydrogenase increased	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Blood potassium decreased	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blood pressure increased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea decreased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	5	(7.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**26**	**(36.6)**	**4**	**(66.7)**	**12**	**(36.4)**	**3**	**(60.0)**
Cytomegalovirus test positive	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Electrocardiogram QT prolonged	7	(9.9)	0	(0.0)	0	(0.0)	2	(40.0)
Electrocardiogram ST segment elevation	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Eosinophil count increased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.4)	0	(0.0)	4	(12 1)	0	(0.0)
Liver function test increased	0	(0.0)	1	(16.7)	2	(6 1)	0	(0.0)
Neutrophil count decreased	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Platelet count decreased	5	(7.0)	0	(0.0)	2	(6 1)	0	(0.0)
Renal function test abnormal	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Weight decreased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	1	(1.4)	1	(16.7)	1	(3.0)	0	(0.0)
Metabolism and nutrition disorders	**28**	**(39.4)**	**3**	**(50.0)**	**4**	**(12 1)**	**1**	**(20.0)**
Decreased appetite	13	(18.3)	1	(16.7)	0	(0.0)	0	(0.0)
Dehydration	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hyperkalaemia	1	(1.4)	0	(0.0)	2	(6 1)	1	(20.0)
Hyperuricaemia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hypoalbuminaemia	4	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycaemia	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	13	(18.3)	3	(50.0)	1	(3.0)	0	(0.0)
Hyponatraemia	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**12**	**(16.9)**	**1**	**(16.7)**	**4**	**(12 1)**	**0**	**(0.0)**
Arthralgia	1	(1.4)	1	(16.7)	0	(0.0)	0	(0.0)
Arthritis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**12**	**(16.9)**	**1**	**(16.7)**	**4**	**(12 1)**	**0**	**(0.0)**
Back pain	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Chondrocalcinosis pyrophosphate	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cytarabine syndrome	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Joint effusion	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Muscular weakness	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal pain	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Osteoporosis	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Pain in extremity	2	(2.8)	0	(0.0)	2	(6 1)	0	(0.0)
Periarthritis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(4.2)**	**1**	**(16.7)**	**1**	**(3.0)**	**1**	**(20.0)**
Acute myeloid leukaemia	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Cancer pain	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gastric cancer	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Lung cancer metastatic	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Skin papilloma	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Squamous cell carcinoma of lung	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tumour associated fever	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tumour inflammation	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**8**	**(11.3)**	**0**	**(0.0)**	**8**	**(24 2)**	**0**	**(0.0)**

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**8**	**(11.3)**	**0**	**(0.0)**	**8**	**(24 2)**	**0**	**(0.0)**
Dizziness	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	1	(1.4)	0	(0.0)	3	(9 1)	0	(0.0)
Head discomfort	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Headache	3	(4.2)	0	(0.0)	1	(3.0)	0	(0.0)
Hypoaesthesia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hypogeusia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Loss of consciousness	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Neuropathy peripheral	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Parosmia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Psychiatric disorders	**5**	**(7.0)**	**0**	**(0.0)**	**11**	**(33 3)**	**1**	**(20.0)**
Anxiety	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Delirium	0	(0.0)	0	(0.0)	3	(9 1)	0	(0.0)
Hallucination	0	(0.0)	0	(0.0)	3	(9 1)	0	(0.0)
Hallucination, auditory	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Insomnia	3	(4.2)	0	(0.0)	5	(15 2)	1	(20.0)
Mental disorder	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**6**	**(8.5)**	**0**	**(0.0)**	**3**	**(9 1)**	**0**	**(0.0)**
Acute kidney injury	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonic bladder	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**6**	**(8.5)**	**0**	**(0.0)**	**3**	**(9 1)**	**0**	**(0.0)**
Neurogenic bladder	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Pollakiuria	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Renal impairment	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Urethral pain	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Urinary incontinence	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Reproductive system and breast disorders	**3**	**(4.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Benign prostatic hyperplasia	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**20**	**(28.2)**	**3**	**(50.0)**	**7**	**(21 2)**	**2**	**(40.0)**
Asthma	1	(1.4)	1	(16.7)	2	(6 1)	0	(0.0)
Bronchitis chronic	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Chronic obstructive pulmonary disease	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	2	(2.8)	1	(16.7)	1	(3.0)	0	(0.0)
Haemoptysis	4	(5.6)	0	(0.0)	1	(3.0)	0	(0.0)
Hypercapnia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Laryngeal pain	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Oropharyngeal discomfort	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Oropharyngeal pain	4	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**20**	**(28.2)**	**3**	**(50.0)**	**7**	**(21 2)**	**2**	**(40.0)**
Pneumothorax	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Pneumothorax spontaneous	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Upper respiratory tract inflammation	1	(1.4)	0	(0.0)	1	(3.0)	1	(20.0)
Skin and subcutaneous tissue disorders	**21**	**(29.6)**	**5**	**(83.3)**	**7**	**(21 2)**	**1**	**(20.0)**
Alopecia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Decubitus ulcer	1	(1.4)	1	(16.7)	0	(0.0)	0	(0.0)
Dermatitis acneiform	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis contact	1	(1.4)	1	(16.7)	1	(3.0)	0	(0.0)
Drug eruption	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	4	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema asteatotic	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(1.4)	2	(33.3)	0	(0.0)	0	(0.0)
Erythema nodosum	1	(1.4)	1	(16.7)	0	(0.0)	0	(0.0)
Hyperhidrosis	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hyperkeratosis	0	(0.0)	1	(16.7)	1	(3.0)	0	(0.0)
Ingrowing nail	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Perivascular dermatitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Petechiae	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Photosensitivity reaction	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Rash	6	(8.5)	0	(0.0)	1	(3.0)	1	(20.0)
Rash maculo-papular	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Rash pruritic	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**21**	**(29.6)**	**5**	**(83.3)**	**7**	**(21 2)**	**1**	**(20.0)**
Skin exfoliation	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Skin irritation	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**14**	**(19.7)**	**1**	**(16.7)**	**2**	**(6 1)**	**0**	**(0.0)**
Hypertension	13	(18.3)	1	(16.7)	1	(3.0)	0	(0.0)
Orthostatic hypotension	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombophlebitis	0	(0.0)	0	(0.0)	1	(3.0)	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]

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付録 2.7.4-171　　性別ごとの副作用の発現例数（%）（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 by Gender (Incidence > 0% in Any Column)
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 drug-related adverse events	52	(73.2)	4	(66.7)	31	(93 9)	3	(60.0)
with no drug-related adverse events	19	(26.8)	2	(33.3)	2	(6 1)	2	(40.0)
Blood and lymphatic system disorders	**2**	**(2.8)**	**0**	**(0.0)**	**1**	**(3.0)**	**0**	**(0.0)**
Anaemia	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Thrombocytopenia	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(2.8)**	**0**	**(0.0)**	**2**	**(6 1)**	**0**	**(0.0)**
Bundle branch block right	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Cardiac failure	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Supraventricular extrasystoles	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.0)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Eye disorders	**2**	**(2.8)**	**0**	**(0.0)**	**21**	**(63.6)**	**2**	**(40.0)**
Colour blindness acquired	0	(0.0)	0	(0.0)	4	(12 1)	1	(20.0)
Diplopia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dyschromatopsia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Photophobia	0	(0.0)	0	(0.0)	9	(27 3)	2	(40.0)
Vision blurred	1	(1.4)	0	(0.0)	4	(12 1)	0	(0.0)
Visual impairment	0	(0.0)	0	(0.0)	5	(15 2)	0	(0.0)
Gastrointestinal disorders	**8**	**(11.3)**	**1**	**(16.7)**	**7**	**(21 2)**	**0**	**(0.0)**

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Subjects With Drug-Related Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**8**	**(11.3)**	**1**	**(16.7)**	**7**	**(21 2)**	**0**	**(0.0)**
Abdominal discomfort	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Constipation	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal pain	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Lip dry	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Nausea	3	(4.2)	1	(16.7)	1	(3.0)	0	(0.0)
Oral discomfort	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Oral dysaesthesia	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)
Stomatitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
General disorders and administration site conditions	**22**	**(31.0)**	**2**	**(33.3)**	**4**	**(12 1)**	**0**	**(0.0)**
Chest pain	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Malaise	2	(2.8)	0	(0.0)	1	(3.0)	0	(0.0)
Oedema	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	1	(1.4)	2	(33.3)	0	(0.0)	0	(0.0)
Pyrexia	17	(23.9)	0	(0.0)	0	(0.0)	0	(0.0)
Thirst	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**10**	**(14.1)**	**0**	**(0.0)**	**8**	**(24 2)**	**0**	**(0.0)**
Hepatic function abnormal	10	(14.1)	0	(0.0)	6	(18 2)	0	(0.0)
Hepatobiliary disease	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**4**	**(5.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cellulitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**12**	**(16.9)**	**3**	**(50.0)**	**8**	**(24 2)**	**2**	**(40.0)**
Alanine aminotransferase increased	5	(7.0)	2	(33.3)	2	(6 1)	0	(0.0)
Aspartate aminotransferase increased	5	(7.0)	2	(33.3)	3	(9 1)	0	(0.0)
Blood alkaline phosphatase increased	1	(1.4)	1	(16.7)	3	(9 1)	1	(20.0)
Blood creatinine increased	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Blood lactate dehydrogenase increased	1	(1.4)	0	(0.0)	1	(3.0)	0	(0.0)
Blood potassium decreased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Electrocardiogram QT prolonged	6	(8.5)	0	(0.0)	0	(0.0)	2	(40.0)
Electrocardiogram ST segment elevation	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(1.4)	0	(0.0)	4	(12 1)	0	(0.0)
Liver function test increased	0	(0.0)	1	(16.7)	1	(3.0)	0	(0.0)
Platelet count decreased	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**16**	**(22.5)**	**2**	**(33.3)**	**2**	**(6 1)**	**0**	**(0.0)**
Decreased appetite	9	(12.7)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Hypokalaemia	8	(11.3)	2	(33.3)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(4.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Arthralgia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**3**	**(4.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Arthritis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**1**	**(1.4)**	**0**	**(0.0)**	**4**	**(12 1)**	**0**	**(0.0)**
Dizziness	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Head discomfort	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hypogeusia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Psychiatric disorders	**2**	**(2.8)**	**0**	**(0.0)**	**9**	**(27 3)**	**0**	**(0.0)**
Delirium	0	(0.0)	0	(0.0)	2	(6 1)	0	(0.0)
Hallucination	0	(0.0)	0	(0.0)	3	(9 1)	0	(0.0)
Hallucination, auditory	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Insomnia	2	(2.8)	0	(0.0)	3	(9 1)	0	(0.0)
Renal and urinary disorders	**1**	**(1.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertonic bladder	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**4**	**(5.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Epistaxis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Gender (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592				Voriconazole			
	Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**9**	**(12.7)**	**1**	**(16.7)**	**3**	**(9 1)**	**0**	**(0.0)**
Dermatitis acneiform	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	3	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(1.4)	1	(16.7)	0	(0.0)	0	(0.0)
Hyperhidrosis	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Photosensitivity reaction	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)
Rash	4	(5.6)	0	(0.0)	1	(3.0)	0	(0.0)
Rash maculo-papular	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**10**	**(14.1)**	**1**	**(16.7)**	**1**	**(3.0)**	**0**	**(0.0)**
Hypertension	10	(14.1)	1	(16.7)	1	(3.0)	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]

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付録 2.7.4-172　　人種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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Subjects Reporting Any Adverse Event	**471 (98.3)**	**124 (98.4)**	**421 (98.4)**	**110 (99 1)**	**49 (100.0)**	**9 (100.0)**
Blood And Lymphatic System Disorders	**298 (62.2)**	**82 (65 1)**	**267 (62.4)**	**63 (56.8)**	**32 (65.3)**	**9 (100.0)**
Anaemia	128 (26.7)	33 (26 2)	106 (24.8)	30 (27.0)	13 (26.5)	6 (66.7)
Bone Marrow Disorder	0	0	1 (0.2)	0	0	0
Bone Marrow Failure	4 (0.8)	1 (0.8)	0	0	0	0
Coagulation Factor Deficiency	1 (0.2)	0	0	0	0	0
Coagulopathy	11 (2.3)	1 (0.8)	14 (3.3)	0	1 (2.0)	0
Disseminated Intravascular Coagulation	1 (0.2)	2 (1.6)	4 (0.9)	1 (0.9)	0	0
Eosinophilia	1 (0.2)	0	0	0	0	0
Febrile Neutropenia	78 (16.3)	40 (31.7)	62 (14.5)	23 (20.7)	17 (34.7)	6 (66.7)
Granulocytopenia	1 (0.2)	0	3 (0.7)	0	0	0
Haemolysis	5 (1.0)	0	1 (0.2)	3 (2.7)	0	0
Haemolytic Anaemia	0	0	1 (0.2)	0	0	0
Haemolytic Uraemic Syndrome	5 (1.0)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Haemorrhagic Diathesis	2 (0.4)	0	4 (0.9)	0	0	0
Haemorrhagic Disorder	1 (0.2)	0	0	0	0	0
Hypercoagulation	1 (0.2)	0	0	0	0	0
Hypofibrinogenaemia	0	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Hypoglobulinaemia	1 (0.2)	0	0	1 (0.9)	0	0
Hypoprothrombinaemia	0	2 (1.6)	4 (0.9)	1 (0.9)	0	0
Increased Tendency To Bruise	0	0	2 (0.5)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Iron Deficiency Anaemia	0	0	1 (0.2)	0	0	0
Leukocytosis	3 (0.6)	0	6 (1.4)	0	0	0
Leukopenia	27 (5.6)	9 (7.1)	34 (7.9)	7 (6 3)	2 (4.1)	3 (33.3)
Lymph Node Pain	3 (0.6)	0	0	0	1 (2.0)	0
Lymphadenitis	1 (0.2)	0	2 (0.5)	0	0	0
Lymphadenopathy	9 (1.9)	2 (1.6)	8 (1.9)	1 (0.9)	2 (4.1)	0
Lymphopenia	0	0	1 (0.2)	0	1 (2.0)	0
Macrocytosis	1 (0.2)	0	0	1 (0.9)	0	0
Microangiopathic Haemolytic Anaemia	0	0	1 (0.2)	0	0	0
Monocytosis	0	0	0	1 (0.9)	0	0
Neutropenia	114 (23.8)	31 (24.6)	101 (23.6)	26 (23.4)	19 (38.8)	4 (44.4)
Pancytopenia	17 (3.5)	1 (0.8)	15 (3.5)	6 (5.4)	1 (2.0)	0
Polychromasia	0	0	0	1 (0.9)	0	0
Polycythaemia	0	0	0	1 (0.9)	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 (2.3)	0	5 (1.2)	2 (1.8)	0	0
Thrombocytopenia	146 (30.5)	43 (34 1)	134 (31.3)	27 (24.3)	15 (30.6)	6 (66.7)
Thrombocytosis	0	0	2 (0.5)	0	0	1 (11.1)
Thrombotic Microangiopathy	0	0	1 (0.2)	0	0	0
Thrombotic Thrombocytopenic Purpura	8 (1.7)	1 (0.8)	1 (0.2)	2 (1.8)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Cardiac Disorders	**112 (23.4)**	**32 (25.4)**	**113 (26.4)**	**26 (23.4)**	**11 (22.4)**	**3 (33.3)**
Acute Myocardial Infarction	1 (0.2)	2 (1.6)	0	0	0	0
Angina Pectoris	3 (0.6)	1 (0.8)	4 (0.9)	0	0	0
Aortic Valve Incompetence	1 (0.2)	0	1 (0.2)	0	0	0
Arrhythmia	3 (0.6)	1 (0.8)	2 (0.5)	0	0	0
Arrhythmia Supraventricular	0	0	1 (0.2)	0	0	0
Arteriosclerosis Coronary Artery	1 (0.2)	0	0	0	0	0
Atrial Fibrillation	10 (2.1)	1 (0.8)	15 (3.5)	2 (1.8)	2 (4.1)	0
Atrial Flutter	3 (0.6)	0	3 (0.7)	0	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)	0	0	0
Atrioventricular Block Complete	1 (0.2)	0	0	0	0	0
Atrioventricular Block Second Degree	1 (0.2)	0	0	0	0	0
Bradycardia	8 (1.7)	2 (1.6)	6 (1.4)	2 (1.8)	2 (4.1)	0
Bundle Branch Block	0	0	1 (0.2)	0	0	0
Bundle Branch Block Left	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Bundle Branch Block Right	1 (0.2)	0	3 (0.7)	0	0	0
Cardiac Arrest	5 (1.0)	2 (1.6)	6 (1.4)	0	1 (2.0)	0
Cardiac Disorder	0	1 (0.8)	0	0	0	0
Cardiac Failure	3 (0.6)	1 (0.8)	4 (0.9)	0	0	0
Cardiac Failure Congestive	2 (0.4)	1 (0.8)	4 (0.9)	1 (0.9)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Cardiac Flutter	0	0	1 (0.2)	0	0	0
Cardiac Hypertrophy	2 (0.4)	0	0	0	0	0
Cardiac Tamponade	0	0	1 (0.2)	0	0	0
Cardio-Respiratory Arrest	2 (0.4)	1 (0.8)	3 (0.7)	3 (2.7)	0	0
Cardiomegaly	3 (0.6)	3 (2.4)	0	0	1 (2.0)	0
Cardiomyopathy	1 (0.2)	0	0	1 (0.9)	1 (2.0)	0
Cardiopulmonary Failure	1 (0.2)	0	0	0	0	0
Cardiotoxicity	0	0	1 (0.2)	0	0	0
Cardiovascular Disorder	0	0	1 (0.2)	0	0	0
Cardiovascular Insufficiency	3 (0.6)	0	2 (0.5)	0	0	0
Congestive Cardiomyopathy	1 (0.2)	0	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	0	1 (0.9)	0	0
Endocarditis Noninfective	0	0	1 (0.2)	0	0	0
Extrasystoles	1 (0.2)	0	4 (0.9)	0	0	0
Intracardiac Mass	1 (0.2)	0	1 (0.2)	0	0	0
Left Atrial Dilatation	0	1 (0.8)	0	0	0	0
Left Ventricular Dysfunction	4 (0.8)	0	4 (0.9)	1 (0.9)	0	0
Left Ventricular Hypertrophy	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Mitral Valve Disease	1 (0.2)	0	0	0	0	0
Mitral Valve Incompetence	2 (0.4)	2 (1.6)	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Myocardial Infarction	3 (0.6)	0	0	0	0	0
Myocardial Ischaemia	2 (0.4)	0	0	0	0	0
Myocarditis	0	1 (0.8)	1 (0.2)	0	0	0
Palpitations	3 (0.6)	2 (1.6)	6 (1.4)	0	0	1 (11.1)
Pericardial Effusion	5 (1.0)	3 (2.4)	13 (3.0)	4 (3.6)	1 (2.0)	0
Pericardial Mass	0	0	1 (0.2)	0	0	0
Pericardial Rub	0	0	1 (0.2)	0	0	0
Pericarditis	1 (0.2)	1 (0.8)	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	0	1 (0.9)	2 (4.1)	0
Sinus Tachycardia	6 (1.3)	5 (4.0)	5 (1.2)	5 (4.5)	1 (2.0)	1 (11.1)
Subendocardial Ischaemia	0	0	0	2 (1.8)	0	0
Supraventricular Extrasystoles	3 (0.6)	0	1 (0.2)	0	0	0
Supraventricular Tachycardia	2 (0.4)	2 (1.6)	3 (0.7)	0	1 (2.0)	0
Tachycardia	50 (10.4)	15 (11 9)	59 (13.8)	10 (9.0)	4 (8.2)	1 (11.1)
Tachycardia Paroxysmal	0	0	1 (0.2)	0	0	0
Torsade De Pointes	1 (0.2)	0	0	1 (0.9)	0	0
Tricuspid Valve Incompetence	1 (0.2)	1 (0.8)	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Ventricular Extrasystoles	7 (1.5)	2 (1.6)	1 (0.2)	0	1 (2.0)	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 (0.6)**	**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	**45 (9.4)**	**7 (5.6)**	**31 (7.2)**	**5 (4.5)**	**3 (6.1)**	**1 (11.1)**
Deafness	1 (0.2)	0	2 (0.5)	0	0	0
Ear Congestion	0	0	3 (0.7)	0	1 (2.0)	0
Ear Discomfort	4 (0.8)	0	3 (0.7)	1 (0.9)	0	0
Ear Disorder	2 (0.4)	0	0	0	0	0
Ear Haemorrhage	2 (0.4)	0	1 (0.2)	0	0	0
Ear Pain	14 (2.9)	3 (2.4)	9 (2.1)	3 (2.7)	1 (2.0)	0
Ear Pruritus	0	1 (0.8)	0	0	0	1 (11.1)
Ear Swelling	1 (0.2)	0	1 (0.2)	0	0	0
Eustachian Tube Obstruction	0	0	0	0	1 (2.0)	0
Excessive Cerumen Production	1 (0.2)	0	0	0	0	0
Hypoacusis	7 (1.5)	1 (0.8)	2 (0.5)	0	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Middle Ear Effusion	1 (0.2)	1 (0.8)	0	0	0	0
Otorrhoea	1 (0.2)	1 (0.8)	0	0	0	0
Sudden Hearing Loss	1 (0.2)	0	0	0	0	0
Tinnitus	5 (1.0)	0	2 (0.5)	1 (0.9)	0	0
Vertigo	9 (1.9)	1 (0.8)	9 (2.1)	0	0	0
Endocrine Disorders	**29 (6.1)**	**3 (2.4)**	**31 (7.2)**	**4 (3.6)**	**1 (2.0)**	**0**
Addison's Disease	0	1 (0.8)	0	0	0	0
Adrenal Insufficiency	2 (0.4)	0	2 (0.5)	0	1 (2.0)	0
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)	0	0	0	0	0
Cushingoid	22 (4.6)	2 (1.6)	23 (5.4)	3 (2.7)	0	0
Euthyroid Sick Syndrome	0	0	0	1 (0.9)	0	0
Goitre	1 (0.2)	0	1 (0.2)	0	0	0
Hypogonadism	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Hypothyroidism	0	0	2 (0.5)	0	0	0
Inappropriate Antidiuretic Hormone Secretion	0	0	2 (0.5)	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	**105 (21.9)**	**20 (15 9)**	**108 (25.2)**	**27 (24.3)**	**9 (18.4)**	**1 (11.1)**

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Abnormal Sensation In Eye	1 (0.2)	0	0	0	0	0
Blepharitis	0	0	0	0	1 (2.0)	0
Cataract	2 (0.4)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Choroiditis	0	0	0	1 (0.9)	0	0
Conjunctival Deposit	0	0	0	0	1 (2.0)	0
Conjunctival Discolouration	0	0	1 (0.2)	0	0	0
Conjunctival Disorder	0	0	0	1 (0.9)	0	0
Conjunctival Haemorrhage	6 (1.3)	2 (1.6)	11 (2.6)	3 (2.7)	1 (2.0)	0
Conjunctival Hyperaemia	1 (0.2)	1 (0.8)	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)	0	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	0	1 (0.9)	0	0
Diplopia	1 (0.2)	0	2 (0.5)	0	0	0
Dry Eye	20 (4.2)	2 (1.6)	22 (5.1)	4 (3.6)	1 (2.0)	0
Episcleritis	0	0	1 (0.2)	0	0	0
Erythema Of Eyelid	2 (0.4)	0	0	0	0	0
Exophthalmos	0	0	1 (0.2)	0	0	0
Eye Discharge	0	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Eye Disorder	0	0	1 (0.2)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Eye Haemorrhage	3 (0.6)	0	7 (1.6)	0	2 (4.1)	0
Eye Inflammation	0	0	0	1 (0.9)	0	0
Eye Irritation	8 (1.7)	4 (3.2)	4 (0.9)	2 (1.8)	1 (2.0)	0
Eye Movement Disorder	1 (0.2)	0	0	0	0	0
Eye Oedema	1 (0.2)	0	2 (0.5)	0	0	0
Eye Pain	8 (1.7)	1 (0.8)	7 (1.6)	4 (3.6)	1 (2.0)	0
Eye Pruritus	3 (0.6)	1 (0.8)	5 (1.2)	0	0	0
Eye Swelling	4 (0.8)	0	2 (0.5)	0	1 (2.0)	0
Eyelid Oedema	4 (0.8)	0	2 (0.5)	0	0	0
Eyelid Pain	0	0	0	0	1 (2.0)	0
Foreign Body Sensation In Eyes	2 (0.4)	0	0	0	1 (2.0)	0
Glaucoma	1 (0.2)	0	0	0	0	0
Halo Vision	2 (0.4)	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	0	1 (0.8)	0	0	0	0
Lacrimation Decreased	0	0	1 (0.2)	0	0	0
Lacrimation Increased	6 (1.3)	0	8 (1.9)	1 (0.9)	0	1 (11.1)
Mydriasis	0	1 (0.8)	0	2 (1.8)	0	0
Myopia	1 (0.2)	0	0	0	0	0
Ocular Discomfort	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Ocular Hyperaemia	3 (0.6)	2 (1.6)	3 (0.7)	0	1 (2.0)	1 (11.1)
Ophthalmoplegia	1 (0.2)	0	1 (0.2)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Orbital Oedema	0	0	0	1 (0.9)	0	0
Periorbital Oedema	3 (0.6)	0	1 (0.2)	0	0	0
Photophobia	5 (1.0)	1 (0.8)	5 (1.2)	2 (1.8)	0	0
Photopsia	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Punctate Keratitis	0	0	1 (0.2)	0	0	0
Pupils Unequal	0	1 (0.8)	0	1 (0.9)	0	0
Retinal Exudates	1 (0.2)	0	0	0	1 (2.0)	0
Retinal Haemorrhage	3 (0.6)	2 (1.6)	3 (0.7)	0	1 (2.0)	0
Retinal Oedema	1 (0.2)	0	0	0	0	0
Retinopathy Haemorrhagic	0	0	0	1 (0.9)	0	0
Scleral Discolouration	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Scleral Haemorrhage	1 (0.2)	0	0	1 (0.9)	0	0
Scleral Oedema	0	0	1 (0.2)	0	0	0
Vision Blurred	23 (4.8)	3 (2.4)	23 (5.4)	8 (7.2)	2 (4.1)	1 (11.1)
Visual Acuity Reduced	4 (0.8)	0	5 (1.2)	0	0	0
Visual Impairment	9 (1.9)	0	8 (1.9)	1 (0.9)	3 (6.1)	0
Vitreous Detachment	0	0	0	1 (0.9)	0	0
Vitreous Floaters	1 (0.2)	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Vitreous Haemorrhage	1 (0.2)	0	0	1 (0.9)	0	0
Gastrointestinal Disorders	**391 (81.6)**	**97 (77.0)**	**349 (81.5)**	**80 (72.1)**	**46 (93.9)**	**9 (100.0)**
Abdominal Compartment Syndrome	0	0	1 (0.2)	0	0	0
Abdominal Discomfort	21 (4.4)	5 (4.0)	8 (1.9)	0	1 (2.0)	1 (11.1)

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Number (%) of Subjects

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Abdominal Distension	32 (6.7)	8 (6.3)	32 (7.5)	12 (10.8)	2 (4.1)	2 (22.2)
Abdominal Hernia	1 (0.2)	0	0	0	0	0
Abdominal Mass	0	0	1 (0.2)	0	0	0
Abdominal Pain	83 (17.3)	30 (23.8)	93 (21.7)	19 (17.1)	13 (26.5)	2 (22.2)
Abdominal Pain Lower	10 (2.1)	1 (0.8)	7 (1.6)	0	0	0
Abdominal Pain Upper	37 (7.7)	7 (5.6)	33 (7.7)	10 (9.0)	12 (24.5)	2 (22.2)
Abdominal Rigidity	1 (0.2)	0	3 (0.7)	0	0	0
Abdominal Tenderness	9 (1.9)	1 (0.8)	10 (2.3)	1 (0.9)	2 (4.1)	0
Acute Abdomen	1 (0.2)	0	1 (0.2)	0	0	0
Anal Fissure	6 (1.3)	3 (2.4)	2 (0.5)	0	2 (4.1)	0
Anal Fistula	0	0	0	0	1 (2.0)	0
Anal Haemorrhage	1 (0.2)	0	0	0	2 (4.1)	0
Anal Incontinence	6 (1.3)	0	10 (2.3)	2 (1.8)	0	0
Anal Inflammation	0	0	1 (0.2)	0	0	0
Anal Pruritus	0	2 (1.6)	0	0	0	0
Anal Ulcer	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Anorectal Discomfort	3 (0.6)	0	1 (0.2)	0	0	0
Aphthous Ulcer	5 (1.0)	0	2 (0.5)	0	2 (4.1)	0
Aptyalism	2 (0.4)	0	0	0	0	0
Ascites	19 (4.0)	4 (3.2)	12 (2.8)	3 (2.7)	0	1 (11.1)
Breath Odour	1 (0.2)	0	0	0	0	0
Change Of Bowel Habit	1 (0.2)	0	0	0	0	0
Chapped Lips	3 (0.6)	0	4 (0.9)	0	1 (2.0)	1 (11.1)

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All Randomized Subjects
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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Cheilitis	2 (0.4)	0	1 (0.2)	0	0	0
Colitis	12 (2.5)	3 (2.4)	6 (1.4)	5 (4.5)	2 (4.1)	1 (11.1)
Colitis Ulcerative	1 (0.2)	1 (0.8)	0	0	0	0
Constipation	101 (21.1)	24 (19.0)	82 (19.2)	13 (11.7)	5 (10.2)	1 (11.1)
Crohn's Disease	1 (0.2)	0	0	0	0	0
Dental Alveolar Anomaly	0	0	1 (0.2)	0	0	0
Diarrhoea	197 (41.1)	54 (42.9)	178 (41.6)	35 (31.5)	31 (63.3)	5 (55.6)
Diarrhoea Haemorrhagic	3 (0.6)	1 (0.8)	6 (1.4)	2 (1.8)	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	29 (6.1)	3 (2.4)	24 (5.6)	3 (2.7)	2 (4.1)	0
Duodenal Perforation	1 (0.2)	0	0	0	0	0
Duodenitis	5 (1.0)	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Duodenitis Haemorrhagic	0	0	1 (0.2)	0	0	0
Dyschezia	1 (0.2)	2 (1.6)	0	0	0	0
Dyspepsia	37 (7.7)	14 (11 1)	37 (8.6)	13 (11.7)	4 (8.2)	1 (11.1)
Dysphagia	8 (1.7)	1 (0.8)	15 (3.5)	5 (4.5)	4 (8.2)	0
Enteritis	3 (0.6)	0	1 (0.2)	0	0	0
Enterocolitis	1 (0.2)	1 (0.8)	0	1 (0.9)	0	0
Epigastric Discomfort	2 (0.4)	2 (1.6)	2 (0.5)	1 (0.9)	0	0
Erosive Oesophagitis	1 (0.2)	0	0	0	0	0
Eructation	3 (0.6)	0	0	0	0	0
Faecal Volume Increased	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
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	0	1 (11.1)
Flatulence	15 (3.1)	3 (2.4)	24 (5.6)	4 (3.6)	2 (4.1)	0
Frequent Bowel Movements	0	1 (0.8)	1 (0.2)	0	0	0
Gastric Disorder	3 (0.6)	0	1 (0.2)	0	5 (10.2)	0
Gastric Haemorrhage	0	1 (0.8)	0	0	0	0
Gastric Ulcer	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Gastric Ulcer Haemorrhage	2 (0.4)	0	1 (0.2)	0	0	0
Gastric Varices	1 (0.2)	0	0	0	0	0
Gastritis	22 (4.6)	2 (1.6)	17 (4.0)	4 (3.6)	0	1 (11.1)
Gastritis Erosive	1 (0.2)	0	0	1 (0.9)	0	0
Gastritis Haemorrhagic	1 (0.2)	0	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	22 (4.6)	1 (0.8)	14 (3.3)	5 (4.5)	0	0
Gastrointestinal Hypomotility	1 (0.2)	0	0	0	0	0
Gastrointestinal Inflammation	0	0	1 (0.2)	0	1 (2.0)	0
Gastrointestinal Obstruction	1 (0.2)	0	0	0	0	0
Gastrointestinal Pain	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Gastrointestinal Sounds Abnormal	4 (0.8)	0	5 (1.2)	2 (1.8)	0	0
Gastrointestinal Ulcer Haemorrhage	2 (0.4)	0	0	0	0	0
Gastrooesophageal Reflux Disease	19 (4.0)	1 (0.8)	9 (2.1)	4 (3.6)	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Gingival Bleeding	15 (3.1)	10 (7.9)	6 (1.4)	5 (4.5)	1 (2.0)	0
Gingival Erosion	0	0	0	0	1 (2.0)	0
Gingival Hypertrophy	1 (0.2)	0	0	1 (0.9)	0	0
Gingival Pain	1 (0.2)	1 (0.8)	4 (0.9)	0	0	0
Gingival Swelling	2 (0.4)	0	1 (0.2)	0	0	0
Gingival Ulceration	1 (0.2)	0	0	0	1 (2.0)	0
Glossitis	0	0	1 (0.2)	0	0	0
Glossodynia	4 (0.8)	0	1 (0.2)	0	0	0
Haematemesis	10 (2.1)	4 (3 2)	5 (1.2)	3 (2.7)	0	0
Haematochezia	14 (2.9)	3 (2.4)	6 (1.4)	3 (2.7)	2 (4.1)	0
Haemorrhoidal Haemorrhage	8 (1.7)	1 (0.8)	4 (0.9)	0	0	0
Haemorrhoids	29 (6.1)	9 (7.1)	28 (6.5)	4 (3.6)	11 (22.4)	0
Haemorrhoids Thrombosed	1 (0.2)	0	0	0	0	0
Hiatus Hernia	2 (0.4)	1 (0.8)	1 (0.2)	2 (1.8)	0	0
Hyperchlorhydria	1 (0.2)	0	0	0	0	0
Hypoaesthesia Oral	2 (0.4)	1 (0.8)	0	1 (0.9)	0	0
Ileus	4 (0.8)	0	4 (0.9)	1 (0.9)	0	0
Ileus Paralytic	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Impaired Gastric Emptying	3 (0.6)	0	2 (0.5)	0	0	0
Inguinal Hernia	1 (0.2)	0	1 (0.2)	0	0	0
Intestinal Angioedema	0	0	0	1 (0.9)	0	0
Intestinal Haemorrhage	1 (0.2)	0	2 (0.5)	0	0	0
Intestinal Infarction	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Intestinal Ischaemia	1 (0.2)	0	0	0	0	0
Intestinal Mass	0	0	0	1 (0.9)	0	0
Intestinal Obstruction	3 (0.6)	0	1 (0.2)	1 (0.9)	0	0
Intestinal Ulcer	2 (0.4)	0	1 (0.2)	0	0	0
Intra-Abdominal Fluid Collection	1 (0.2)	0	0	1 (0.9)	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	1 (0.2)	1 (0.8)	4 (0.9)	0	0	0
Lip Blister	1 (0.2)	1 (0.8)	0	0	0	0
Lip Dry	3 (0.6)	0	8 (1.9)	2 (1.8)	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 (0.5)	0	1 (2.0)	0
Lip Pain	2 (0.4)	0	2 (0.5)	0	0	0
Lip Swelling	0	1 (0.8)	0	0	0	0
Lip Ulceration	3 (0.6)	1 (0.8)	2 (0.5)	0	0	0
Loose Tooth	0	0	1 (0.2)	1 (0.9)	0	0
Lower Gastrointestinal Haemorrhage	1 (0.2)	0	0	0	0	0
Malabsorption	1 (0.2)	0	0	0	0	0
Melaena	13 (2.7)	1 (0.8)	7 (1.6)	5 (4.5)	1 (2.0)	0
Mouth Haemorrhage	14 (2.9)	3 (2.4)	4 (0.9)	0	2 (4.1)	0
Mouth Ulceration	17 (3.5)	5 (4.0)	14 (3.3)	2 (1.8)	3 (6.1)	1 (11.1)
Mucous Stools	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Nausea	194 (40.5)	49 (38 9)	168 (39.3)	35 (31.5)	29 (59.2)	4 (44.4)
Neutropenic Colitis	6 (1.3)	0	0	1 (0.9)	0	2 (22.2)
Odynophagia	4 (0.8)	3 (2.4)	2 (0.5)	1 (0.9)	1 (2.0)	0
Oedema Mouth	0	0	1 (0.2)	0	0	0
Oesophageal Pain	0	0	2 (0.5)	0	1 (2.0)	0
Oesophageal Ulcer	2 (0.4)	0	0	0	0	0
Oesophagitis	10 (2.1)	1 (0.8)	5 (1.2)	1 (0.9)	0	0
Oesophagitis Ulcerative	1 (0.2)	0	0	0	0	0
Oral Discomfort	0	1 (0.8)	1 (0.2)	0	0	0
Oral Disorder	11 (2.3)	1 (0.8)	8 (1.9)	0	1 (2.0)	0
Oral Mucosal Blistering	4 (0.8)	1 (0.8)	0	1 (0.9)	2 (4.1)	0
Oral Mucosal Discolouration	0	0	1 (0.2)	0	0	0
Oral Mucosal Erythema	5 (1.0)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Oral Mucosal Exfoliation	1 (0.2)	0	0	1 (0.9)	0	0
Oral Mucosal Hypertrophy	0	0	1 (0.2)	0	0	0
Oral Pain	20 (4.2)	6 (4.8)	20 (4.7)	4 (3.6)	2 (4.1)	1 (11.1)
Palatal Disorder	0	0	1 (0.2)	0	0	0
Palatal Swelling	1 (0.2)	0	0	0	0	0
Pancreatitis	0	1 (0.8)	2 (0.5)	0	0	0
Pancreatitis Acute	1 (0.2)	0	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 (2.0)	0
Perianal Erythema	2 (0.4)	0	0	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Periodontal Disease	1 (0.2)	0	0	0	0	0
Pneumoperitoneum	1 (0.2)	0	0	0	0	0
Proctalgia	5 (1.0)	4 (3 2)	10 (2.3)	7 (6.3)	3 (6.1)	2 (22.2)
Proctitis	2 (0.4)	0	1 (0.2)	0	1 (2.0)	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	9 (1.9)	6 (4.8)	5 (1.2)	2 (1.8)	2 (4.1)	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)	0	0	0	0	0
Rectal Ulcer	0	0	1 (0.2)	0	0	0
Retching	6 (1.3)	0	4 (0.9)	1 (0.9)	0	0
Retroperitoneal Haemorrhage	2 (0.4)	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 (0.5)	0	1 (2.0)	0
Sensitivity Of Teeth	1 (0.2)	0	0	0	0	0
Small Intestinal Obstruction	2 (0.4)	0	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

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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Stomatitis	16 (3.3)	2 (1.6)	5 (1.2)	4 (3.6)	6 (12.2)	0
Subileus	1 (0.2)	0	0	0	0	0
Swollen Tongue	0	0	0	1 (0.9)	0	0
Tongue Blistering	1 (0.2)	0	0	0	0	0
Tongue Coated	7 (1.5)	3 (2.4)	4 (0.9)	0	0	0
Tongue Discolouration	2 (0.4)	1 (0.8)	2 (0.5)	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	0	2 (1.6)	1 (0.2)	0	0	0
Tongue Haematoma	2 (0.4)	0	0	0	1 (2.0)	0
Tongue Haemorrhage	1 (0.2)	0	0	0	0	0
Tongue Ulceration	2 (0.4)	2 (1.6)	8 (1.9)	1 (0.9)	3 (6.1)	0
Tooth Discolouration	1 (0.2)	0	0	0	0	0
Tooth Loss	0	0	2 (0.5)	0	0	0
Toothache	6 (1.3)	3 (2.4)	7 (1.6)	6 (5.4)	1 (2.0)	1 (11.1)
Trichoglossia	3 (0.6)	1 (0.8)	2 (0.5)	0	0	0
Umbilical Hernia	1 (0.2)	0	0	0	0	0
Upper Gastrointestinal Haemorrhage	3 (0.6)	1 (0.8)	0	0	0	0
Uvulitis	1 (0.2)	0	0	0	0	0
Vomiting	133 (27.8)	45 (35.7)	149 (34.8)	26 (23.4)	22 (44.9)	2 (22.2)
General Disorders And Administration Site Conditions	**370 (77.2)**	**96 (76 2)**	**337 (78.7)**	**76 (68.5)**	**46 (93.9)**	**9 (100.0)**
Adverse Drug Reaction	0	1 (0.8)	0	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Application Site Burn	1 (0.2)	0	0	0	0	0
Application Site Discomfort	1 (0.2)	0	0	0	0	0
Asthenia	51 (10.6)	9 (7.1)	47 (11.0)	13 (11.7)	2 (4.1)	1 (11.1)
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 (0.7)	0	0	0
Catheter Site Discharge	3 (0.6)	0	0	0	1 (2.0)	0
Catheter Site Erosion	0	0	1 (0.2)	0	0	0
Catheter Site Erythema	31 (6.5)	8 (6.3)	29 (6.8)	3 (2.7)	7 (14.3)	4 (44.4)
Catheter Site Haematoma	1 (0.2)	2 (1.6)	5 (1.2)	0	0	0
Catheter Site Haemorrhage	13 (2.7)	2 (1.6)	6 (1.4)	0	0	1 (11.1)
Catheter Site Inflammation	8 (1.7)	0	3 (0.7)	0	6 (12.2)	1 (11.1)
Catheter Site Oedema	0	0	1 (0.2)	1 (0.9)	0	0
Catheter Site Pain	27 (5.6)	6 (4.8)	27 (6.3)	6 (5.4)	2 (4.1)	1 (11.1)
Catheter Site Phlebitis	2 (0.4)	0	2 (0.5)	0	0	0
Catheter Site Pruritus	1 (0.2)	2 (1.6)	1 (0.2)	0	0	1 (11.1)
Catheter Site Rash	1 (0.2)	0	0	0	0	0
Catheter Site Related Reaction	4 (0.8)	0	4 (0.9)	1 (0.9)	0	0
Catheter Site Swelling	3 (0.6)	0	0	1 (0.9)	0	0
Chest Discomfort	5 (1.0)	3 (2.4)	4 (0.9)	2 (1.8)	1 (2.0)	2 (22.2)
Chest Pain	43 (9.0)	9 (7 1)	27 (6.3)	8 (7.2)	3 (6.1)	0
Chills	92 (19.2)	25 (19.8)	70 (16.4)	11 (9 9)	11 (22.4)	6 (66.7)
Complication Associated With Device	4 (0.8)	0	6 (1.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Crepitations	2 (0.4)	2 (1.6)	3 (0.7)	2 (1.8)	0	0
Death	0	0	1 (0.2)	0	0	0
Device Related Thrombosis	3 (0.6)	0	2 (0.5)	1 (0.9)	0	0
Disease Progression	4 (0.8)	0	5 (1.2)	0	0	0
Drug Interaction	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Drug Intolerance	1 (0.2)	0	2 (0.5)	0	0	0
Drug Withdrawal Syndrome	1 (0.2)	0	2 (0.5)	0	0	0
Early Satiety	0	0	2 (0.5)	1 (0.9)	0	0
Effusion	0	1 (0.8)	0	0	0	0
Exercise Tolerance Decreased	2 (0.4)	0	1 (0.2)	0	0	0
Face Oedema	6 (1.3)	0	6 (1.4)	2 (1.8)	0	0
Facial Pain	2 (0.4)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Fatigue	92 (19.2)	12 (9.5)	90 (21.0)	13 (11.7)	3 (6.1)	0
Feeling Cold	2 (0.4)	2 (1.6)	6 (1.4)	2 (1.8)	0	0
Feeling Hot	1 (0.2)	0	0	0	0	0
Feeling Jittery	4 (0.8)	0	1 (0.2)	1 (0.9)	0	0
Gait Disturbance	8 (1.7)	1 (0.8)	8 (1.9)	3 (2.7)	0	0
Gait Inability	0	0	0	1 (0.9)	0	0
General Physical Health Deterioration	3 (0.6)	0	0	1 (0.9)	0	0
General Symptom	0	1 (0.8)	0	0	0	0
Generalised Oedema	14 (2.9)	1 (0.8)	17 (4.0)	2 (1.8)	1 (2.0)	0
Granuloma	2 (0.4)	1 (0.8)	0	0	0	0
Gravitational Oedema	0	0	1 (0.2)	0	0	0

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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Hyperpyrexia	0	0	0	0	0	1 (11.1)
Hyperthermia	4 (0.8)	0	1 (0.2)	0	3 (6.1)	0
Hypothermia	0	2 (1.6)	4 (0.9)	0	0	0
Impaired Healing	1 (0.2)	0	1 (0.2)	0	0	0
Induration	2 (0.4)	0	1 (0.2)	0	0	0
Inflammation	2 (0.4)	0	0	0	0	0
Influenza Like Illness	2 (0.4)	0	2 (0.5)	0	0	0
Infusion Site Erythema	0	0	1 (0.2)	0	0	0
Infusion Site Extravasation	0	0	2 (0.5)	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
Infusion Site Pain	4 (0.8)	2 (1.6)	0	0	0	0
Infusion Site Swelling	0	0	0	1 (0.9)	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 (0.5)	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 (2.0)	0
Localised Oedema	2 (0.4)	0	2 (0.5)	0	1 (2.0)	0
Malaise	11 (2.3)	4 (3.2)	6 (1.4)	4 (3.6)	2 (4.1)	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Mass	1 (0.2)	1 (0.8)	0	0	0	0
Mucosa Vesicle	0	1 (0.8)	1 (0.2)	0	0	0
Mucosal Haemorrhage	1 (0.2)	0	2 (0.5)	0	0	0
Mucosal Hyperaemia	1 (0.2)	0	0	0	0	0
Mucosal Inflammation	74 (15.4)	25 (19.8)	55 (12.9)	10 (9.0)	12 (24.5)	2 (22.2)
Mucous Membrane Disorder	1 (0.2)	0	0	0	0	0
Multi-Organ Disorder	1 (0.2)	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	14 (2.9)	1 (0.8)	8 (1.9)	1 (0 9)	2 (4.1)	0
Necrosis	3 (0.6)	0	0	0	0	0
Nodule	1 (0.2)	1 (0.8)	3 (0.7)	0	0	0
Non-Cardiac Chest Pain	0	0	0	0	0	1 (11.1)
Obstruction	1 (0.2)	0	0	0	3 (6.1)	0
Oedema	35 (7.3)	4 (3 2)	42 (9.8)	6 (5.4)	4 (8.2)	0
Oedema Mucosal	0	0	0	1 (0.9)	0	0
Oedema Peripheral	84 (17.5)	12 (9.5)	71 (16.6)	8 (7 2)	8 (16.3)	4 (44.4)
Pain	31 (6.5)	11 (8.7)	22 (5.1)	4 (3.6)	3 (6.1)	2 (22.2)
Paradoxical Drug Reaction	0	0	1 (0.2)	0	0	0
Performance Status Decreased	2 (0.4)	0	0	0	0	0
Peripheral Swelling	12 (2.5)	4 (3.2)	11 (2.6)	1 (0.9)	1 (2.0)	0
Puncture Site Pain	2 (0.4)	1 (0.8)	0	0	0	0
Puncture Site Reaction	2 (0.4)	1 (0.8)	0	0	0	0
Pyrexia	207 (43.2)	59 (46.8)	204 (47.7)	47 (42.3)	28 (57.1)	3 (33.3)
Secretion Discharge	1 (0.2)	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Sudden Death	0	0	1 (0.2)	0	0	0
Swelling	1 (0.2)	0	1 (0.2)	0	0	0
Tenderness	2 (0.4)	0	0	0	0	0
Therapeutic Product Ineffective	0	0	0	1 (0.9)	0	0
Therapy Non-Responder	4 (0.8)	0	3 (0.7)	0	0	0
Thirst	3 (0.6)	2 (1.6)	0	4 (3.6)	0	0
Ulcer	2 (0.4)	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 (0.4)	0	2 (0.5)	0	0	0
Xerosis	1 (0.2)	0	0	0	0	0
Hepatobiliary Disorders	**84 (17.5)**	**12 (9.5)**	**66 (15.4)**	**11 (9 9)**	**9 (18.4)**	**3 (33.3)**
Acute Hepatic Failure	1 (0.2)	0	0	0	0	0
Cholecystitis	1 (0.2)	0	2 (0.5)	0	1 (2.0)	0
Cholecystitis Acute	0	0	0	0	1 (2.0)	0
Cholelithiasis	6 (1.3)	1 (0.8)	6 (1.4)	1 (0.9)	1 (2.0)	1 (11.1)
Cholestasis	4 (0.8)	1 (0.8)	2 (0.5)	0	0	0
Drug-Induced Liver Injury	0	0	1 (0.2)	0	0	0
Gallbladder Enlargement	0	0	1 (0.2)	0	0	0
Gallbladder Polyp	2 (0.4)	0	0	0	0	0
Hepatic Cyst	2 (0.4)	0	2 (0.5)	0	0	0
Hepatic Failure	7 (1.5)	1 (0.8)	3 (0.7)	1 (0.9)	0	0

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Hepatic Function Abnormal	3 (0.6)	0	6 (1.4)	2 (1.8)	0	0
Hepatic Lesion	4 (0.8)	0	0	0	0	0
Hepatic Necrosis	1 (0.2)	0	0	0	0	0
Hepatic Steatosis	1 (0.2)	0	2 (0.5)	0	0	0
Hepatitis	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Hepatitis Acute	1 (0.2)	0	0	0	0	0
Hepatocellular Injury	2 (0.4)	1 (0.8)	0	0	0	0
Hepatomegaly	9 (1.9)	1 (0.8)	5 (1.2)	0	1 (2.0)	0
Hepatosplenomegaly	3 (0.6)	0	3 (0.7)	0	0	0
Hepatotoxicity	4 (0.8)	0	4 (0.9)	0	0	0
Hyperbilirubinaemia	23 (4.8)	5 (4.0)	21 (4.9)	5 (4.5)	6 (12.2)	2 (22.2)
Hypertransaminasaemia	1 (0.2)	0	1 (0.2)	0	0	0
Jaundice	25 (5.2)	2 (1.6)	20 (4.7)	4 (3.6)	1 (2.0)	0
Jaundice Cholestatic	1 (0.2)	0	0	0	0	0
Liver Disorder	0	1 (0.8)	2 (0.5)	0	0	0
Liver Injury	2 (0.4)	0	0	0	0	0
Ocular Icterus	9 (1.9)	2 (1.6)	3 (0.7)	0	0	0
Perihepatic Discomfort	1 (0.2)	0	0	0	0	0
Portal Hypertension	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Portal Vein Thrombosis	0	1 (0.8)	1 (0.2)	0	0	0
Venoocclusive Liver Disease	0	0	1 (0.2)	0	0	0
Immune System Disorders	**99 (20.7)**	**12 (9.5)**	**91 (21.3)**	**20 (18.0)**	**3 (6.1)**	**0**

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Acute Graft Versus Host Disease In Liver	0	0	0	1 (0.9)	0	0
Acute Graft Versus Host Disease In Skin	0	0	1 (0.2)	0	0	0
Anaphylactic Reaction	1 (0.2)	0	2 (0.5)	0	0	0
Chronic Graft Versus Host Disease	2 (0.4)	0	0	1 (0.9)	0	0
Contrast Media Allergy	1 (0.2)	0	0	0	0	0
Drug Hypersensitivity	11 (2.3)	3 (2.4)	5 (1.2)	2 (1.8)	3 (6.1)	0
Graft Versus Host Disease	55 (11.5)	6 (4.8)	42 (9.8)	13 (11.7)	0	0
Graft Versus Host Disease In Gastrointestinal Tract	24 (5.0)	3 (2.4)	19 (4.4)	2 (1.8)	0	0
Graft Versus Host Disease In Liver	10 (2.1)	4 (3.2)	9 (2.1)	1 (0.9)	0	0
Graft Versus Host Disease In Lung	0	0	4 (0.9)	1 (0.9)	0	0
Graft Versus Host Disease In Skin	23 (4.8)	2 (1.6)	25 (5.8)	2 (1.8)	0	0
Hypersensitivity	1 (0.2)	0	4 (0.9)	1 (0.9)	0	0
Hypogammaglobulinaemia	3 (0.6)	0	2 (0.5)	1 (0.9)	0	0
Immune System Disorder	0	0	1 (0.2)	0	0	0
Sarcoidosis	1 (0.2)	0	0	0	0	0
Seasonal Allergy	2 (0.4)	0	2 (0.5)	0	0	0
Transplant Rejection	3 (0.6)	0	0	0	0	0
Infections And Infestations	**351 (73.3)**	**86 (68 3)**	**336 (78.5)**	**78 (70.3)**	**43 (87.8)**	**8 (88.9)**
Abscess Fungal	0	0	1 (0.2)	0	0	0
Abscess Jaw	0	0	1 (0.2)	0	0	0
Abscess Limb	0	1 (0.8)	1 (0.2)	2 (1.8)	0	0
Abscess Neck	1 (0.2)	0	0	1 (0.9)	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Acarodermatitis	0	1 (0.8)	0	1 (0.9)	0	0
Acid Fast Bacilli Infection	1 (0.2)	0	0	0	0	0
Acinetobacter Bacteraemia	0	0	1 (0.2)	0	0	0
Acinetobacter Infection	0	0	3 (0.7)	1 (0.9)	0	0
Acute Sinusitis	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Adenovirus Infection	0	0	2 (0.5)	1 (0.9)	0	0
Alpha Haemolytic Streptococcal Infection	1 (0.2)	0	4 (0.9)	1 (0.9)	0	0
Amoebic Dysentery	0	1 (0.8)	0	0	0	0
Anal Abscess	4 (0.8)	1 (0.8)	3 (0.7)	2 (1.8)	0	0
Anal Infection	0	0	0	1 (0.9)	0	0
Angular Cheilitis	0	0	1 (0.2)	0	0	0
Anorectal Cellulitis	0	0	1 (0.2)	0	0	0
Anorectal Infection	0	1 (0.8)	0	0	1 (2.0)	0
Aspergilloma	0	0	1 (0.2)	0	0	0
Aspergillus Infection	4 (0.8)	1 (0.8)	12 (2.8)	2 (1.8)	1 (2.0)	0
Atypical Pneumonia	1 (0.2)	0	0	0	0	0
Bacillus Bacteraemia	1 (0.2)	0	0	0	0	0
Bacillus Infection	0	1 (0.8)	0	0	0	0
Bacteraemia	45 (9.4)	11 (8.7)	39 (9.1)	6 (5.4)	8 (16.3)	0
Bacterial Disease Carrier	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Bacterial Infection	14 (2.9)	0	12 (2.8)	0	1 (2.0)	0
Bacterial Sepsis	4 (0.8)	1 (0.8)	4 (0.9)	1 (0.9)	0	1 (11.1)
Bacteriuria	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Bartholin's Abscess	0	1 (0.8)	0	0	0	0
Bartholinitis	1 (0.2)	0	0	0	0	0
Bk Virus Infection	1 (0.2)	0	0	0	0	0
Body Tinea	0	0	2 (0.5)	0	0	0
Bronchiolitis	3 (0.6)	1 (0.8)	0	0	0	0
Bronchitis	12 (2.5)	2 (1.6)	8 (1.9)	2 (1.8)	0	0
Bronchopulmonary Aspergillosis	3 (0.6)	0	8 (1.9)	1 (0.9)	1 (2.0)	1 (11.1)
Campylobacter Infection	1 (0.2)	0	0	0	0	0
Candida Infection	7 (1.5)	2 (1.6)	7 (1.6)	2 (1.8)	1 (2.0)	0
Candida Sepsis	1 (0.2)	0	0	0	0	0
Catheter Site Cellulitis	4 (0.8)	0	3 (0.7)	0	1 (2.0)	0
Catheter Site Infection	7 (1.5)	3 (2.4)	7 (1.6)	2 (1.8)	1 (2.0)	0
Cavernous Sinus Thrombosis	0	0	1 (0.2)	0	0	0
Cellulitis	8 (1.7)	7 (5.6)	14 (3.3)	3 (2.7)	1 (2.0)	0
Cellulitis Staphylococcal	1 (0.2)	0	0	0	0	0
Cerebral Fungal Infection	0	0	0	1 (0.9)	0	0
Cerebral Toxoplasmosis	1 (0.2)	0	2 (0.5)	0	0	0
Chlamydial Infection	0	0	1 (0.2)	0	0	0
Chronic Sinusitis	1 (0.2)	0	1 (0.2)	0	0	0
Citrobacter Infection	1 (0.2)	0	0	0	0	0
Clostridial Infection	5 (1.0)	0	0	0	0	0
Clostridium Bacteraemia	0	0	1 (0.2)	0	0	0
Clostridium Colitis	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Clostridium Difficile Colitis	7 (1.5)	1 (0.8)	7 (1.6)	3 (2.7)	1 (2.0)	0
Clostridium Difficile Infection	8 (1.7)	1 (0.8)	6 (1.4)	1 (0.9)	1 (2.0)	0
Conjunctivitis	16 (3.3)	7 (5.6)	16 (3.7)	6 (5.4)	0	0
Corynebacterium Bacteraemia	1 (0.2)	0	3 (0.7)	0	0	0
Corynebacterium Infection	0	0	3 (0.7)	0	0	0
Corynebacterium Sepsis	2 (0.4)	0	0	0	1 (2.0)	0
Cystitis	8 (1.7)	2 (1.6)	3 (0.7)	1 (0.9)	0	0
Cystitis Escherichia	0	0	1 (0.2)	0	0	0
Cystitis Klebsiella	1 (0.2)	0	0	0	0	0
Cytomegalovirus Colitis	4 (0.8)	1 (0.8)	2 (0.5)	0	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)	0	0	0
Cytomegalovirus Gastroenteritis	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Cytomegalovirus Hepatitis	0	0	0	2 (1.8)	0	0
Cytomegalovirus Infection	35 (7.3)	5 (4.0)	28 (6.5)	1 (0.9)	0	0
Cytomegalovirus Viraemia	10 (2.1)	2 (1.6)	7 (1.6)	0	0	0
Device Related Infection	23 (4.8)	6 (4.8)	26 (6.1)	7 (6 3)	3 (6.1)	0
Device Related Sepsis	3 (0.6)	1 (0.8)	3 (0.7)	0	1 (2.0)	0
Ear Infection	4 (0.8)	0	1 (0.2)	0	0	0
Emphysematous Cystitis	1 (0.2)	0	0	0	0	0
Encephalitis	2 (0.4)	0	1 (0.2)	0	0	0
Encephalitis Viral	0	0	1 (0.2)	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Enterobacter Bacteraemia	2 (0.4)	2 (1.6)	1 (0.2)	0	0	0
Enterobacter Infection	3 (0.6)	1 (0.8)	3 (0.7)	0	0	0
Enterobacter Sepsis	2 (0.4)	0	0	1 (0.9)	0	0
Enterococcal Bacteraemia	7 (1.5)	1 (0.8)	2 (0.5)	1 (0.9)	1 (2.0)	2 (22.2)
Enterococcal Infection	2 (0.4)	1 (0.8)	8 (1.9)	2 (1.8)	0	0
Enterococcal Sepsis	0	0	2 (0.5)	0	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 (0.8)	0	4 (0.9)	0	0	0
Erysipelas	0	0	1 (0.2)	0	1 (2.0)	0
Escherichia Bacteraemia	6 (1.3)	5 (4.0)	5 (1.2)	0	0	0
Escherichia Infection	1 (0.2)	1 (0.8)	2 (0.5)	0	0	1 (11.1)
Escherichia Sepsis	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Escherichia Urinary Tract Infection	2 (0.4)	1 (0.8)	2 (0.5)	0	0	0
Eye Infection	1 (0.2)	1 (0.8)	0	0	1 (2.0)	0
Eye Infection Staphylococcal	0	0	1 (0.2)	0	0	0
Eyelid Infection	0	0	0	1 (0.9)	0	0
Febrile Infection	0	0	1 (0.2)	0	0	0
Folliculitis	9 (1.9)	2 (1.6)	11 (2.6)	2 (1.8)	3 (6.1)	0
Fungaemia	0	0	1 (0.2)	0	0	0
Fungal Infection	12 (2.5)	1 (0.8)	16 (3.7)	1 (0.9)	3 (6.1)	0
Fungal Oesophagitis	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Fungal Rhinitis	0	0	1 (0.2)	0	0	0
Fungal Sepsis	1 (0.2)	0	1 (0.2)	0	0	0
Fungal Skin Infection	2 (0.4)	0	2 (0.5)	0	0	0
Furuncle	0	0	1 (0.2)	0	0	0
Fusobacterium Infection	1 (0.2)	0	1 (0.2)	0	0	0
Gangrene	0	0	2 (0.5)	0	0	0
Gastroenteritis	2 (0.4)	0	1 (0.2)	1 (0.9)	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)	0	0	0
Gastroenteritis Viral	1 (0.2)	0	2 (0.5)	0	0	0
Gastrointestinal Candidiasis	0	0	0	1 (0.9)	0	0
Gastrointestinal Infection	0	1 (0.8)	0	0	0	0
Genital Herpes	4 (0.8)	1 (0.8)	0	1 (0.9)	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	0	1 (0.8)	0	0	0	0
Gingivitis	3 (0.6)	1 (0.8)	6 (1.4)	0	1 (2.0)	0
Haemophilus Infection	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0
Hepatitis B	1 (0.2)	0	0	0	0	0
Herpes Dermatitis	0	1 (0.8)	1 (0.2)	0	0	0
Herpes Oesophagitis	0	0	0	1 (0.9)	1 (2.0)	0
Herpes Pharyngitis	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Herpes Simplex	13 (2.7)	1 (0.8)	15 (3.5)	1 (0.9)	0	0
Herpes Virus Infection	14 (2.9)	2 (1.6)	4 (0.9)	4 (3.6)	3 (6.1)	0
Herpes Zoster	16 (3.3)	5 (4.0)	8 (1.9)	2 (1.8)	1 (2.0)	0
Herpes Zoster Disseminated	0	1 (0.8)	1 (0.2)	0	0	0
Hookworm Infection	0	0	0	1 (0.9)	0	0
Hordeolum	0	0	0	1 (0.9)	0	0
Human Herpesvirus 6 Infection	1 (0.2)	0	2 (0.5)	0	0	0
Impetigo	0	0	0	1 (0.9)	0	0
Infected Skin Ulcer	0	1 (0.8)	0	0	0	0
Infection	7 (1.5)	1 (0.8)	3 (0.7)	0	1 (2.0)	0
Infectious Disease Carrier	1 (0.2)	0	2 (0.5)	0	0	0
Influenza	2 (0.4)	3 (2.4)	3 (0.7)	1 (0.9)	0	0
Infusion Site Infection	0	0	1 (0.2)	0	0	0
Klebsiella Bacteraemia	0	4 (3 2)	4 (0.9)	2 (1.8)	0	1 (11.1)
Klebsiella Infection	1 (0.2)	1 (0.8)	6 (1.4)	0	0	0
Klebsiella Sepsis	1 (0.2)	0	0	0	0	0
Lactobacillus Infection	0	0	1 (0.2)	0	0	0
Laryngitis	3 (0.6)	0	1 (0.2)	0	0	0
Leptotrichia Infection	0	0	0	1 (0.9)	0	0
Lip Infection	0	0	1 (0.2)	0	0	0
Liver Abscess	0	0	1 (0.2)	0	0	0
Localised Infection	3 (0.6)	0	4 (0.9)	0	0	0
Lower Respiratory Tract Infection	10 (2.1)	0	6 (1.4)	1 (0.9)	0	0

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Lower Respiratory Tract Infection Fungal	0	0	0	1 (0.9)	0	0
Lung Abscess	1 (0.2)	0	0	0	0	0
Lung Infection	0	0	0	0	1 (2.0)	0
Lymphangitis	1 (0.2)	0	1 (0.2)	0	0	0
Mastitis	1 (0.2)	0	0	0	0	0
Mastoiditis	2 (0.4)	2 (1.6)	0	1 (0.9)	0	0
Meningitis Listeria	0	0	1 (0.2)	0	0	0
Meningococcal Infection	0	0	1 (0.2)	0	0	0
Micrococcus Infection	1 (0.2)	0	1 (0.2)	0	0	0
Mycobacterial Infection	0	0	1 (0.2)	0	0	0
Mycobacterium Avium Complex Infection	0	0	1 (0.2)	0	0	0
Myelitis	1 (0.2)	0	0	0	0	0
Nail Infection	1 (0.2)	0	0	0	0	0
Nasopharyngitis	11 (2.3)	3 (2.4)	14 (3.3)	4 (3.6)	3 (6.1)	0
Neisseria Infection	0	0	1 (0.2)	0	0	0
Neutropenic Sepsis	2 (0.4)	4 (3.2)	1 (0.2)	0	2 (4.1)	3 (33.3)
Nocardia Sepsis	0	0	1 (0.2)	0	0	0
Nocardiosis	0	1 (0.8)	1 (0.2)	0	0	0
Oesophageal Candidiasis	0	0	1 (0.2)	1 (0.9)	0	0
Onychomycosis	1 (0.2)	0	0	0	1 (2.0)	0
Ophthalmic Herpes Simplex	0	0	1 (0.2)	0	0	0
Oral Candidiasis	14 (2.9)	3 (2.4)	15 (3.5)	3 (2.7)	2 (4.1)	0
Oral Fungal Infection	0	0	0	0	1 (2.0)	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Oral Herpes	44 (9.2)	12 (9.5)	29 (6.8)	4 (3.6)	8 (16.3)	0
Oral Infection	0	0	1 (0.2)	0	1 (2.0)	0
Oropharyngeal Candidiasis	0	0	3 (0.7)	0	1 (2.0)	0
Osteomyelitis	0	0	1 (0.2)	0	0	0
Otitis Externa	0	0	2 (0.5)	0	0	0
Otitis Media	2 (0.4)	0	4 (0.9)	0	0	0
Parainfluenzae Virus Infection	1 (0.2)	0	3 (0.7)	1 (0.9)	0	0
Paronychia	1 (0.2)	0	1 (0.2)	0	0	0
Parotitis	0	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Pericoronitis	0	1 (0.8)	0	0	0	0
Perineal Abscess	1 (0.2)	0	0	0	0	0
Periodontitis	1 (0.2)	1 (0.8)	0	1 (0.9)	0	1 (11.1)
Periorbital Cellulitis	0	0	0	0	1 (2.0)	0
Perirectal Abscess	0	2 (1.6)	1 (0.2)	0	0	0
Peritonitis	0	0	1 (0.2)	0	0	0
Peritonitis Bacterial	0	0	1 (0.2)	0	0	0
Pharyngitis	5 (1.0)	5 (4.0)	7 (1.6)	1 (0.9)	1 (2.0)	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 (2.0)	0
Pneumocystis Jirovecii Infection	1 (0.2)	0	1 (0.2)	0	0	0
Pneumocystis Jirovecii Pneumonia	0	2 (1.6)	2 (0.5)	0	1 (2.0)	0
Pneumonia	44 (9.2)	11 (8.7)	45 (10.5)	8 (7 2)	4 (8.2)	3 (33.3)

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Pneumonia Bacterial	4 (0.8)	3 (2.4)	0	0	0	0
Pneumonia Cytomegaloviral	3 (0.6)	3 (2.4)	0	0	0	0
Pneumonia Fungal	3 (0.6)	1 (0.8)	5 (1.2)	1 (0.9)	1 (2.0)	0
Pneumonia Klebsiella	4 (0.8)	0	5 (1.2)	0	0	0
Pneumonia Necrotising	0	0	1 (0.2)	0	0	0
Pneumonia Pseudomonal	1 (0.2)	0	2 (0.5)	0	0	0
Pneumonia Staphylococcal	2 (0.4)	0	2 (0.5)	0	0	0
Pneumonia Streptococcal	0	0	1 (0.2)	0	0	0
Pneumonia Viral	0	1 (0.8)	0	0	0	0
Polyomavirus-Associated Nephropathy	1 (0.2)	0	2 (0.5)	0	0	0
Progressive Multifocal Leukoencephalopathy	0	0	1 (0.2)	0	0	0
Pseudomembranous Colitis	2 (0.4)	0	0	0	1 (2.0)	0
Pseudomonal Bacteraemia	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Pseudomonal Sepsis	3 (0.6)	0	1 (0.2)	1 (0.9)	0	0
Pseudomonas Infection	8 (1.7)	1 (0.8)	5 (1.2)	1 (0.9)	0	0
Pulmonary Mycosis	2 (0.4)	1 (0.8)	5 (1.2)	0	0	0
Pulmonary Tuberculosis	0	1 (0.8)	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 (0.4)	0	3 (0.7)	0	0	0
Relapsing Fever	0	0	1 (0.2)	0	0	0
Respiratory Moniliasis	0	0	1 (0.2)	0	0	0

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Respiratory Syncytial Virus Infection	5 (1.0)	1 (0.8)	2 (0.5)	2 (1.8)	0	0
Respiratory Tract Infection	2 (0.4)	0	1 (0.2)	0	0	0
Rhinitis	9 (1.9)	1 (0.8)	8 (1.9)	2 (1.8)	1 (2.0)	0
Rhinovirus Infection	0	0	0	0	0	1 (11.1)
Rotavirus Infection	3 (0.6)	0	2 (0.5)	0	0	0
Salmonellosis	1 (0.2)	0	0	0	0	0
Scedosporium Infection	0	0	1 (0.2)	0	0	0
Sepsis	17 (3.5)	2 (1.6)	20 (4.7)	3 (2.7)	2 (4.1)	1 (11.1)
Sepsis Syndrome	1 (0.2)	0	0	0	0	0
Septic Embolus	0	1 (0.8)	0	0	0	0
Septic Rash	1 (0.2)	0	0	0	0	0
Septic Shock	13 (2.7)	3 (2.4)	10 (2.3)	6 (5.4)	5 (10.2)	1 (11.1)
Serratia Infection	3 (0.6)	0	0	0	0	0
Sialoadenitis	1 (0.2)	0	0	0	0	0
Sinusitis	19 (4.0)	5 (4.0)	18 (4.2)	7 (6.3)	1 (2.0)	1 (11.1)
Sinusitis Bacterial	1 (0.2)	1 (0.8)	0	0	0	0
Sinusitis Fungal	0	0	0	0	1 (2.0)	0
Skin Bacterial Infection	1 (0.2)	0	1 (0.2)	0	0	0
Skin Candida	0	0	0	1 (0.9)	0	0
Skin Infection	0	0	4 (0.9)	0	0	0
Soft Tissue Infection	0	0	0	0	1 (2.0)	0
Sputum Purulent	0	0	1 (0.2)	0	0	0
Staphylococcal Abscess	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Staphylococcal Bacteraemia	22 (4.6)	3 (2.4)	27 (6.3)	1 (0 9)	3 (6.1)	0
Staphylococcal Infection	21 (4.4)	5 (4.0)	18 (4.2)	2 (1.8)	1 (2.0)	1 (11.1)
Staphylococcal Sepsis	5 (1.0)	2 (1.6)	4 (0.9)	1 (0.9)	0	1 (11.1)
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	5 (1.0)	1 (0.8)	9 (2.1)	2 (1.8)	1 (2.0)	0
Streptococcal Infection	4 (0.8)	0	4 (0.9)	1 (0.9)	0	0
Streptococcal Sepsis	3 (0.6)	0	1 (0.2)	0	0	0
Strongyloidiasis	0	0	0	1 (0.9)	0	0
Subcutaneous Abscess	2 (0.4)	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Superinfection	1 (0.2)	0	0	0	0	0
Systemic Candida	4 (0.8)	1 (0.8)	2 (0.5)	0	0	0
Systemic Mycosis	0	1 (0.8)	2 (0.5)	2 (1.8)	1 (2.0)	0
Tinea Infection	0	0	1 (0.2)	0	0	0
Tonsillitis	0	0	2 (0.5)	1 (0.9)	2 (4.1)	0
Tooth Abscess	4 (0.8)	0	1 (0.2)	0	1 (2.0)	0
Tooth Infection	1 (0.2)	1 (0.8)	0	1 (0.9)	0	0
Toxoplasmosis	0	0	1 (0.2)	0	0	0
Tracheobronchitis	3 (0.6)	2 (1.6)	2 (0.5)	2 (1.8)	0	0
Tracheobronchitis Viral	0	0	1 (0.2)	0	0	0
Trichomoniasis	0	1 (0.8)	0	0	0	0
Tuberculosis	0	0	1 (0.2)	0	0	0
Upper Respiratory Tract Infection	25 (5.2)	4 (3.2)	30 (7.0)	5 (4.5)	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Urethritis	0	0	1 (0.2)	0	0	0
Urinary Tract Infection	18 (3.8)	7 (5.6)	20 (4.7)	6 (5.4)	4 (8.2)	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)	0	1 (0.2)	0	0	0
Urinary Tract Infection Staphylococcal	1 (0.2)	0	0	0	0	0
Urinary Tract Infection Viral	0	0	0	1 (0.9)	0	0
Varicella	1 (0.2)	0	0	0	0	0
Varicella Zoster Pneumonia	1 (0.2)	0	0	0	0	0
Varicella Zoster Virus Infection	2 (0.4)	1 (0.8)	0	0	0	0
Viral Haemorrhagic Cystitis	1 (0.2)	0	1 (0.2)	0	0	0
Viral Infection	2 (0.4)	0	4 (0.9)	1 (0.9)	0	0
Vulval Abscess	0	0	1 (0.2)	0	0	0
Vulvitis	1 (0.2)	0	0	0	1 (2.0)	0
Vulvovaginal Candidiasis	0	0	4 (0.9)	0	0	0
Vulvovaginal Mycotic Infection	0	1 (0.8)	0	0	0	0
Vulvovaginitis	1 (0.2)	0	0	0	0	0
Wound Infection	0	0	0	0	1 (2.0)	0
Injury, Poisoning And Procedural Complications	**114 (23.8)**	**24 (19.0)**	**106 (24.8)**	**17 (15.3)**	**19 (38.8)**	**2 (22.2)**
Accidental Overdose	0	0	1 (0.2)	0	0	0
Allergic Transfusion Reaction	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Anal Injury	2 (0.4)	0	0	0	0	0

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Animal Bite	0	0	0	0	1 (2.0)	0
Arthropod Bite	1 (0.2)	0	0	0	0	0
Back Injury	1 (0.2)	0	0	0	0	0
Brain Herniation	0	0	0	0	1 (2.0)	0
Chemical Eye Injury	0	0	1 (0.2)	0	0	0
Complications Of Transplant Surgery	1 (0.2)	0	0	0	0	0
Compression Fracture	1 (0.2)	0	0	0	0	0
Contusion	14 (2.9)	2 (1.6)	16 (3.7)	2 (1.8)	1 (2.0)	0
Eschar	2 (0.4)	0	2 (0.5)	0	0	0
Excoriation	3 (0.6)	0	2 (0.5)	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	19 (4.0)	1 (0.8)	16 (3.7)	3 (2.7)	4 (8.2)	1 (11.1)
Femoral Neck Fracture	1 (0.2)	0	1 (0.2)	0	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	0	1 (0.8)	0	0	0	0
Head Injury	1 (0.2)	0	2 (0.5)	0	0	0
Hip Fracture	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Incision Site Erythema	0	0	0	0	1 (2.0)	0
Incision Site Haemorrhage	1 (0.2)	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Incision Site Pain	2 (0.4)	0	1 (0.2)	0	0	0
Inflammation Of Wound	1 (0.2)	0	1 (0.2)	0	1 (2.0)	0
Infusion Related Reaction	4 (0.8)	3 (2.4)	10 (2.3)	1 (0.9)	0	0
Injury	0	0	1 (0.2)	0	0	0
Injury Corneal	0	0	1 (0.2)	0	0	0
Joint Injury	0	1 (0.8)	1 (0.2)	0	0	0
Keratorhexis	0	0	0	1 (0.9)	0	0
Laceration	9 (1.9)	0	8 (1.9)	0	0	0
Ligament Sprain	1 (0.2)	0	0	1 (0.9)	0	0
Lip Injury	1 (0.2)	0	0	0	0	0
Lumbar Vertebral Fracture	1 (0.2)	0	0	0	0	0
Mouth Injury	2 (0.4)	0	1 (0.2)	0	0	0
Muscle Rupture	0	0	1 (0.2)	0	0	0
Muscle Strain	2 (0.4)	0	1 (0.2)	0	0	0
Overdose	0	0	1 (0.2)	0	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	1 (0.2)	1 (0.8)	0	0	0	0
Post Procedural Complication	2 (0.4)	0	0	0	1 (2.0)	0
Post Procedural Discomfort	0	0	1 (0.2)	0	0	0
Post Procedural Haematoma	1 (0.2)	0	3 (0.7)	1 (0.9)	0	0
Post Procedural Haemorrhage	3 (0.6)	0	6 (1.4)	0	0	0
Post Procedural Oedema	0	1 (0.8)	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Post-Traumatic Pain	1 (0.2)	0	0	0	0	0
Postoperative Fever	1 (0.2)	0	2 (0.5)	0	0	0
Procedural Hypertension	0	1 (0.8)	0	0	0	0
Procedural Pain	13 (2.7)	5 (4.0)	13 (3.0)	3 (2.7)	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 (0.5)	0	0	0
Sedation Complication	1 (0.2)	0	0	0	0	0
Skin Abrasion	5 (1.0)	0	4 (0.9)	0	0	0
Skin Injury	2 (0.4)	0	0	0	0	0
Spinal Fracture	0	1 (0.8)	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	0	2 (1.6)	0	0	1 (2.0)	0
Subcutaneous Haematoma	0	0	0	0	1 (2.0)	0
Subdural Haematoma	2 (0.4)	0	3 (0.7)	0	0	0
Thermal Burn	1 (0.2)	0	2 (0.5)	0	0	0
Tooth Fracture	1 (0.2)	0	1 (0.2)	0	0	1 (11.1)
Toxicity To Various Agents	8 (1.7)	0	5 (1.2)	2 (1.8)	0	0
Transfusion Reaction	28 (5.8)	6 (4.8)	18 (4.2)	3 (2.7)	10 (20.4)	0
Transplant Failure	1 (0.2)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Traumatic Haematoma	1 (0.2)	0	1 (0.2)	0	0	0
Vaginal Laceration	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Vascular Injury	0	0	1 (0.2)	0	0	0
Wound	3 (0.6)	0	10 (2.3)	0	0	0
Wound Complication	2 (0.4)	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	**265 (55.3)**	**63 (50.0)**	**226 (52.8)**	**61 (55.0)**	**26 (53.1)**	**7 (77.8)**
Activated Partial Thromboplastin Time Prolonged	0	0	1 (0.2)	2 (1.8)	0	0
Activated Partial Thromboplastin Time Shortened	0	0	1 (0.2)	0	0	0
Alanine Aminotransferase Abnormal	1 (0.2)	0	2 (0.5)	0	0	0
Alanine Aminotransferase Decreased	1 (0.2)	0	0	0	0	0
Alanine Aminotransferase Increased	28 (5.8)	9 (7.1)	15 (3.5)	11 (9 9)	3 (6.1)	0
Ammonia Increased	1 (0.2)	0	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	16 (3.3)	3 (2.4)	11 (2.6)	6 (5.4)	3 (6.1)	0
Aspergillus Test Positive	0	0	2 (0.5)	0	0	0
Aspiration Bronchial	0	1 (0.8)	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	10 (2.1)	2 (1.6)	16 (3.7)	2 (1.8)	0	0

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Basophil Count Increased	1 (0.2)	0	0	0	0	0
Bilirubin Conjugated Increased	1 (0.2)	0	1 (0.2)	0	0	0
Blast Cells Present	1 (0.2)	0	0	0	0	0
Bleeding Time Prolonged	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Blood Albumin Abnormal	1 (0.2)	0	0	0	0	0
Blood Albumin Decreased	6 (1.3)	0	5 (1.2)	1 (0.9)	1 (2.0)	0
Blood Albumin Increased	0	0	2 (0.5)	0	0	0
Blood Alkaline Phosphatase Decreased	0	0	0	0	1 (2.0)	0
Blood Alkaline Phosphatase Increased	13 (2.7)	3 (2.4)	14 (3.3)	5 (4.5)	0	1 (11.1)
Blood Bicarbonate Decreased	1 (0.2)	2 (1.6)	4 (0.9)	1 (0.9)	1 (2.0)	0
Blood Bilirubin Abnormal	0	1 (0.8)	0	0	0	0
Blood Bilirubin Increased	24 (5.0)	5 (4.0)	20 (4.7)	6 (5.4)	4 (8.2)	0
Blood Calcium Decreased	2 (0.4)	0	6 (1.4)	1 (0.9)	0	0
Blood Chloride Increased	0	1 (0.8)	0	0	0	0
Blood Cholesterol Increased	2 (0.4)	3 (2.4)	1 (0.2)	0	0	0
Blood Creatine Decreased	0	0	0	1 (0.9)	0	0
Blood Creatine Increased	2 (0.4)	0	0	0	0	0
Blood Creatine Phosphokinase Increased	1 (0.2)	0	0	0	0	0
Blood Creatinine Decreased	0	0	0	1 (0.9)	0	0
Blood Creatinine Increased	31 (6.5)	3 (2.4)	39 (9.1)	9 (8 1)	2 (4.1)	0
Blood Culture Positive	14 (2.9)	3 (2.4)	7 (1.6)	2 (1.8)	1 (2.0)	0
Blood Electrolytes Abnormal	0	0	1 (0.2)	0	0	0
Blood Gastrin Increased	0	0	1 (0.2)	0	0	0

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Blood Glucose Increased	3 (0.6)	2 (1.6)	4 (0.9)	2 (1.8)	0	0
Blood Immunoglobulin G Decreased	2 (0.4)	0	1 (0.2)	0	0	0
Blood Lactate Dehydrogenase	0	0	1 (0.2)	0	0	0
Blood Lactate Dehydrogenase Increased	15 (3.1)	3 (2.4)	13 (3.0)	4 (3.6)	0	0
Blood Magnesium Decreased	11 (2.3)	0	8 (1.9)	0	0	0
Blood Magnesium Increased	0	1 (0.8)	0	0	0	0
Blood Phosphorus Decreased	4 (0.8)	0	3 (0.7)	0	0	0
Blood Phosphorus Increased	1 (0.2)	0	2 (0.5)	0	0	0
Blood Potassium	1 (0.2)	0	0	0	0	0
Blood Potassium Abnormal	0	0	0	0	1 (2.0)	0
Blood Potassium Decreased	8 (1.7)	0	7 (1.6)	1 (0.9)	1 (2.0)	0
Blood Potassium Increased	0	0	2 (0.5)	0	0	0
Blood Pressure Decreased	0	0	1 (0.2)	0	0	0
Blood Pressure Diastolic Increased	0	1 (0.8)	0	0	0	0
Blood Pressure Increased	5 (1.0)	1 (0.8)	6 (1.4)	0	0	0
Blood Pressure Orthostatic	2 (0.4)	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	0	2 (1.6)	3 (0.7)	0	0	0
Blood Urea Decreased	0	0	0	1 (0.9)	0	0
Blood Urea Increased	3 (0.6)	2 (1.6)	10 (2.3)	3 (2.7)	0	0
Blood Uric Acid Decreased	0	0	1 (0.2)	0	0	0

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Blood Uric Acid Increased	5 (1.0)	0	5 (1.2)	0	0	0
Blood Urine Present	3 (0.6)	0	0	1 (0.9)	0	0
Body Temperature	1 (0.2)	0	0	0	0	0
Body Temperature Increased	4 (0.8)	0	0	0	0	0
Breath Sounds Abnormal	17 (3.5)	1 (0.8)	11 (2.6)	0	0	0
Bronchoscopy	0	0	1 (0.2)	0	0	0
C-Reactive Protein Abnormal	0	1 (0.8)	0	0	0	0
C-Reactive Protein Increased	4 (0.8)	0	3 (0.7)	0	2 (4.1)	0
Carbon Dioxide Decreased	1 (0.2)	0	0	1 (0.9)	0	0
Carbon Monoxide Diffusing Capacity Decreased	0	0	1 (0.2)	0	0	0
Cardiac Murmur	13 (2.7)	1 (0.8)	5 (1.2)	2 (1.8)	0	0
Central Venous Pressure Decreased	1 (0.2)	0	0	0	0	0
Chest X-Ray Abnormal	4 (0.8)	2 (1.6)	6 (1.4)	0	0	0
Clostridium Test	1 (0.2)	0	1 (0.2)	0	0	0
Clostridium Test Positive	5 (1.0)	2 (1.6)	5 (1.2)	1 (0.9)	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 (0.4)	0	2 (0.5)	0	0	0
Coagulation Time Prolonged	1 (0.2)	0	0	1 (0.9)	0	0
Coagulation Time Shortened	0	1 (0.8)	1 (0.2)	0	0	0
Colour Vision Tests Abnormal	0	0	0	1 (0.9)	0	0
Computerised Tomogram Abnormal	0	1 (0.8)	2 (0.5)	2 (1.8)	1 (2.0)	0
Creatinine Renal Clearance Decreased	1 (0.2)	1 (0.8)	4 (0.9)	2 (1.8)	0	0

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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 (0.4)	0	1 (0.2)	0	0	0
Culture Wound Positive	0	0	1 (0.2)	0	0	0
Cytomegalovirus Test	4 (0.8)	1 (0.8)	4 (0.9)	2 (1.8)	0	0
Cytomegalovirus Test Positive	23 (4.8)	4 (3.2)	18 (4.2)	4 (3.6)	0	0
Drug Level Changed	0	1 (0.8)	1 (0.2)	0	0	0
Drug Level Increased	5 (1.0)	0	3 (0.7)	0	0	0
Echocardiogram Abnormal	1 (0.2)	0	0	0	0	0
Ejection Fraction Decreased	2 (0.4)	0	0	0	0	0
Electrocardiogram Abnormal	3 (0.6)	0	2 (0.5)	0	0	0
Electrocardiogram Qt Interval	0	0	0	0	1 (2.0)	0
Electrocardiogram Qt Prolonged	18 (3.8)	6 (4.8)	15 (3.5)	4 (3.6)	3 (6.1)	2 (22.2)
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	3 (0.6)	1 (0.8)	0	0	0	0
Electrocardiogram T Wave Inversion	1 (0.2)	0	0	0	0	0
Electroencephalogram Abnormal	1 (0.2)	0	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

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Fungal Test	0	0	0	0	1 (2.0)	0
Fungal Test Positive	3 (0.6)	0	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	1 (0.2)	0	0	0
Gamma-Glutamyltransferase Increased	28 (5.8)	13 (10 3)	25 (5.8)	13 (11.7)	3 (6.1)	1 (11.1)
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	0	1 (0.8)	0	0	0	0
Haematocrit Decreased	0	0	2 (0.5)	0	0	0
Haemoglobin Decreased	6 (1.3)	2 (1.6)	1 (0.2)	1 (0.9)	1 (2.0)	0
Heart Rate Increased	0	0	1 (0.2)	1 (0.9)	0	0
Heart Rate Irregular	5 (1.0)	0	3 (0.7)	0	0	0
Heart Sounds Abnormal	1 (0.2)	0	0	0	0	0
Hepatic Enzyme Abnormal	0	1 (0.8)	2 (0.5)	0	0	0
Hepatic Enzyme Increased	6 (1.3)	3 (2.4)	11 (2.6)	1 (0.9)	0	0
Herpes Simplex Test Positive	1 (0.2)	0	0	0	0	0
High Density Lipoprotein Increased	0	1 (0.8)	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	1 (0.2)	1 (0.8)	0	0	0	0
International Normalised Ratio Increased	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Liver Function Test Abnormal	2 (0.4)	0	3 (0.7)	0	0	0
Liver Function Test Increased	16 (3.3)	2 (1.6)	13 (3.0)	3 (2.7)	1 (2.0)	0
Lymphocyte Count Decreased	0	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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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Lymphocyte Count Increased	0	0	1 (0.2)	0	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	0	2 (1.6)	0	0	0	0
Neutrophil Count Decreased	3 (0.6)	0	1 (0.2)	0	1 (2.0)	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	1 (0.2)	0	0	0
Nuclear Magnetic Resonance Imaging Brain Abnormal	0	1 (0.8)	0	0	0	0
Nutritional Condition Abnormal	0	0	2 (0.5)	0	0	0
Occult Blood Positive	7 (1.5)	0	7 (1.6)	0	1 (2.0)	0
Oxygen Consumption Decreased	0	0	1 (0.2)	0	0	0
Oxygen Saturation Decreased	9 (1.9)	0	8 (1.9)	1 (0.9)	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	7 (1.5)	2 (1.6)	5 (1.2)	1 (0.9)	1 (2.0)	0
Po2 Decreased	1 (0.2)	0	0	0	0	0
Protein Total Decreased	1 (0.2)	0	1 (0.2)	0	1 (2.0)	0
Protein Total Increased	0	0	1 (0.2)	0	0	0
Prothrombin Time Prolonged	2 (0.4)	3 (2.4)	5 (1.2)	7 (6.3)	0	3 (33.3)
Prothrombin Time Ratio Decreased	0	0	1 (0.2)	0	0	0
Prothrombin Time Shortened	3 (0.6)	0	2 (0.5)	0	1 (2.0)	0
Pulmonary Function Test Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Pulse Absent	0	0	0	1 (0.9)	0	0
Qrs Axis Abnormal	0	0	1 (0.2)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Red Blood Cell Count Decreased	1 (0.2)	0	0	0	0	0
Red Blood Cell Schistocytes Present	0	0	1 (0.2)	0	0	0
Respiratory Rate Increased	1 (0.2)	0	2 (0.5)	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)	0	0	0	0	0
Scan Bone Marrow Abnormal	0	1 (0.8)	0	0	0	0
Serum Ferritin Increased	1 (0.2)	0	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	0	1 (0.8)	0	0	0	0
Toxoplasma Serology Positive	1 (0.2)	0	0	0	0	0
Transaminases Increased	9 (1.9)	4 (3.2)	11 (2.6)	3 (2.7)	0	0
Troponin I Increased	0	0	0	1 (0.9)	0	0
Troponin Increased	1 (0.2)	0	2 (0.5)	0	0	0
Urine Output Decreased	2 (0.4)	1 (0.8)	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 (2.0)	0
Weight Decreased	30 (6.3)	11 (8.7)	38 (8.9)	12 (10.8)	3 (6.1)	1 (11.1)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Weight Increased	11 (2.3)	1 (0.8)	8 (1.9)	1 (0.9)	4 (8.2)	1 (11.1)
White Blood Cell Count Abnormal	0	1 (0.8)	0	0	0	0
White Blood Cell Count Decreased	1 (0.2)	0	3 (0.7)	0	1 (2.0)	0
White Blood Cell Count Increased	0	2 (1.6)	0	0	0	0
X-Ray Abnormal	1 (0.2)	0	0	0	0	0
Metabolism And Nutrition Disorders	**285 (59.5)**	**69 (54 8)**	**260 (60.7)**	**54 (48.6)**	**37 (75.5)**	**8 (88.9)**
Acidosis	8 (1.7)	3 (2.4)	6 (1.4)	0	2 (4.1)	0
Appetite Disorder	1 (0.2)	0	1 (0.2)	0	0	0
Cachexia	2 (0.4)	0	0	0	0	0
Calcium Deficiency	0	0	1 (0.2)	0	0	0
Decreased Appetite	74 (15.4)	14 (11 1)	74 (17.3)	13 (11.7)	14 (28.6)	3 (33.3)
Dehydration	20 (4.2)	6 (4.8)	23 (5.4)	4 (3.6)	2 (4.1)	0
Diabetes Mellitus	16 (3.3)	1 (0.8)	7 (1.6)	0	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	1 (2.0)	0
Electrolyte Depletion	0	1 (0.8)	0	0	0	0
Electrolyte Imbalance	5 (1.0)	1 (0.8)	1 (0.2)	2 (1.8)	4 (8.2)	0
Enzyme Abnormality	0	0	1 (0.2)	0	0	0
Failure To Thrive	1 (0.2)	0	3 (0.7)	1 (0.9)	0	0
Feeding Disorder	0	0	1 (0.2)	0	0	0
Fluid Imbalance	0	0	0	1 (0.9)	0	0
Fluid Overload	22 (4.6)	5 (4.0)	15 (3.5)	2 (1.8)	1 (2.0)	1 (11.1)
Fluid Retention	15 (3.1)	3 (2.4)	22 (5.1)	2 (1.8)	3 (6.1)	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Food Aversion	1 (0.2)	0	0	0	0	0
Food Craving	0	1 (0.8)	0	0	0	0
Food Intolerance	0	1 (0.8)	0	0	0	0
Glucose Tolerance Impaired	0	0	0	1 (0.9)	0	0
Gout	2 (0.4)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Haemochromatosis	0	0	1 (0.2)	0	0	0
Haemosiderosis	0	0	1 (0.2)	0	0	0
Hypercalcaemia	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Hyperchloraemia	0	1 (0.8)	0	0	0	0
Hypercholesterolaemia	4 (0.8)	0	0	0	0	0
Hypercreatininaemia	1 (0.2)	0	0	0	0	0
Hyperferritinaemia	0	0	1 (0.2)	0	0	0
Hyperglycaemia	53 (11.1)	13 (10 3)	62 (14.5)	9 (8.1)	2 (4.1)	0
Hyperhomocysteinaemia	1 (0.2)	0	0	0	0	0
Hyperinsulinaemic Hypoglycaemia	1 (0.2)	0	0	0	0	0
Hyperkalaemia	12 (2.5)	3 (2.4)	18 (4.2)	5 (4.5)	1 (2.0)	1 (11.1)
Hyperlipidaemia	0	0	1 (0.2)	0	0	0
Hypermagnesaemia	5 (1.0)	1 (0.8)	2 (0.5)	1 (0.9)	1 (2.0)	2 (22.2)
Hypernatraemia	3 (0.6)	3 (2.4)	2 (0.5)	2 (1.8)	1 (2.0)	1 (11.1)
Hyperosmolar State	1 (0.2)	0	0	0	0	0
Hyperphagia	0	1 (0.8)	0	0	0	0
Hyperphosphataemia	5 (1.0)	1 (0.8)	5 (1.2)	3 (2.7)	0	0
Hypertriglyceridaemia	2 (0.4)	0	0	1 (0.9)	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Hyperuricaemia	3 (0.6)	1 (0.8)	7 (1.6)	3 (2.7)	0	0
Hypervolaemia	1 (0.2)	0	1 (0.2)	2 (1.8)	0	0
Hypoalbuminaemia	22 (4.6)	6 (4.8)	14 (3.3)	4 (3.6)	1 (2.0)	1 (11.1)
Hypocalcaemia	44 (9.2)	9 (7.1)	32 (7.5)	14 (12.6)	4 (8.2)	1 (11.1)
Hypochloraemia	0	0	1 (0.2)	0	0	0
Hypoglycaemia	8 (1.7)	2 (1.6)	7 (1.6)	2 (1.8)	0	0
Hypokalaemia	138 (28.8)	34 (27.0)	106 (24.8)	30 (27.0)	24 (49.0)	5 (55.6)
Hypomagnesaemia	80 (16.7)	18 (14 3)	60 (14.0)	15 (13.5)	10 (20.4)	1 (11.1)
Hyponatraemia	23 (4.8)	7 (5.6)	24 (5.6)	5 (4.5)	3 (6.1)	0
Hypophagia	8 (1.7)	2 (1.6)	8 (1.9)	3 (2.7)	0	0
Hypophosphataemia	32 (6.7)	15 (11 9)	29 (6.8)	8 (7 2)	5 (10.2)	1 (11.1)
Hypoproteinaemia	5 (1.0)	0	3 (0.7)	0	1 (2.0)	0
Hypovitaminosis	2 (0.4)	0	0	0	0	0
Hypovolaemia	2 (0.4)	1 (0.8)	4 (0.9)	0	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 (1.0)	0	13 (3.0)	2 (1.8)	0	0
Metabolic Acidosis	9 (1.9)	1 (0.8)	2 (0.5)	4 (3.6)	1 (2.0)	1 (11.1)
Metabolic Alkalosis	0	0	2 (0.5)	0	0	0
Obesity	0	0	2 (0.5)	0	0	0
Phosphorus Metabolism Disorder	1 (0.2)	0	0	0	0	0
Polydipsia	1 (0.2)	2 (1.6)	0	0	0	0
Vitamin B12 Deficiency	1 (0.2)	0	0	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
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 (0.5)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**195 (40.7)**	**54 (42 9)**	**203 (47.4)**	**43 (38.7)**	**18 (36.7)**	**2 (22.2)**
Arthralgia	43 (9.0)	15 (11 9)	44 (10.3)	12 (10.8)	3 (6.1)	0
Arthritis	3 (0.6)	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Axillary Mass	0	1 (0.8)	0	0	0	0
Back Pain	43 (9.0)	18 (14 3)	60 (14.0)	6 (5.4)	4 (8.2)	0
Bone Pain	20 (4.2)	6 (4.8)	7 (1.6)	4 (3.6)	3 (6.1)	0
Bursitis	0	1 (0.8)	0	1 (0.9)	0	0
Chondritis	1 (0.2)	0	0	0	0	0
Clubbing	0	0	1 (0.2)	0	0	0
Coccydynia	2 (0.4)	0	0	0	0	0
Flank Pain	6 (1.3)	3 (2.4)	6 (1.4)	1 (0.9)	1 (2.0)	0
Groin Pain	2 (0.4)	0	3 (0.7)	0	1 (2.0)	0
Haemarthrosis	2 (0.4)	0	1 (0.2)	0	0	0
Inguinal Mass	2 (0.4)	0	0	0	0	0
Intervertebral Disc Degeneration	0	0	1 (0.2)	0	0	0
Intervertebral Disc Protrusion	1 (0.2)	0	1 (0.2)	0	0	0
Joint Contracture	1 (0.2)	0	0	0	0	0
Joint Effusion	2 (0.4)	1 (0.8)	0	0	0	0
Joint Stiffness	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0

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Joint Swelling	9 (1.9)	0	5 (1.2)	1 (0.9)	0	0
Kyphoscoliosis	1 (0.2)	0	0	0	0	0
Limb Discomfort	1 (0.2)	0	2 (0.5)	0	0	0
Mobility Decreased	1 (0.2)	0	0	0	0	0
Muscle Atrophy	4 (0.8)	0	1 (0.2)	0	0	0
Muscle Contracture	1 (0.2)	0	0	0	0	0
Muscle Fatigue	1 (0.2)	0	0	1 (0.9)	0	0
Muscle Spasms	26 (5.4)	5 (4.0)	32 (7.5)	6 (5.4)	0	0
Muscle Swelling	0	0	1 (0.2)	0	0	1 (11.1)
Muscle Tightness	1 (0.2)	0	0	0	0	0
Muscle Twitching	4 (0.8)	0	2 (0.5)	1 (0.9)	0	0
Muscular Weakness	23 (4.8)	5 (4.0)	22 (5.1)	6 (5.4)	0	1 (11.1)
Musculoskeletal Chest Pain	9 (1.9)	3 (2.4)	11 (2.6)	1 (0.9)	0	0
Musculoskeletal Discomfort	2 (0.4)	2 (1.6)	2 (0.5)	1 (0.9)	0	0
Musculoskeletal Pain	15 (3.1)	1 (0.8)	17 (4.0)	3 (2.7)	4 (8.2)	0
Musculoskeletal Stiffness	5 (1.0)	0	10 (2.3)	0	1 (2.0)	0
Myalgia	26 (5.4)	5 (4.0)	27 (6.3)	6 (5.4)	0	1 (11.1)
Myopathy	16 (3.3)	4 (3 2)	9 (2.1)	2 (1.8)	0	0
Myositis	0	1 (0.8)	0	0	0	0
Neck Mass	1 (0.2)	0	2 (0.5)	0	0	0
Neck Pain	9 (1.9)	0	16 (3.7)	4 (3.6)	1 (2.0)	0
Nuchal Rigidity	0	0	1 (0.2)	0	0	0
Osteoarthritis	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Osteolysis	0	0	1 (0.2)	0	0	0
Osteonecrosis	2 (0.4)	0	3 (0.7)	0	0	0
Osteopenia	2 (0.4)	0	0	0	0	0
Osteoporosis	0	0	2 (0.5)	0	0	0
Pain In Extremity	46 (9.6)	12 (9.5)	35 (8.2)	13 (11.7)	4 (8.2)	1 (11.1)
Pain In Jaw	4 (0.8)	2 (1.6)	2 (0.5)	0	1 (2.0)	0
Pathological Fracture	0	0	1 (0.2)	0	0	0
Plantar Fasciitis	1 (0.2)	0	0	0	0	0
Polychondritis	0	0	0	0	1 (2.0)	0
Scoliosis	1 (0.2)	0	0	0	0	0
Sjogren's Syndrome	3 (0.6)	0	0	1 (0.9)	0	0
Soft Tissue Disorder	0	0	3 (0.7)	0	0	0
Spinal Osteoarthritis	2 (0.4)	1 (0.8)	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 (0.6)	0	0	0	2 (4.1)	0
Tenosynovitis	1 (0.2)	0	0	0	0	0
Torticollis	1 (0.2)	0	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**48 (10.0)**	**13 (10 3)**	**48 (11.2)**	**9 (8 1)**	**3 (6.1)**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	4 (0.9)	2 (1.8)	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Acute Myeloid Leukaemia	7 (1.5)	6 (4.8)	8 (1.9)	1 (0.9)	1 (2.0)	0
Acute Myeloid Leukaemia Recurrent	10 (2.1)	2 (1.6)	4 (0.9)	2 (1.8)	0	0
Adenoma Benign	0	0	1 (0.2)	0	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	1 (0.2)	0	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)	0	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	0	1 (0.8)	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)	0	0	0	0	0
Colon Adenoma	1 (0.2)	0	0	0	0	0
Haemangioma Of Liver	1 (0.2)	0	2 (0.5)	0	0	0
Hodgkin's Disease	0	0	1 (0.2)	0	0	0
Hodgkin's Disease Recurrent	0	0	1 (0.2)	0	0	0
Leukaemia	2 (0.4)	2 (1.6)	3 (0.7)	0	0	0
Leukaemia Cutis	0	0	0	0	1 (2.0)	0
Leukaemia Recurrent	5 (1.0)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Lipoma	2 (0.4)	0	0	0	0	0
Lymphoma	6 (1.3)	0	2 (0.5)	0	0	0
Malignant Melanoma	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Melanocytic Naevus	0	0	1 (0.2)	0	0	0
Meningioma	1 (0.2)	0	1 (0.2)	0	0	0
Metastases To Kidney	0	0	1 (0.2)	0	0	0
Metastases To Liver	0	0	1 (0.2)	0	0	0
Metastatic Neoplasm	1 (0.2)	0	0	0	0	0
Myelodysplastic Syndrome	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Nasal Neoplasm	1 (0.2)	0	0	0	0	0
Neoplasm Malignant	1 (0.2)	0	3 (0.7)	0	0	0
Neuroma	1 (0.2)	0	0	0	0	0
Non-Hodgkin's Lymphoma	1 (0.2)	0	2 (0.5)	2 (1.8)	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	2 (0.5)	0	0	0
Plasma Cell Myeloma	0	0	1 (0.2)	0	0	0
Post Transplant Lymphoproliferative Disorder	1 (0.2)	0	1 (0.2)	0	0	0
Pyogenic Granuloma	0	0	1 (0.2)	0	0	0
Renal Cancer	1 (0.2)	0	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 (0.4)	0	0	1 (0.9)	0	0
Thyroid Adenoma	0	1 (0.8)	0	0	0	0
Tumour Associated Fever	0	0	0	0	1 (2.0)	0
Tumour Pain	2 (0.4)	0	0	0	0	0
Uterine Leiomyoma	1 (0.2)	1 (0.8)	0	0	0	0

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Number (%) of Subjects

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Vaginal Neoplasm	1 (0.2)	0	0	0	0	0
Nervous System Disorders	**234 (48.9)**	**61 (48.4)**	**231 (54.0)**	**55 (49.5)**	**26 (53.1)**	**5 (55.6)**
Ageusia	1 (0.2)	0	2 (0.5)	0	0	0
Akathisia	0	0	1 (0.2)	0	0	0
Akinesia	0	0	0	1 (0.9)	0	0
Amnesia	3 (0.6)	0	1 (0.2)	0	0	0
Aphasia	1 (0.2)	0	1 (0.2)	0	0	0
Areflexia	2 (0.4)	0	0	0	0	0
Asterixis	0	1 (0.8)	0	0	0	0
Ataxia	2 (0.4)	0	2 (0.5)	0	0	0
Athetosis	0	0	1 (0.2)	0	0	0
Balance Disorder	5 (1.0)	0	4 (0.9)	0	0	0
Brachial Plexopathy	0	0	1 (0.2)	0	0	0
Brain Compression	0	0	0	0	1 (2.0)	0
Brain Oedema	1 (0.2)	3 (2.4)	0	2 (1.8)	0	0
Burning Sensation	6 (1.3)	2 (1.6)	2 (0.5)	0	0	0
Central Nervous System Lesion	0	1 (0.8)	1 (0.2)	0	0	0
Cerebellar Haemorrhage	2 (0.4)	0	0	0	1 (2.0)	0
Cerebral Haemorrhage	3 (0.6)	2 (1.6)	2 (0.5)	3 (2.7)	0	0
Cerebral Hypoperfusion	0	0	1 (0.2)	0	0	0
Cerebral Infarction	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Cerebrovascular Accident	2 (0.4)	0	1 (0.2)	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Clonus	1 (0.2)	0	0	0	0	0
Cluster Headache	1 (0.2)	0	0	0	0	0
Cognitive Disorder	3 (0.6)	0	1 (0.2)	0	0	0
Coma	2 (0.4)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Demyelination	4 (0.8)	0	0	0	0	0
Depressed Level Of Consciousness	3 (0.6)	0	3 (0.7)	0	1 (2.0)	0
Disturbance In Attention	0	0	6 (1.4)	0	0	0
Dizziness	46 (9.6)	15 (11 9)	46 (10.7)	6 (5.4)	5 (10.2)	0
Dizziness Postural	3 (0.6)	1 (0.8)	3 (0.7)	0	0	0
Dysaesthesia	1 (0.2)	0	0	0	0	0
Dysarthria	2 (0.4)	0	2 (0.5)	1 (0.9)	1 (2.0)	0
Dysgeusia	8 (1.7)	1 (0.8)	7 (1.6)	2 (1.8)	0	0
Encephalopathy	5 (1.0)	0	2 (0.5)	1 (0.9)	0	0
Epilepsy	0	0	1 (0.2)	0	0	0
Extrapyramidal Disorder	1 (0.2)	1 (0.8)	0	0	0	0
Facial Paralysis	1 (0.2)	0	2 (0.5)	0	0	0
Facial Paresis	0	1 (0.8)	1 (0.2)	0	0	0
Generalised Tonic-Clonic Seizure	0	0	1 (0.2)	1 (0.9)	0	0
Guillain-Barre Syndrome	0	0	0	1 (0.9)	0	0
Haemorrhage Intracranial	0	2 (1.6)	4 (0.9)	2 (1.8)	0	0
Haemorrhagic Stroke	1 (0.2)	0	1 (0.2)	0	0	0
Head Discomfort	1 (0.2)	0	0	0	0	0
Headache	132 (27.6)	39 (31.0)	112 (26.2)	27 (24.3)	19 (38.8)	3 (33.3)

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Hemiparesis	0	0	4 (0.9)	3 (2.7)	0	0
Hemiplegia	1 (0.2)	0	3 (0.7)	0	0	0
Hydrocephalus	0	0	0	0	1 (2.0)	0
Hyperreflexia	0	0	0	2 (1.8)	0	0
Hypertonia	0	0	3 (0.7)	0	0	0
Hypoaesthesia	5 (1.0)	1 (0.8)	12 (2.8)	1 (0.9)	1 (2.0)	2 (22.2)
Hypogeusia	1 (0.2)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Hypoglycaemic Coma	1 (0.2)	0	0	0	0	0
Hypokinesia	0	0	1 (0.2)	0	0	0
Hyporeflexia	3 (0.6)	0	1 (0.2)	1 (0.9)	0	0
Hypotonia	1 (0.2)	0	3 (0.7)	0	0	0
Incoherent	0	0	1 (0.2)	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	0	1 (11.1)
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	12 (2.5)	7 (5.6)	17 (4.0)	5 (4.5)	2 (4.1)	1 (11.1)
Leukoencephalopathy	1 (0.2)	1 (0.8)	0	0	0	0
Loss Of Consciousness	1 (0.2)	3 (2.4)	2 (0.5)	3 (2.7)	1 (2.0)	0
Memory Impairment	3 (0.6)	0	2 (0.5)	1 (0.9)	0	0
Meningism	1 (0.2)	0	0	0	0	0
Mental Impairment	0	0	1 (0.2)	0	0	0
Metabolic Encephalopathy	3 (0.6)	0	0	0	0	0

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All Randomized Subjects
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	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Migraine	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Myoclonus	0	2 (1.6)	0	1 (0.9)	0	0
Nerve Compression	1 (0.2)	0	0	0	0	0
Nervous System Disorder	2 (0.4)	0	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	8 (1.7)	1 (0.8)	11 (2.6)	1 (0.9)	0	0
Neurotoxicity	0	0	1 (0.2)	1 (0.9)	0	0
Nystagmus	0	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Paraesthesia	16 (3.3)	1 (0.8)	18 (4.2)	3 (2.7)	1 (2.0)	0
Paralysis	2 (0.4)	0	0	0	0	0
Paresis	0	0	1 (0.2)	0	0	0
Parosmia	1 (0.2)	0	0	0	0	0
Peripheral Sensory Neuropathy	0	0	1 (0.2)	0	1 (2.0)	0
Peroneal Nerve Palsy	2 (0.4)	0	1 (0.2)	0	0	0
Polyneuropathy	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Poor Quality Sleep	1 (0.2)	0	1 (0.2)	0	0	0
Post Herpetic Neuralgia	0	2 (1.6)	2 (0.5)	1 (0.9)	0	0
Presyncope	3 (0.6)	0	0	0	2 (4.1)	0
Psychomotor Hyperactivity	3 (0.6)	0	1 (0.2)	0	0	0
Reflexes Abnormal	0	1 (0.8)	1 (0.2)	0	0	0
Sciatica	1 (0.2)	0	2 (0.5)	0	0	0
Sedation	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Seizure	7 (1.5)	2 (1.6)	5 (1.2)	2 (1.8)	0	0
Sensory Disturbance	1 (0.2)	0	0	0	0	0
Sensory Loss	3 (0.6)	1 (0.8)	2 (0.5)	0	0	0
Sinus Headache	3 (0.6)	0	0	0	0	0
Somnolence	15 (3.1)	2 (1.6)	7 (1.6)	5 (4.5)	0	0
Speech Disorder	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Stupor	1 (0.2)	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Syncope	16 (3.3)	0	4 (0.9)	1 (0.9)	1 (2.0)	0
Tension Headache	0	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Tonic Convulsion	0	1 (0.8)	0	0	0	0
Toxic Neuropathy	0	1 (0.8)	0	0	0	0
Transient Ischaemic Attack	0	1 (0.8)	0	0	0	0
Tremor	44 (9.2)	4 (3 2)	36 (8.4)	8 (7.2)	1 (2.0)	1 (11.1)
Trigeminal Neuralgia	0	0	1 (0.2)	0	0	0
Unresponsive To Stimuli	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Visual Field Defect	2 (0.4)	0	1 (0.2)	0	0	0
Pregnancy, Puerperium And Perinatal Conditions	**0**	**1 (0.8)**	**0**	**0**	**0**	**0**
Pregnancy	0	1 (0.8)	0	0	0	0
Product Issues	**13 (2.7)**	**3 (2.4)**	**13 (3.0)**	**1 (0.9)**	**0**	**0**
Device Breakage	0	0	0	1 (0.9)	0	0
Device Leakage	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0

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Device Occlusion	9 (1.9)	1 (0.8)	7 (1.6)	0	0	0
Thrombosis In Device	2 (0.4)	1 (0.8)	5 (1.2)	0	0	0
Psychiatric Disorders	**180 (37.6)**	**40 (31.7)**	**171 (40.0)**	**29 (26.1)**	**24 (49.0)**	**3 (33.3)**
Abnormal Behaviour	0	0	1 (0.2)	0	0	0
Abnormal Dreams	0	0	0	1 (0.9)	0	0
Adjustment Disorder With Depressed Mood	0	1 (0.8)	1 (0.2)	0	0	0
Affect Lability	4 (0.8)	0	2 (0.5)	0	0	0
Affective Disorder	2 (0.4)	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	14 (2.9)	2 (1.6)	12 (2.8)	2 (1.8)	0	0
Anger	1 (0.2)	0	2 (0.5)	0	0	0
Anxiety	42 (8.8)	11 (8.7)	43 (10.0)	13 (11.7)	9 (18.4)	0
Aversion	0	0	0	0	1 (2.0)	0
Claustrophobia	0	0	1 (0.2)	0	0	0
Confusional State	25 (5.2)	4 (3 2)	25 (5.8)	3 (2.7)	2 (4.1)	1 (11.1)
Delirium	4 (0.8)	1 (0.8)	2 (0.5)	0	0	0
Depressed Mood	5 (1.0)	0	3 (0.7)	1 (0.9)	0	1 (11.1)
Depression	43 (9.0)	8 (6 3)	37 (8.6)	8 (7.2)	3 (6.1)	0
Depression Suicidal	0	0	1 (0.2)	0	0	0
Disorientation	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Disturbance In Social Behaviour	1 (0.2)	0	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Eating Disorder	0	0	2 (0.5)	0	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	1 (0.2)	1 (0.8)	0	0	0	0
Fear	0	0	1 (0.2)	0	0	0
Feeling Of Despair	1 (0.2)	0	0	0	0	0
Flat Affect	2 (0.4)	0	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	5 (1.0)	1 (0.8)	5 (1.2)	0	1 (2.0)	0
Hallucination, Visual	2 (0.4)	0	1 (0.2)	0	2 (4.1)	0
Hypomania	1 (0.2)	0	0	0	0	0
Insomnia	82 (17.1)	19 (15 1)	78 (18.2)	16 (14.4)	11 (22.4)	1 (11.1)
Irritability	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0
Mania	0	0	2 (0.5)	0	0	0
Mental Disorder	0	0	1 (0.2)	0	0	0
Mental Status Changes	10 (2.1)	0	10 (2.3)	1 (0.9)	0	0
Mood Altered	6 (1.3)	0	3 (0.7)	0	0	0
Mood Swings	0	0	2 (0.5)	1 (0.9)	0	0
Nervousness	2 (0.4)	0	0	0	1 (2.0)	0
Nightmare	3 (0.6)	0	2 (0.5)	0	0	0
Obsessive-Compulsive Disorder	1 (0.2)	0	0	0	0	0
Paranoia	0	0	2 (0.5)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Phonophobia	0	0	1 (0.2)	0	0	0
Posturing	0	0	1 (0.2)	0	0	0
Psychotic Disorder	2 (0.4)	0	1 (0.2)	0	0	0
Restlessness	5 (1.0)	0	2 (0.5)	0	3 (6.1)	0
Sleep Disorder	2 (0.4)	1 (0.8)	4 (0.9)	0	0	0
Sleep Disorder Due To General Medical Condition, Insomnia Type	1 (0.2)	0	0	0	0	0
Stress	2 (0.4)	0	3 (0.7)	0	0	0
Substance-Induced Psychotic Disorder	0	0	1 (0.2)	0	0	0
Suicidal Ideation	1 (0.2)	1 (0.8)	0	1 (0.9)	0	0
Tachyphrenia	0	0	1 (0.2)	0	0	0
Tearfulness	0	0	1 (0.2)	0	0	0
Renal And Urinary Disorders	**139 (29.0)**	**29 (23.0)**	**132 (30.8)**	**23 (20.7)**	**12 (24.5)**	**3 (33.3)**
Acute Kidney Injury	13 (2.7)	1 (0.8)	9 (2.1)	3 (2.7)	2 (4.1)	0
Acute Prerenal Failure	1 (0.2)	0	0	0	0	0
Anuria	4 (0.8)	0	1 (0.2)	0	0	0
Azotaemia	1 (0.2)	0	1 (0.2)	0	0	0
Bilirubinuria	0	0	1 (0.2)	0	0	0
Bladder Dilatation	0	0	1 (0.2)	0	0	0
Bladder Pain	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Bladder Spasm	5 (1.0)	0	3 (0.7)	0	0	0
Choluria	1 (0.2)	0	0	0	0	0

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Chromaturia	1 (0.2)	1 (0.8)	2 (0.5)	1 (0.9)	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 (2.3)	0	8 (1.9)	3 (2.7)	0	0
Dysuria	30 (6.3)	6 (4.8)	24 (5.6)	5 (4.5)	1 (2.0)	0
Glycosuria	1 (0.2)	0	1 (0.2)	0	0	0
Haematuria	33 (6.9)	6 (4.8)	33 (7.7)	5 (4.5)	5 (10.2)	2 (22.2)
Hydronephrosis	1 (0.2)	1 (0.8)	0	0	0	1 (11.1)
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 (0.8)	0	1 (0.2)	1 (0.9)	0	0
Nephrolithiasis	4 (0.8)	0	0	0	0	0
Nephropathy	0	0	1 (0.2)	0	0	0
Nocturia	3 (0.6)	0	4 (0.9)	1 (0.9)	0	0
Obstructive Nephropathy	0	0	1 (0.2)	0	0	0
Oliguria	8 (1.7)	2 (1.6)	2 (0.5)	1 (0.9)	1 (2.0)	0
Pollakiuria	16 (3.3)	1 (0.8)	12 (2.8)	0	0	0
Polyuria	7 (1.5)	1 (0.8)	0	1 (0.9)	0	0
Proteinuria	0	1 (0.8)	1 (0.2)	0	0	0
Renal Cyst	1 (0.2)	0	2 (0.5)	0	1 (2.0)	0
Renal Disorder	2 (0.4)	0	0	0	0	0

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Renal Failure	33 (6.9)	7 (5.6)	56 (13.1)	7 (6 3)	2 (4.1)	0
Renal Haematoma	1 (0.2)	0	0	0	0	0
Renal Hypertension	0	0	1 (0.2)	0	0	0
Renal Impairment	10 (2.1)	2 (1.6)	13 (3.0)	3 (2.7)	0	1 (11.1)
Renal Mass	0	0	0	0	1 (2.0)	0
Renal Pain	1 (0.2)	0	0	0	0	0
Renal Tubular Necrosis	0	0	3 (0.7)	0	0	0
Renal Vein Thrombosis	0	1 (0.8)	0	0	0	0
Stress Urinary Incontinence	1 (0.2)	1 (0.8)	0	0	0	0
Tubulointerstitial Nephritis	0	0	0	2 (1.8)	0	0
Urethral Discharge	0	0	0	1 (0.9)	0	0
Urethral Haemorrhage	1 (0.2)	0	0	0	0	0
Urinary Hesitation	0	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Urinary Incontinence	10 (2.1)	2 (1.6)	9 (2.1)	2 (1.8)	0	0
Urinary Retention	7 (1.5)	1 (0.8)	9 (2.1)	0	2 (4.1)	0
Urine Abnormality	1 (0.2)	0	0	0	0	0
Urine Odour Abnormal	1 (0.2)	0	0	0	0	0
Urogenital Disorder	0	1 (0.8)	0	0	0	0
Reproductive System And Breast Disorders	**45 (9.4)**	**17 (13 5)**	**42 (9.8)**	**17 (15.3)**	**7 (14.3)**	**1 (11.1)**
Adnexa Uteri Cyst	1 (0.2)	0	0	0	0	0
Balanoposthitis	1 (0.2)	0	1 (0.2)	0	1 (2.0)	0
Bartholin's Cyst	0	1 (0.8)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Benign Prostatic Hyperplasia	2 (0.4)	0	0	0	0	0
Breast Mass	0	1 (0.8)	0	0	0	0
Breast Pain	0	1 (0.8)	1 (0.2)	0	0	0
Dysfunctional Uterine Bleeding	1 (0.2)	0	0	0	0	0
Dysmenorrhoea	1 (0.2)	1 (0.8)	4 (0.9)	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)	0	0	1 (0.9)	0	0
Genital Erosion	0	0	1 (0.2)	0	0	0
Genital Erythema	0	0	2 (0.5)	0	0	0
Genital Lesion	0	0	1 (0.2)	1 (0.9)	0	0
Genital Swelling	0	0	1 (0.2)	0	1 (2.0)	1 (11.1)
Genital Ulceration	1 (0.2)	0	1 (0.2)	0	0	0
Gynaecomastia	1 (0.2)	0	0	0	0	0
Menopausal Symptoms	1 (0.2)	1 (0.8)	0	0	0	0
Menorrhagia	1 (0.2)	1 (0.8)	5 (1.2)	0	1 (2.0)	0
Menstrual Disorder	1 (0.2)	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Metrorrhagia	4 (0.8)	1 (0.8)	5 (1.2)	1 (0.9)	0	0
Pelvic Discomfort	1 (0.2)	0	1 (0.2)	0	0	0
Pelvic Haematoma	0	1 (0.8)	0	0	0	0
Pelvic Pain	2 (0.4)	0	1 (0.2)	0	0	0
Penile Discharge	0	0	1 (0.2)	0	0	0
Penile Haemorrhage	1 (0.2)	0	0	1 (0.9)	0	0

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Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Penile Necrosis	1 (0.2)	0	0	0	0	0
Penile Oedema	1 (0.2)	0	1 (0.2)	0	0	0
Penile Pain	0	1 (0.8)	0	2 (1.8)	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	0	1 (0.8)	1 (0.2)	0	0	0
Pruritus Genital	2 (0.4)	0	0	0	0	0
Scrotal Oedema	2 (0.4)	0	3 (0.7)	0	0	0
Scrotal Pain	0	0	0	1 (0.9)	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 (0.5)	0	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)	0	0	0
Vaginal Discharge	0	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Vaginal Dysplasia	0	0	1 (0.2)	0	0	0
Vaginal Haemorrhage	15 (3.1)	9 (7.1)	8 (1.9)	12 (10.8)	3 (6.1)	0
Vulval Oedema	1 (0.2)	0	0	0	0	0
Vulval Ulceration	0	0	1 (0.2)	0	0	0
Vulvovaginal Burning Sensation	2 (0.4)	0	0	0	0	0
Vulvovaginal Discomfort	1 (0.2)	0	2 (0.5)	0	0	0

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Vulvovaginal Dryness	1 (0.2)	0	0	0	0	0
Vulvovaginal Pain	0	1 (0.8)	0	0	0	0
Vulvovaginal Pruritus	1 (0.2)	0	1 (0.2)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**283 (59.1)**	**79 (62.7)**	**270 (63.1)**	**56 (50.5)**	**35 (71.4)**	**9 (100.0)**
Acute Promyelocytic Leukaemia Differentiation Syndrome	1 (0.2)	0	0	0	1 (2.0)	0
Acute Pulmonary Oedema	0	2 (1.6)	2 (0.5)	0	0	0
Acute Respiratory Distress Syndrome	6 (1.3)	0	5 (1.2)	2 (1.8)	1 (2.0)	0
Acute Respiratory Failure	4 (0.8)	1 (0.8)	1 (0.2)	0	0	0
Apnoea	1 (0.2)	1 (0.8)	0	0	0	0
Asthma	4 (0.8)	0	1 (0.2)	0	0	0
Atelectasis	19 (4.0)	6 (4.8)	8 (1.9)	4 (3.6)	1 (2.0)	2 (22.2)
Bronchial Hyperreactivity	0	0	0	1 (0.9)	0	0
Bronchial Obstruction	0	0	1 (0.2)	1 (0.9)	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)	0	0	0	0	0
Bronchospasm	4 (0.8)	5 (4.0)	6 (1.4)	3 (2.7)	0	0
Chronic Obstructive Pulmonary Disease	3 (0.6)	0	2 (0.5)	0	0	0
Cough	116 (24.2)	40 (31.7)	115 (26.9)	23 (20.7)	9 (18.4)	7 (77.8)
Diaphragmalgia	1 (0.2)	0	0	0	0	0
Diaphragmatic Disorder	0	0	1 (0.2)	0	0	0
Diffuse Alveolar Damage	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Dry Throat	1 (0.2)	0	2 (0.5)	0	0	0
Dysphonia	4 (0.8)	2 (1.6)	8 (1.9)	0	0	0
Dyspnoea	82 (17.1)	19 (15 1)	93 (21.7)	13 (11.7)	9 (18.4)	4 (44.4)
Dyspnoea Exertional	21 (4.4)	2 (1.6)	16 (3.7)	2 (1.8)	1 (2.0)	0
Dyspnoea Paroxysmal Nocturnal	0	0	0	1 (0.9)	0	0
Emphysema	0	1 (0.8)	1 (0.2)	0	0	0
Epiglottis Ulcer	1 (0.2)	0	0	0	0	0
Epistaxis	67 (14.0)	13 (10 3)	60 (14.0)	12 (10.8)	12 (24.5)	0
Haemoptysis	12 (2.5)	10 (7.9)	16 (3.7)	4 (3.6)	2 (4.1)	1 (11.1)
Haemothorax	0	0	1 (0.2)	1 (0.9)	0	0
Hiccups	10 (2.1)	2 (1.6)	7 (1.6)	0	1 (2.0)	0
Hydrothorax	1 (0.2)	0	1 (0.2)	0	0	0
Hypercapnia	1 (0.2)	0	0	0	0	0
Hyperventilation	1 (0.2)	2 (1.6)	0	0	0	0
Hypocapnia	1 (0.2)	0	0	0	0	0
Hypoxia	19 (4.0)	3 (2.4)	32 (7.5)	2 (1.8)	4 (8.2)	3 (33.3)
Increased Bronchial Secretion	3 (0.6)	1 (0.8)	1 (0.2)	0	0	0
Increased Upper Airway Secretion	2 (0.4)	0	4 (0.9)	0	0	0
Increased Viscosity Of Bronchial Secretion	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Interstitial Lung Disease	2 (0.4)	2 (1.6)	1 (0.2)	1 (0.9)	0	0
Laryngeal Infiltration	0	0	1 (0.2)	0	0	0
Laryngeal Oedema	1 (0.2)	0	0	0	1 (2.0)	0
Lung Consolidation	1 (0.2)	1 (0.8)	1 (0.2)	1 (0.9)	0	2 (22.2)

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Lung Disorder	4 (0.8)	0	0	1 (0.9)	1 (2.0)	0
Lung Infiltration	19 (4.0)	2 (1.6)	22 (5.1)	1 (0 9)	0	0
Nasal Congestion	19 (4.0)	6 (4.8)	13 (3.0)	8 (7.2)	1 (2.0)	1 (11.1)
Nasal Discomfort	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Nasal Dryness	0	1 (0.8)	4 (0.9)	0	0	0
Nasal Inflammation	0	0	1 (0.2)	0	0	0
Nasal Necrosis	0	0	0	1 (0.9)	0	0
Nasal Obstruction	2 (0.4)	0	1 (0.2)	0	0	0
Nasal Septum Disorder	0	1 (0.8)	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	1 (0.2)	1 (0.9)	0	0
Obstructive Airways Disorder	0	0	1 (0.2)	0	0	0
Organising Pneumonia	2 (0.4)	0	0	0	0	0
Oropharyngeal Pain	49 (10.2)	15 (11 9)	48 (11.2)	6 (5.4)	11 (22.4)	0
Oropharyngeal Swelling	1 (0.2)	0	0	0	0	0
Orthopnoea	1 (0.2)	0	3 (0.7)	0	0	0
Painful Respiration	2 (0.4)	0	0	0	0	0
Paranasal Sinus Discomfort	2 (0.4)	1 (0.8)	0	0	0	0
Paranasal Sinus Hypersecretion	1 (0.2)	0	0	0	0	0
Pharyngeal Erythema	5 (1.0)	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Pharyngeal Lesion	1 (0.2)	0	0	0	0	0
Pharyngeal Ulceration	0	0	1 (0.2)	0	1 (2.0)	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Pleural Effusion	37 (7.7)	10 (7.9)	32 (7.5)	7 (6.3)	1 (2.0)	3 (33.3)
Pleural Rub	0	0	1 (0.2)	0	0	0
Pleurisy	1 (0.2)	0	1 (0.2)	0	0	0
Pleuritic Pain	6 (1.3)	0	4 (0.9)	3 (2.7)	0	0
Pneumomediastinum	0	0	1 (0.2)	0	0	0
Pneumonia Aspiration	2 (0.4)	1 (0.8)	3 (0.7)	0	0	0
Pneumonitis	4 (0.8)	3 (2.4)	3 (0.7)	1 (0.9)	0	0
Pneumothorax	5 (1.0)	0	3 (0.7)	2 (1.8)	1 (2.0)	0
Productive Cough	24 (5.0)	6 (4.8)	24 (5.6)	9 (8.1)	1 (2.0)	1 (11.1)
Prolonged Expiration	1 (0.2)	0	0	0	0	0
Pulmonary Alveolar Haemorrhage	1 (0.2)	2 (1.6)	1 (0.2)	1 (0.9)	1 (2.0)	0
Pulmonary Congestion	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Pulmonary Embolism	7 (1.5)	0	2 (0.5)	0	0	0
Pulmonary Fibrosis	0	0	1 (0.2)	0	0	0
Pulmonary Haemorrhage	4 (0.8)	3 (2.4)	4 (0.9)	2 (1.8)	0	0
Pulmonary Haemosiderosis	0	0	1 (0.2)	0	0	0
Pulmonary Hypertension	3 (0.6)	0	0	1 (0.9)	0	0
Pulmonary Mass	5 (1.0)	3 (2.4)	7 (1.6)	1 (0.9)	0	0
Pulmonary Oedema	12 (2.5)	4 (3.2)	16 (3.7)	3 (2.7)	3 (6.1)	0
Rales	28 (5.8)	7 (5.6)	25 (5.8)	5 (4.5)	5 (10.2)	0
Respiratory Acidosis	0	2 (1.6)	2 (0.5)	0	0	0
Respiratory Alkalosis	0	0	1 (0.2)	1 (0.9)	0	0
Respiratory Arrest	1 (0.2)	0	0	0	0	0

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Respiratory Disorder	2 (0.4)	0	1 (0.2)	0	1 (2.0)	0
Respiratory Distress	10 (2.1)	0	7 (1.6)	0	2 (4.1)	0
Respiratory Failure	19 (4.0)	6 (4.8)	31 (7.2)	6 (5.4)	2 (4.1)	0
Respiratory Tract Congestion	3 (0.6)	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Respiratory Tract Haemorrhage	1 (0.2)	0	0	0	0	0
Restrictive Pulmonary Disease	1 (0.2)	0	1 (0.2)	0	0	0
Rhinalgia	1 (0.2)	0	1 (0.2)	0	0	0
Rhinitis Allergic	0	0	1 (0.2)	0	0	0
Rhinorrhoea	23 (4.8)	7 (5.6)	19 (4.4)	3 (2.7)	2 (4.1)	2 (22.2)
Rhonchi	7 (1.5)	0	8 (1.9)	2 (1.8)	0	0
Sinus Congestion	16 (3.3)	1 (0.8)	13 (3.0)	1 (0.9)	0	0
Sinus Disorder	0	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Sinus Pain	4 (0.8)	0	8 (1.9)	2 (1.8)	0	0
Sinus Polyp	1 (0.2)	1 (0.8)	0	0	0	0
Sleep Apnoea Syndrome	0	0	1 (0.2)	0	0	0
Sneezing	2 (0.4)	0	2 (0.5)	1 (0.9)	1 (2.0)	0
Sputum Discoloured	3 (0.6)	0	1 (0.2)	0	0	0
Sputum Increased	1 (0.2)	0	1 (0.2)	0	0	0
Tachypnoea	13 (2.7)	5 (4.0)	12 (2.8)	3 (2.7)	1 (2.0)	4 (44.4)
Throat Irritation	0	1 (0.8)	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)	0	0	0	0	0

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Tonsillar Ulcer	0	1 (0.8)	0	0	0	0
Upper-Airway Cough Syndrome	8 (1.7)	1 (0.8)	4 (0.9)	0	0	0
Vocal Cord Inflammation	1 (0.2)	0	0	0	0	0
Wheezing	17 (3.5)	2 (1.6)	16 (3.7)	7 (6.3)	4 (8.2)	2 (22.2)
Skin And Subcutaneous Tissue Disorders	**249 (52.0)**	**59 (46 8)**	**225 (52.6)**	**42 (37.8)**	**35 (71.4)**	**7 (77.8)**
Acne	0	2 (1.6)	5 (1.2)	3 (2.7)	0	0
Actinic Cheilitis	1 (0.2)	0	0	0	0	0
Acute Febrile Neutrophilic Dermatosis	0	0	1 (0.2)	0	1 (2.0)	0
Alopecia	21 (4.4)	10 (7.9)	14 (3.3)	10 (9.0)	3 (6.1)	0
Alopecia Totalis	1 (0.2)	0	0	0	0	0
Angioedema	1 (0.2)	0	1 (0.2)	0	0	0
Blister	10 (2.1)	0	5 (1.2)	0	0	0
Blood Blister	5 (1.0)	0	2 (0.5)	0	2 (4.1)	0
Cold Sweat	2 (0.4)	0	0	0	0	0
Cutaneous Vasculitis	1 (0.2)	0	0	0	0	0
Decubitus Ulcer	5 (1.0)	0	8 (1.9)	0	0	0
Dermal Cyst	0	0	1 (0.2)	0	0	0
Dermatitis	7 (1.5)	0	4 (0.9)	1 (0.9)	1 (2.0)	0
Dermatitis Acneiform	1 (0.2)	0	0	0	0	0
Dermatitis Allergic	12 (2.5)	0	6 (1.4)	0	0	0
Dermatitis Bullous	0	0	2 (0.5)	0	0	0
Dermatitis Contact	1 (0.2)	1 (0.8)	0	0	1 (2.0)	0

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Dermatitis Exfoliative	0	0	1 (0.2)	0	0	0
Drug Eruption	5 (1.0)	0	7 (1.6)	0	2 (4.1)	0
Dry Skin	12 (2.5)	4 (3 2)	12 (2.8)	1 (0.9)	0	1 (11.1)
Ecchymosis	7 (1.5)	1 (0.8)	14 (3.3)	3 (2.7)	3 (6.1)	0
Eczema	4 (0.8)	0	0	0	0	0
Erythema	32 (6.7)	9 (7.1)	28 (6.5)	4 (3.6)	4 (8.2)	1 (11.1)
Erythema Multiforme	0	0	0	1 (0.9)	0	0
Erythema Nodosum	0	0	0	0	1 (2.0)	0
Erythrosis	1 (0.2)	0	0	0	0	0
Exfoliative Rash	0	0	1 (0.2)	0	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 (0.6)	0	0	0	0	0
Hirsutism	1 (0.2)	1 (0.8)	0	0	0	0
Hyperhidrosis	17 (3.5)	3 (2.4)	17 (4.0)	2 (1.8)	3 (6.1)	0
Hypersensitivity Vasculitis	1 (0.2)	1 (0.8)	0	0	0	0
Hypertrichosis	2 (0.4)	0	1 (0.2)	0	0	0
Ingrowing Nail	1 (0.2)	3 (2.4)	0	1 (0.9)	0	0
Leukoplakia	1 (0.2)	0	0	1 (0.9)	0	0
Lichenification	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Lichenoid Keratosis	0	0	0	1 (0.9)	0	0
Lipohypertrophy	0	0	0	1 (0.9)	0	0
Livedo Reticularis	0	0	1 (0.2)	0	0	0

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Macule	1 (0.2)	0	1 (0.2)	0	0	0
Madarosis	0	0	0	1 (0.9)	0	0
Nail Disorder	1 (0.2)	0	0	0	0	0
Neurodermatitis	1 (0.2)	0	0	0	0	0
Night Sweats	16 (3.3)	2 (1.6)	9 (2.1)	1 (0.9)	1 (2.0)	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 (0.8)	0	6 (1.4)	0	0	0
Palmar Erythema	2 (0.4)	0	2 (0.5)	0	0	1 (11.1)
Palmar-Plantar Erythrodysaesthesia Syndrome	3 (0.6)	1 (0.8)	1 (0.2)	0	0	0
Papule	1 (0.2)	1 (0.8)	3 (0.7)	0	2 (4.1)	1 (11.1)
Penile Ulceration	0	0	1 (0.2)	0	0	0
Petechiae	49 (10.2)	10 (7.9)	43 (10.0)	9 (8 1)	7 (14.3)	2 (22.2)
Photosensitivity Reaction	0	1 (0.8)	2 (0.5)	0	0	0
Pigmentation Disorder	2 (0.4)	0	3 (0.7)	1 (0.9)	0	0
Prurigo	0	1 (0.8)	0	0	0	0
Pruritus	47 (9.8)	13 (10 3)	43 (10.0)	13 (11.7)	6 (12.2)	3 (33.3)
Pruritus Allergic	0	0	2 (0.5)	0	0	0
Pruritus Generalised	3 (0.6)	3 (2.4)	1 (0.2)	2 (1.8)	0	1 (11.1)
Psoriasis	0	0	1 (0.2)	0	0	0
Purpura	7 (1.5)	3 (2.4)	2 (0.5)	3 (2.7)	2 (4.1)	0
Purpura Senile	1 (0.2)	0	0	0	0	0
Rash	87 (18.2)	13 (10 3)	78 (18.2)	10 (9.0)	19 (38.8)	4 (44.4)

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Rash Erythematous	6 (1.3)	2 (1.6)	4 (0.9)	2 (1.8)	0	1 (11.1)
Rash Follicular	2 (0.4)	0	3 (0.7)	0	0	0
Rash Generalised	2 (0.4)	3 (2.4)	5 (1.2)	0	1 (2.0)	1 (11.1)
Rash Macular	4 (0.8)	1 (0.8)	1 (0.2)	1 (0.9)	2 (4.1)	0
Rash Maculo-Papular	8 (1.7)	6 (4.8)	7 (1.6)	0	0	1 (11.1)
Rash Papular	4 (0.8)	0	3 (0.7)	1 (0.9)	0	0
Rash Pruritic	5 (1.0)	2 (1.6)	11 (2.6)	1 (0.9)	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	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0
Skin Burning Sensation	1 (0.2)	0	1 (0.2)	0	0	0
Skin Discolouration	2 (0.4)	0	2 (0.5)	0	0	0
Skin Disorder	7 (1.5)	0	7 (1.6)	2 (1.8)	0	1 (11.1)
Skin Dystrophy	0	0	0	1 (0.9)	0	0
Skin Exfoliation	6 (1.3)	2 (1.6)	8 (1.9)	1 (0.9)	0	1 (11.1)
Skin Fissures	0	0	1 (0.2)	0	0	0
Skin Haemorrhage	1 (0.2)	0	0	0	0	0
Skin Hyperpigmentation	6 (1.3)	1 (0.8)	2 (0.5)	2 (1.8)	0	0
Skin Hypopigmentation	0	1 (0.8)	0	0	0	0
Skin Irritation	0	0	1 (0.2)	0	0	0
Skin Lesion	18 (3.8)	2 (1.6)	12 (2.8)	2 (1.8)	3 (6.1)	0
Skin Mass	4 (0.8)	1 (0.8)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Skin Necrosis	0	0	1 (0.2)	0	0	0
Skin Oedema	1 (0.2)	0	0	0	0	0
Skin Striae	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Skin Ulcer	4 (0.8)	1 (0.8)	2 (0.5)	0	0	0
Subcutaneous Emphysema	1 (0.2)	0	0	0	0	0
Swelling Face	5 (1.0)	2 (1.6)	1 (0.2)	0	1 (2.0)	0
Transient Acantholytic Dermatosis	1 (0.2)	0	0	0	0	0
Urticaria	9 (1.9)	4 (3 2)	8 (1.9)	2 (1.8)	0	1 (11.1)
Vascular Skin Disorder	0	1 (0.8)	0	0	0	0
Vitiligo	0	0	0	1 (0.9)	0	0
Xanthomatosis	0	0	1 (0.2)	0	0	0
Social Circumstances	**1 (0.2)**	**1 (0.8)**	**2 (0.5)**	**0**	**0**	**0**
Loss Of Personal Independence In Daily Activities	0	0	1 (0.2)	0	0	0
Menopause	0	1 (0.8)	0	0	0	0
Social Problem	1 (0.2)	0	0	0	0	0
Treatment Noncompliance	0	0	1 (0.2)	0	0	0
Surgical And Medical Procedures	**14 (2.9)**	**3 (2.4)**	**13 (3.0)**	**3 (2.7)**	**3 (6.1)**	**0**
Abscess Drainage	0	0	0	1 (0.9)	0	0
Analgesic Therapy	0	0	1 (0.2)	0	0	0
Artificial Crown Procedure	0	0	0	1 (0.9)	0	0
Astringent Therapy	1 (0.2)	0	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Blood Stem Cell Harvest	1 (0.2)	0	0	0	0	0
Bone Marrow Transplant	1 (0.2)	1 (0.8)	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 (0.5)	0	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	0	1 (0.8)	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 (1.0)	0	2 (0.5)	1 (0.9)	0	0
Stem Cell Transplant	1 (0.2)	0	0	0	0	0
Surgery	0	0	0	0	1 (2.0)	0
Therapeutic Procedure	1 (0.2)	0	0	0	0	0
Tooth Extraction	0	1 (0.8)	1 (0.2)	0	0	0
Wisdom Teeth Removal	1 (0.2)	0	1 (0.2)	0	0	0
Vascular Disorders	**186 (38.8)**	**45 (35.7)**	**174 (40.7)**	**42 (37.8)**	**21 (42.9)**	**3 (33.3)**
Air Embolism	1 (0.2)	0	0	0	0	0
Angiodysplasia	0	0	0	0	1 (2.0)	0
Arteriovenous Fistula	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 by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Capillary Leak Syndrome	1 (0.2)	0	0	0	0	0
Circulatory Collapse	1 (0.2)	1 (0.8)	3 (0.7)	3 (2.7)	0	0
Deep Vein Thrombosis	5 (1.0)	2 (1.6)	7 (1.6)	1 (0.9)	1 (2.0)	0
Diastolic Hypertension	0	0	1 (0.2)	0	0	0
Embolism Arterial	0	0	1 (0.2)	0	0	0
Flushing	5 (1.0)	0	10 (2.3)	0	3 (6.1)	0
Haematoma	13 (2.7)	3 (2.4)	13 (3.0)	3 (2.7)	5 (10.2)	0
Haemodynamic Instability	2 (0.4)	0	1 (0.2)	0	0	0
Haemorrhage	4 (0.8)	2 (1.6)	4 (0.9)	1 (0.9)	0	0
Haemorrhagic Infarction	0	0	1 (0.2)	0	0	0
Hot Flush	0	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Hyperaemia	1 (0.2)	0	0	0	0	0
Hypertension	92 (19.2)	18 (14 3)	83 (19.4)	12 (10.8)	5 (10.2)	0
Hypertensive Crisis	1 (0.2)	0	1 (0.2)	0	0	0
Hypotension	64 (13.4)	20 (15 9)	59 (13.8)	20 (18.0)	8 (16.3)	3 (33.3)
Hypovolaemic Shock	0	2 (1.6)	3 (0.7)	1 (0.9)	0	0
Intermittent Claudication	1 (0.2)	0	0	0	0	0
Ischaemia	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Jugular Vein Thrombosis	0	0	1 (0.2)	0	0	0
Labile Hypertension	0	0	0	1 (0.9)	0	0
Microangiopathy	1 (0.2)	0	0	0	0	0
Orthostatic Hypotension	15 (3.1)	1 (0.8)	4 (0.9)	3 (2.7)	1 (2.0)	0
Pallor	6 (1.3)	1 (0.8)	3 (0.7)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Peripheral Circulatory Failure	1 (0.2)	0	0	0	0	0
Peripheral Coldness	0	0	1 (0.2)	0	0	0
Peripheral Vascular Disorder	1 (0.2)	0	0	0	0	0
Peripheral Venous Disease	1 (0.2)	0	0	0	0	0
Phlebitis	3 (0.6)	4 (3.2)	4 (0.9)	4 (3.6)	1 (2.0)	0
Poor Peripheral Circulation	0	0	2 (0.5)	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	3 (0.7)	1 (0.9)	0	0
Subclavian Vein Thrombosis	2 (0.4)	0	0	0	0	0
Superior Vena Cava Stenosis	0	0	1 (0.2)	0	0	0
Thrombophlebitis	5 (1.0)	0	6 (1.4)	0	0	0
Thrombophlebitis Superficial	0	0	1 (0.2)	0	1 (2.0)	0
Thrombosis	1 (0.2)	0	2 (0.5)	0	0	0
Varicose Vein	1 (0.2)	0	0	0	0	0
Vasculitis	1 (0.2)	0	0	0	1 (2.0)	0
Vasodilatation	0	0	1 (0.2)	0	1 (2.0)	0
Vein Disorder	1 (0.2)	0	0	0	0	0
Vena Cava Embolism	0	0	1 (0.2)	0	0	0
Venous Thrombosis	3 (0.6)	0	6 (1.4)	0	0	0

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Pooled Prophylaxis Safety Analysis: CI98-316, P01899
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
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.
MedDRA Version 20.1

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付録 2.7.4-173　　人種別の重度／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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Subjects Reporting Any Adverse Event	**355 (74.1)**	**93 (73 8)**	**306 (71.5)**	**75 (67.6)**	**38 (77.6)**	**9 (100.0)**
Blood And Lymphatic System Disorders	**187 (39.0)**	**52 (41 3)**	**169 (39.5)**	**42 (37.8)**	**22 (44.9)**	**6 (66.7)**
Anaemia	46 (9.6)	21 (16.7)	36 (8.4)	12 (10.8)	7 (14.3)	5 (55.6)
Bone Marrow Disorder	0	0	1 (0.2)	0	0	0
Bone Marrow Failure	3 (0.6)	0	0	0	0	0
Coagulopathy	0	0	4 (0.9)	0	1 (2.0)	0
Disseminated Intravascular Coagulation	1 (0.2)	1 (0.8)	4 (0.9)	0	0	0
Febrile Neutropenia	36 (7.5)	13 (10 3)	30 (7.0)	10 (9.0)	5 (10.2)	2 (22.2)
Granulocytopenia	1 (0.2)	0	1 (0.2)	0	0	0
Haemolysis	1 (0.2)	0	0	2 (1.8)	0	0
Haemolytic Uraemic Syndrome	4 (0.8)	1 (0.8)	1 (0.2)	0	0	0
Haemorrhagic Diathesis	0	0	2 (0.5)	0	0	0
Leukocytosis	1 (0.2)	0	1 (0.2)	0	0	0
Leukopenia	13 (2.7)	6 (4.8)	16 (3.7)	4 (3.6)	2 (4.1)	3 (33.3)
Lymphadenitis	0	0	1 (0.2)	0	0	0
Lymphadenopathy	1 (0.2)	0	2 (0.5)	0	1 (2.0)	0
Lymphopenia	0	0	1 (0.2)	0	0	0
Microangiopathic Haemolytic Anaemia	0	0	1 (0.2)	0	0	0
Neutropenia	72 (15.0)	23 (18 3)	59 (13.8)	20 (18.0)	16 (32.7)	3 (33.3)
Pancytopenia	9 (1.9)	0	8 (1.9)	5 (4.5)	1 (2.0)	0
Splenomegaly	0	0	1 (0.2)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Thrombocytopenia	106 (22.1)	37 (29.4)	100 (23.4)	17 (15.3)	11 (22.4)	5 (55.6)
Thrombocytosis	0	0	1 (0.2)	0	0	0
Thrombotic Microangiopathy	0	0	1 (0.2)	0	0	0
Thrombotic Thrombocytopenic Purpura	7 (1.5)	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Cardiac Disorders	**35 (7.3)**	**11 (8.7)**	**33 (7.7)**	**7 (6.3)**	**5 (10.2)**	**0**
Acute Myocardial Infarction	0	1 (0.8)	0	0	0	0
Angina Pectoris	1 (0.2)	0	0	0	0	0
Arrhythmia	1 (0.2)	1 (0.8)	0	0	0	0
Arrhythmia Supraventricular	0	0	1 (0.2)	0	0	0
Atrial Fibrillation	7 (1.5)	1 (0.8)	7 (1.6)	1 (0 9)	2 (4.1)	0
Atrial Flutter	1 (0.2)	0	2 (0.5)	0	0	0
Atrioventricular Block	0	0	1 (0.2)	0	0	0
Atrioventricular Block Complete	1 (0.2)	0	0	0	0	0
Bradycardia	4 (0.8)	0	0	1 (0.9)	0	0
Bundle Branch Block Left	0	0	1 (0.2)	0	0	0
Bundle Branch Block Right	0	0	1 (0.2)	0	0	0
Cardiac Arrest	5 (1.0)	2 (1.6)	6 (1.4)	0	1 (2.0)	0
Cardiac Failure	2 (0.4)	1 (0.8)	3 (0.7)	0	0	0
Cardiac Failure Congestive	1 (0.2)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Cardio-Respiratory Arrest	2 (0.4)	1 (0.8)	3 (0.7)	3 (2.7)	0	0
Cardiomegaly	0	1 (0.8)	0	0	0	0
Cardiomyopathy	0	0	0	0	1 (2.0)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Cardiopulmonary Failure	1 (0.2)	0	0	0	0	0
Cardiotoxicity	0	0	1 (0.2)	0	0	0
Cardiovascular Disorder	0	0	1 (0.2)	0	0	0
Cardiovascular Insufficiency	3 (0.6)	0	1 (0.2)	0	0	0
Congestive Cardiomyopathy	1 (0.2)	0	0	0	0	0
Endocarditis Noninfective	0	0	1 (0.2)	0	0	0
Intracardiac Mass	0	0	1 (0.2)	0	0	0
Left Atrial Dilatation	0	1 (0.8)	0	0	0	0
Left Ventricular Dysfunction	1 (0.2)	0	0	0	0	0
Left Ventricular Hypertrophy	0	1 (0.8)	0	0	0	0
Mitral Valve Incompetence	0	1 (0.8)	0	0	0	0
Myocardial Infarction	3 (0.6)	0	0	0	0	0
Myocardial Ischaemia	1 (0.2)	0	0	0	0	0
Myocarditis	0	1 (0.8)	0	0	0	0
Palpitations	0	1 (0.8)	0	0	0	0
Pericardial Effusion	0	0	3 (0.7)	0	0	0
Pericarditis	0	1 (0.8)	0	0	0	0
Sinus Tachycardia	1 (0.2)	1 (0.8)	1 (0.2)	2 (1.8)	0	0
Subendocardial Ischaemia	0	0	0	1 (0.9)	0	0
Supraventricular Tachycardia	1 (0.2)	2 (1.6)	2 (0.5)	0	1 (2.0)	0
Tachycardia	5 (1.0)	1 (0.8)	4 (0.9)	0	3 (6.1)	0
Torsade De Pointes	1 (0.2)	0	0	1 (0.9)	0	0
Ventricular Extrasystoles	2 (0.4)	0	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Ear And Labyrinth Disorders	**2 (0.4)**	**1 (0.8)**	**1 (0.2)**	**1 (0.9)**	**0**	**0**
Deafness	0	0	1 (0.2)	0	0	0
Ear Discomfort	0	0	0	1 (0.9)	0	0
Hypoacusis	2 (0.4)	0	0	0	0	0
Vertigo	0	1 (0.8)	0	0	0	0
Endocrine Disorders	**1 (0.2)**	**0**	**0**	**0**	**1 (2.0)**	**0**
Adrenal Insufficiency	0	0	0	0	1 (2.0)	0
Cushing's Syndrome	1 (0.2)	0	0	0	0	0
Eye Disorders	**2 (0.4)**	**2 (1.6)**	**7 (1.6)**	**7 (6.3)**	**0**	**0**
Choroiditis	0	0	0	1 (0.9)	0	0
Conjunctival Haemorrhage	0	0	1 (0.2)	1 (0.9)	0	0
Corneal Degeneration	0	0	1 (0.2)	0	0	0
Diplopia	0	0	1 (0.2)	0	0	0
Dry Eye	0	0	1 (0.2)	0	0	0
Eye Haemorrhage	0	0	1 (0.2)	0	0	0
Eye Oedema	0	0	1 (0.2)	0	0	0
Eye Pain	0	0	1 (0.2)	0	0	0
Eye Pruritus	1 (0.2)	0	0	0	0	0
Glaucoma	1 (0.2)	0	0	0	0	0
Mydriasis	0	0	0	2 (1.8)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Photophobia	0	0	0	1 (0.9)	0	0
Pupils Unequal	0	1 (0.8)	0	1 (0.9)	0	0
Scleral Haemorrhage	0	0	0	1 (0.9)	0	0
Vision Blurred	0	1 (0.8)	0	0	0	0
Visual Acuity Reduced	0	0	1 (0.2)	0	0	0
Visual Impairment	1 (0.2)	0	0	0	0	0
Gastrointestinal Disorders	**98 (20.5)**	**13 (10 3)**	**88 (20.6)**	**14 (12.6)**	**10 (20.4)**	**2 (22.2)**
Abdominal Compartment Syndrome	0	0	1 (0.2)	0	0	0
Abdominal Discomfort	0	0	1 (0.2)	0	0	0
Abdominal Distension	3 (0.6)	0	2 (0.5)	2 (1.8)	0	0
Abdominal Pain	13 (2.7)	3 (2.4)	17 (4.0)	0	0	0
Abdominal Pain Lower	1 (0.2)	0	0	0	0	0
Abdominal Pain Upper	4 (0.8)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Abdominal Rigidity	0	0	1 (0.2)	0	0	0
Abdominal Tenderness	1 (0.2)	0	1 (0.2)	0	0	0
Acute Abdomen	1 (0.2)	0	1 (0.2)	0	0	0
Anal Fissure	1 (0.2)	1 (0.8)	0	0	0	0
Anal Fistula	0	0	0	0	1 (2.0)	0
Anal Incontinence	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Anal Ulcer	1 (0.2)	0	0	0	0	0
Anorectal Discomfort	1 (0.2)	0	0	0	0	0
Ascites	4 (0.8)	1 (0.8)	5 (1.2)	1 (0.9)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Change Of Bowel Habit	1 (0.2)	0	0	0	0	0
Colitis	2 (0.4)	0	2 (0.5)	3 (2.7)	0	1 (11.1)
Colitis Ulcerative	1 (0.2)	0	0	0	0	0
Constipation	1 (0.2)	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Crohn's Disease	1 (0.2)	0	0	0	0	0
Diarrhoea	18 (3.8)	4 (3 2)	23 (5.4)	1 (0.9)	2 (4.1)	1 (11.1)
Diarrhoea Haemorrhagic	2 (0.4)	1 (0.8)	3 (0.7)	2 (1.8)	0	0
Dry Mouth	1 (0.2)	0	0	0	0	0
Duodenal Perforation	1 (0.2)	0	0	0	0	0
Duodenitis Haemorrhagic	0	0	1 (0.2)	0	0	0
Dyspepsia	1 (0.2)	0	2 (0.5)	0	0	0
Dysphagia	2 (0.4)	0	4 (0.9)	2 (1.8)	0	0
Enteritis	1 (0.2)	0	0	0	0	0
Erosive Oesophagitis	1 (0.2)	0	0	0	0	0
Gastric Disorder	1 (0.2)	0	0	0	0	0
Gastric Haemorrhage	0	1 (0.8)	0	0	0	0
Gastric Ulcer	1 (0.2)	0	1 (0.2)	0	0	0
Gastric Ulcer Haemorrhage	2 (0.4)	0	1 (0.2)	0	0	0
Gastritis	0	0	3 (0.7)	0	0	0
Gastritis Erosive	1 (0.2)	0	0	0	0	0
Gastritis Haemorrhagic	1 (0.2)	0	0	0	0	0
Gastrointestinal Haemorrhage	13 (2.7)	0	10 (2.3)	4 (3.6)	0	0
Gastrointestinal Pain	1 (0.2)	0	1 (0.2)	0	0	0

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Gastrointestinal Sounds Abnormal	0	0	1 (0.2)	0	0	0
Gastrointestinal Ulcer Haemorrhage	1 (0.2)	0	0	0	0	0
Gastrooesophageal Reflux Disease	1 (0.2)	0	1 (0.2)	0	0	0
Gingival Bleeding	1 (0.2)	0	1 (0.2)	0	0	0
Glossitis	0	0	1 (0.2)	0	0	0
Haematemesis	4 (0.8)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Haematochezia	0	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Haemorrhoidal Haemorrhage	0	0	1 (0.2)	0	0	0
Haemorrhoids	4 (0.8)	0	0	0	1 (2.0)	0
Ileus	3 (0.6)	0	4 (0.9)	1 (0.9)	0	0
Ileus Paralytic	0	0	2 (0.5)	0	0	0
Inguinal Hernia	0	0	1 (0.2)	0	0	0
Intestinal Haemorrhage	1 (0.2)	0	1 (0.2)	0	0	0
Intestinal Infarction	1 (0.2)	0	0	0	0	0
Intestinal Ischaemia	1 (0.2)	0	0	0	0	0
Intestinal Mass	0	0	0	1 (0.9)	0	0
Intestinal Obstruction	1 (0.2)	0	1 (0.2)	0	0	0
Intestinal Ulcer	1 (0.2)	0	1 (0.2)	0	0	0
Intra-Abdominal Fluid Collection	0	0	0	1 (0.9)	0	0
Malabsorption	1 (0.2)	0	0	0	0	0
Melaena	4 (0.8)	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Mouth Haemorrhage	2 (0.4)	0	1 (0.2)	0	0	0
Nausea	24 (5.0)	2 (1.6)	9 (2.1)	1 (0.9)	3 (6.1)	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Neutropenic Colitis	4 (0.8)	0	0	1 (0.9)	0	1 (11.1)
Odynophagia	0	0	1 (0.2)	0	0	0
Oesophageal Ulcer	1 (0.2)	0	0	0	0	0
Oesophagitis	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Oral Mucosal Blistering	0	0	0	0	1 (2.0)	0
Oral Pain	0	2 (1.6)	0	2 (1.8)	1 (2.0)	0
Pancreatitis	0	1 (0.8)	1 (0.2)	0	0	0
Pancreatitis Acute	1 (0.2)	0	0	0	0	0
Proctalgia	0	0	1 (0.2)	1 (0.9)	1 (2.0)	0
Rectal Haemorrhage	3 (0.6)	0	0	1 (0.9)	0	0
Rectal Tenesmus	1 (0.2)	0	0	0	0	0
Small Intestinal Obstruction	1 (0.2)	0	0	0	0	0
Stomatitis	1 (0.2)	0	1 (0.2)	0	0	0
Subileus	1 (0.2)	0	0	0	0	0
Swollen Tongue	0	0	0	1 (0.9)	0	0
Upper Gastrointestinal Haemorrhage	1 (0.2)	1 (0.8)	0	0	0	0
Vomiting	14 (2.9)	2 (1.6)	13 (3.0)	1 (0.9)	0	0
General Disorders And Administration Site Conditions	**96 (20.0)**	**25 (19 8)**	**89 (20.8)**	**15 (13.5)**	**13 (26.5)**	**2 (22.2)**
Adverse Drug Reaction	0	1 (0.8)	0	0	0	0
Asthenia	11 (2.3)	1 (0.8)	10 (2.3)	2 (1.8)	1 (2.0)	0
Catheter Site Bruise	0	0	1 (0.2)	0	0	0
Catheter Site Erythema	0	0	0	0	1 (2.0)	0

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Catheter Site Haematoma	0	1 (0.8)	0	0	0	0
Catheter Site Haemorrhage	1 (0.2)	0	0	0	0	0
Catheter Site Inflammation	0	0	0	0	1 (2.0)	0
Chest Pain	4 (0.8)	2 (1.6)	5 (1.2)	1 (0.9)	0	0
Chills	8 (1.7)	0	1 (0.2)	1 (0.9)	1 (2.0)	1 (11.1)
Death	0	0	1 (0.2)	0	0	0
Disease Progression	2 (0.4)	0	2 (0.5)	0	0	0
Drug Interaction	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Drug Intolerance	0	0	2 (0.5)	0	0	0
Fatigue	13 (2.7)	3 (2.4)	6 (1.4)	2 (1.8)	0	0
Gait Disturbance	0	0	1 (0.2)	1 (0.9)	0	0
General Physical Health Deterioration	2 (0.4)	0	0	1 (0.9)	0	0
Generalised Oedema	2 (0.4)	0	4 (0.9)	0	0	0
Hyperpyrexia	0	0	0	0	0	1 (11.1)
Hyperthermia	1 (0.2)	0	1 (0.2)	0	0	0
Hypothermia	0	1 (0.8)	1 (0.2)	0	0	0
Malaise	0	0	0	1 (0.9)	0	0
Mucosal Haemorrhage	0	0	1 (0.2)	0	0	0
Mucosal Inflammation	14 (2.9)	3 (2.4)	11 (2.6)	3 (2.7)	1 (2.0)	0
Multi-Organ Disorder	1 (0.2)	0	0	0	0	0
Multiple Organ Dysfunction Syndrome	14 (2.9)	1 (0.8)	8 (1.9)	1 (0 9)	2 (4.1)	0
Necrosis	1 (0.2)	0	0	0	0	0
Nodule	0	0	1 (0.2)	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Oedema	1 (0.2)	0	4 (0.9)	1 (0.9)	0	0
Oedema Peripheral	4 (0.8)	0	1 (0.2)	1 (0.9)	0	0
Pain	2 (0.4)	2 (1.6)	2 (0.5)	0	0	0
Performance Status Decreased	2 (0.4)	0	0	0	0	0
Peripheral Swelling	2 (0.4)	0	0	0	0	0
Pyrexia	31 (6.5)	14 (11 1)	45 (10.5)	7 (6 3)	10 (20.4)	0
Sudden Death	0	0	1 (0.2)	0	0	0
Therapy Non-Responder	4 (0.8)	0	2 (0.5)	0	0	0
Thirst	0	0	0	1 (0.9)	0	0
Hepatobiliary Disorders	**31 (6.5)**	**6 (4.8)**	**23 (5.4)**	**5 (4.5)**	**3 (6.1)**	**2 (22.2)**
Acute Hepatic Failure	1 (0.2)	0	0	0	0	0
Cholecystitis	0	0	1 (0.2)	0	0	0
Cholecystitis Acute	0	0	0	0	1 (2.0)	0
Cholelithiasis	1 (0.2)	0	0	0	0	0
Cholestasis	1 (0.2)	1 (0.8)	0	0	0	0
Drug-Induced Liver Injury	0	0	1 (0.2)	0	0	0
Hepatic Failure	6 (1.3)	1 (0.8)	3 (0.7)	1 (0.9)	0	0
Hepatic Function Abnormal	2 (0.4)	0	3 (0.7)	0	0	0
Hepatic Necrosis	1 (0.2)	0	0	0	0	0
Hepatitis	0	0	1 (0.2)	1 (0.9)	0	0
Hepatitis Acute	1 (0.2)	0	0	0	0	0
Hepatocellular Injury	2 (0.4)	1 (0.8)	0	0	0	0

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Hepatotoxicity	3 (0.6)	0	0	0	0	0
Hyperbilirubinaemia	13 (2.7)	3 (2.4)	10 (2.3)	3 (2.7)	2 (4.1)	2 (22.2)
Hypertransaminasaemia	1 (0.2)	0	0	0	0	0
Jaundice	5 (1.0)	1 (0.8)	5 (1.2)	0	0	0
Liver Disorder	0	0	1 (0.2)	0	0	0
Liver Injury	1 (0.2)	0	0	0	0	0
Ocular Icterus	1 (0.2)	0	0	0	0	0
Immune System Disorders	**44 (9.2)**	**6 (4.8)**	**44 (10.3)**	**9 (8.1)**	**2 (4.1)**	**0**
Acute Graft Versus Host Disease In Liver	0	0	0	1 (0.9)	0	0
Anaphylactic Reaction	1 (0.2)	0	2 (0.5)	0	0	0
Chronic Graft Versus Host Disease	1 (0.2)	0	0	1 (0.9)	0	0
Drug Hypersensitivity	1 (0.2)	0	1 (0.2)	0	2 (4.1)	0
Graft Versus Host Disease	26 (5.4)	5 (4.0)	22 (5.1)	6 (5.4)	0	0
Graft Versus Host Disease In Gastrointestinal Tract	13 (2.7)	2 (1.6)	11 (2.6)	1 (0 9)	0	0
Graft Versus Host Disease In Liver	7 (1.5)	3 (2.4)	4 (0.9)	1 (0.9)	0	0
Graft Versus Host Disease In Lung	0	0	3 (0.7)	0	0	0
Graft Versus Host Disease In Skin	8 (1.7)	1 (0.8)	6 (1.4)	0	0	0
Hypogammaglobulinaemia	1 (0.2)	0	0	0	0	0
Immune System Disorder	0	0	1 (0.2)	0	0	0
Transplant Rejection	2 (0.4)	0	0	0	0	0
Infections And Infestations	**152 (31.7)**	**39 (31.0)**	**140 (32.7)**	**26 (23.4)**	**18 (36.7)**	**6 (66.7)**

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	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Abscess Fungal	0	0	1 (0.2)	0	0	0
Abscess Limb	0	0	1 (0.2)	0	0	0
Acid Fast Bacilli Infection	1 (0.2)	0	0	0	0	0
Acinetobacter Infection	0	0	0	1 (0.9)	0	0
Acute Sinusitis	1 (0.2)	0	0	0	0	0
Anal Abscess	1 (0.2)	0	0	0	0	0
Anorectal Infection	0	1 (0.8)	0	0	0	0
Aspergilloma	0	0	1 (0.2)	0	0	0
Aspergillus Infection	2 (0.4)	1 (0.8)	9 (2.1)	1 (0 9)	1 (2.0)	0
Atypical Pneumonia	1 (0.2)	0	0	0	0	0
Bacteraemia	29 (6.1)	7 (5.6)	17 (4.0)	2 (1.8)	6 (12.2)	0
Bacterial Infection	5 (1.0)	0	3 (0.7)	0	1 (2.0)	0
Bacterial Sepsis	3 (0.6)	1 (0.8)	3 (0.7)	0	0	0
Bk Virus Infection	1 (0.2)	0	0	0	0	0
Bronchitis	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Bronchopulmonary Aspergillosis	3 (0.6)	0	8 (1.9)	1 (0.9)	1 (2.0)	1 (11.1)
Candida Infection	1 (0.2)	0	4 (0.9)	0	0	0
Candida Sepsis	1 (0.2)	0	0	0	0	0
Catheter Site Cellulitis	0	0	1 (0.2)	0	0	0
Catheter Site Infection	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Cavernous Sinus Thrombosis	0	0	1 (0.2)	0	0	0
Cellulitis	3 (0.6)	1 (0.8)	4 (0.9)	0	0	0
Cerebral Toxoplasmosis	0	0	2 (0.5)	0	0	0

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Chronic Sinusitis	1 (0.2)	0	0	0	0	0
Clostridial Infection	2 (0.4)	0	0	0	0	0
Clostridium Bacteraemia	0	0	1 (0.2)	0	0	0
Clostridium Difficile Colitis	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Clostridium Difficile Infection	1 (0.2)	0	0	0	0	0
Conjunctivitis	0	1 (0.8)	1 (0.2)	0	0	0
Corynebacterium Infection	0	0	1 (0.2)	0	0	0
Corynebacterium Sepsis	1 (0.2)	0	0	0	0	0
Cystitis	1 (0.2)	1 (0.8)	0	0	0	0
Cystitis Klebsiella	1 (0.2)	0	0	0	0	0
Cytomegalovirus Colitis	0	1 (0.8)	2 (0.5)	0	0	0
Cytomegalovirus Gastritis	0	0	1 (0.2)	0	0	0
Cytomegalovirus Gastroenteritis	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Cytomegalovirus Infection	9 (1.9)	2 (1.6)	10 (2.3)	1 (0.9)	0	0
Cytomegalovirus Viraemia	2 (0.4)	1 (0.8)	1 (0.2)	0	0	0
Device Related Infection	10 (2.1)	1 (0.8)	7 (1.6)	3 (2.7)	2 (4.1)	0
Device Related Sepsis	2 (0.4)	0	1 (0.2)	0	1 (2.0)	0
Ear Infection	1 (0.2)	0	0	0	0	0
Emphysematous Cystitis	1 (0.2)	0	0	0	0	0
Encephalitis	2 (0.4)	0	1 (0.2)	0	0	0
Encephalitis Viral	0	0	1 (0.2)	0	0	0
Enterobacter Bacteraemia	0	1 (0.8)	0	0	0	0
Enterobacter Infection	1 (0.2)	0	0	0	0	0

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Enterobacter Sepsis	1 (0.2)	0	0	0	0	0
Enterococcal Bacteraemia	2 (0.4)	0	0	0	1 (2.0)	2 (22.2)
Enterococcal Infection	1 (0.2)	0	3 (0.7)	1 (0.9)	0	0
Enterococcal Sepsis	0	0	1 (0.2)	0	0	0
Epstein-Barr Virus Infection	0	0	4 (0.9)	0	0	0
Erysipelas	0	0	1 (0.2)	0	1 (2.0)	0
Escherichia Bacteraemia	3 (0.6)	0	1 (0.2)	0	0	0
Escherichia Infection	0	0	1 (0.2)	0	0	0
Escherichia Sepsis	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Escherichia Urinary Tract Infection	0	0	1 (0.2)	0	0	0
Fungaemia	0	0	1 (0.2)	0	0	0
Fungal Infection	4 (0.8)	0	4 (0.9)	1 (0.9)	0	0
Fungal Rhinitis	0	0	1 (0.2)	0	0	0
Fungal Sepsis	1 (0.2)	0	1 (0.2)	0	0	0
Fusobacterium Infection	0	0	1 (0.2)	0	0	0
Gangrene	0	0	1 (0.2)	0	0	0
Gastroenteritis	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Gastroenteritis Rotavirus	0	0	1 (0.2)	0	0	0
Gastrointestinal Infection	0	1 (0.8)	0	0	0	0
Herpes Dermatitis	0	0	1 (0.2)	0	0	0
Herpes Pharyngitis	0	0	1 (0.2)	0	0	0
Herpes Simplex	3 (0.6)	0	1 (0.2)	0	0	0
Herpes Virus Infection	0	0	1 (0.2)	0	0	0

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Herpes Zoster	1 (0.2)	2 (1.6)	1 (0.2)	0	0	0
Human Herpesvirus 6 Infection	0	0	1 (0.2)	0	0	0
Infection	1 (0.2)	0	1 (0.2)	0	0	0
Influenza	0	0	1 (0.2)	0	0	0
Infusion Site Infection	0	0	1 (0.2)	0	0	0
Klebsiella Bacteraemia	0	2 (1.6)	3 (0.7)	1 (0.9)	0	1 (11.1)
Klebsiella Infection	0	0	2 (0.5)	0	0	0
Klebsiella Sepsis	1 (0.2)	0	0	0	0	0
Leptotrichia Infection	0	0	0	1 (0.9)	0	0
Liver Abscess	0	0	1 (0.2)	0	0	0
Localised Infection	1 (0.2)	0	1 (0.2)	0	0	0
Lower Respiratory Tract Infection	3 (0.6)	0	1 (0.2)	1 (0.9)	0	0
Lung Abscess	1 (0.2)	0	0	0	0	0
Mastoiditis	0	1 (0.8)	0	0	0	0
Meningitis Listeria	0	0	1 (0.2)	0	0	0
Meningococcal Infection	0	0	1 (0.2)	0	0	0
Micrococcus Infection	1 (0.2)	0	0	0	0	0
Mycobacterial Infection	0	0	1 (0.2)	0	0	0
Mycobacterium Avium Complex Infection	0	0	1 (0.2)	0	0	0
Neutropenic Sepsis	1 (0.2)	1 (0.8)	1 (0.2)	0	0	3 (33.3)
Nocardiosis	0	1 (0.8)	1 (0.2)	0	0	0
Oesophageal Candidiasis	0	0	1 (0.2)	1 (0.9)	0	0
Oral Candidiasis	0	0	0	0	1 (2.0)	0

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Oral Herpes	2 (0.4)	1 (0.8)	2 (0.5)	0	0	0
Oropharyngeal Candidiasis	0	0	0	0	1 (2.0)	0
Peritonitis	0	0	1 (0.2)	0	0	0
Peritonitis Bacterial	0	0	1 (0.2)	0	0	0
Pharyngitis	0	1 (0.8)	1 (0.2)	0	0	0
Pneumocystis Jirovecii Pneumonia	0	1 (0.8)	1 (0.2)	0	0	0
Pneumonia	21 (4.4)	5 (4.0)	20 (4.7)	4 (3.6)	1 (2.0)	2 (22.2)
Pneumonia Bacterial	2 (0.4)	1 (0.8)	0	0	0	0
Pneumonia Cytomegaloviral	0	3 (2.4)	0	0	0	0
Pneumonia Fungal	3 (0.6)	1 (0.8)	2 (0.5)	0	1 (2.0)	0
Pneumonia Klebsiella	2 (0.4)	0	4 (0.9)	0	0	0
Pneumonia Necrotising	0	0	1 (0.2)	0	0	0
Pneumonia Pseudomonal	1 (0.2)	0	1 (0.2)	0	0	0
Pneumonia Staphylococcal	2 (0.4)	0	1 (0.2)	0	0	0
Pneumonia Streptococcal	0	0	1 (0.2)	0	0	0
Pneumonia Viral	0	1 (0.8)	0	0	0	0
Pseudomembranous Colitis	2 (0.4)	0	0	0	0	0
Pseudomonal Bacteraemia	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Pseudomonal Sepsis	3 (0.6)	0	1 (0.2)	1 (0.9)	0	0
Pseudomonas Infection	2 (0.4)	0	3 (0.7)	1 (0.9)	0	0
Pulmonary Mycosis	2 (0.4)	1 (0.8)	3 (0.7)	0	0	0
Relapsing Fever	0	0	1 (0.2)	0	0	0
Respiratory Syncytial Virus Infection	0	0	1 (0.2)	0	0	0

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Number (%) of Subjects

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Rhinovirus Infection	0	0	0	0	0	1 (11.1)
Scedosporium Infection	0	0	1 (0.2)	0	0	0
Sepsis	12 (2.5)	2 (1.6)	13 (3.0)	2 (1.8)	2 (4.1)	1 (11.1)
Sepsis Syndrome	1 (0.2)	0	0	0	0	0
Septic Embolus	0	1 (0.8)	0	0	0	0
Septic Shock	13 (2.7)	3 (2.4)	8 (1.9)	6 (5.4)	5 (10.2)	1 (11.1)
Sinusitis	4 (0.8)	0	1 (0.2)	0	0	0
Sinusitis Bacterial	1 (0.2)	0	0	0	0	0
Sinusitis Fungal	0	0	0	0	1 (2.0)	0
Staphylococcal Bacteraemia	6 (1.3)	1 (0.8)	5 (1.2)	0	1 (2.0)	0
Staphylococcal Infection	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Staphylococcal Sepsis	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Streptococcal Bacteraemia	1 (0.2)	0	2 (0.5)	0	1 (2.0)	0
Streptococcal Infection	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Streptococcal Sepsis	3 (0.6)	0	0	0	0	0
Superinfection	1 (0.2)	0	0	0	0	0
Systemic Candida	3 (0.6)	1 (0.8)	2 (0.5)	0	0	0
Systemic Mycosis	0	1 (0.8)	1 (0.2)	2 (1.8)	0	0
Tracheobronchitis	1 (0.2)	0	1 (0.2)	0	0	0
Upper Respiratory Tract Infection	2 (0.4)	1 (0.8)	2 (0.5)	0	0	0
Urinary Tract Infection	2 (0.4)	1 (0.8)	2 (0.5)	0	0	0
Urinary Tract Infection Pseudomonal	1 (0.2)	0	0	0	0	0
Urinary Tract Infection Viral	0	0	0	1 (0.9)	0	0

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Varicella Zoster Pneumonia	1 (0.2)	0	0	0	0	0
Varicella Zoster Virus Infection	2 (0.4)	0	0	0	0	0
Viral Haemorrhagic Cystitis	1 (0.2)	0	0	0	0	0
Viral Infection	1 (0.2)	0	2 (0.5)	0	0	0
Injury, Poisoning And Procedural Complications	**13 (2.7)**	**4 (3.2)**	**18 (4.2)**	**4 (3.6)**	**1 (2.0)**	**0**
Accidental Overdose	0	0	1 (0.2)	0	0	0
Back Injury	1 (0.2)	0	0	0	0	0
Brain Herniation	0	0	0	0	1 (2.0)	0
Complications Of Transplant Surgery	1 (0.2)	0	0	0	0	0
Compression Fracture	1 (0.2)	0	0	0	0	0
Contusion	0	0	0	1 (0.9)	0	0
Fall	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Femoral Neck Fracture	1 (0.2)	0	1 (0.2)	0	0	0
Head Injury	0	0	1 (0.2)	0	0	0
Hip Fracture	1 (0.2)	0	1 (0.2)	0	0	0
Lumbar Vertebral Fracture	1 (0.2)	0	0	0	0	0
Overdose	0	0	1 (0.2)	0	0	0
Post Procedural Haemorrhage	1 (0.2)	0	2 (0.5)	0	0	0
Postoperative Fever	0	0	1 (0.2)	0	0	0
Sedation Complication	1 (0.2)	0	0	0	0	0
Spinal Fracture	0	1 (0.8)	0	0	0	0
Subarachnoid Haemorrhage	0	2 (1.6)	0	0	0	0

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Subdural Haematoma	1 (0.2)	0	3 (0.7)	0	0	0
Toxicity To Various Agents	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Transfusion Reaction	1 (0.2)	0	2 (0.5)	0	0	0
Transplant Failure	1 (0.2)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Investigations	**77 (16.1)**	**22 (17 5)**	**66 (15.4)**	**23 (20.7)**	**5 (10.2)**	**0**
Activated Partial Thromboplastin Time Prolonged	0	0	0	1 (0.9)	0	0
Alanine Aminotransferase Abnormal	1 (0.2)	0	1 (0.2)	0	0	0
Alanine Aminotransferase Increased	8 (1.7)	4 (3.2)	9 (2.1)	5 (4.5)	1 (2.0)	0
Ammonia Increased	1 (0.2)	0	0	0	0	0
Aspartate Aminotransferase Increased	2 (0.4)	1 (0.8)	7 (1.6)	1 (0.9)	0	0
Bacterial Test Positive	3 (0.6)	1 (0.8)	6 (1.4)	0	0	0
Basophil Count Increased	1 (0.2)	0	0	0	0	0
Bilirubin Conjugated Increased	1 (0.2)	0	1 (0.2)	0	0	0
Blast Cells Present	1 (0.2)	0	0	0	0	0
Bleeding Time Prolonged	2 (0.4)	0	0	0	0	0
Blood Albumin Abnormal	1 (0.2)	0	0	0	0	0
Blood Alkaline Phosphatase Increased	5 (1.0)	0	0	0	0	0
Blood Bicarbonate Decreased	0	1 (0.8)	1 (0.2)	0	0	0
Blood Bilirubin Increased	7 (1.5)	0	10 (2.3)	4 (3.6)	2 (4.1)	0
Blood Calcium Decreased	0	0	1 (0.2)	0	0	0
Blood Cholesterol Increased	1 (0.2)	0	0	0	0	0
Blood Creatinine Increased	1 (0.2)	1 (0.8)	4 (0.9)	0	0	0

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Blood Culture Positive	1 (0.2)	0	2 (0.5)	2 (1.8)	0	0
Blood Glucose Increased	0	0	0	1 (0.9)	0	0
Blood Lactate Dehydrogenase	0	0	1 (0.2)	0	0	0
Blood Lactate Dehydrogenase Increased	2 (0.4)	0	6 (1.4)	2 (1.8)	0	0
Blood Magnesium Decreased	1 (0.2)	0	0	0	0	0
Blood Potassium Decreased	1 (0.2)	0	0	0	0	0
Blood Pressure Decreased	0	0	1 (0.2)	0	0	0
Blood Pressure Increased	0	1 (0.8)	1 (0.2)	0	0	0
Blood Urea Increased	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0
Blood Uric Acid Increased	2 (0.4)	0	0	0	0	0
Body Temperature	1 (0.2)	0	0	0	0	0
Breath Sounds Abnormal	1 (0.2)	0	1 (0.2)	0	0	0
Bronchoscopy	0	0	1 (0.2)	0	0	0
C-Reactive Protein Abnormal	0	1 (0.8)	0	0	0	0
C-Reactive Protein Increased	0	0	1 (0.2)	0	1 (2.0)	0
Central Venous Pressure Decreased	1 (0.2)	0	0	0	0	0
Chest X-Ray Abnormal	0	0	1 (0.2)	0	0	0
Clostridium Test Positive	1 (0.2)	0	0	0	0	0
Coagulation Test Abnormal	0	0	1 (0.2)	0	0	0
Computerised Tomogram Abnormal	0	0	0	1 (0.9)	0	0
Cytomegalovirus Test	1 (0.2)	0	0	2 (1.8)	0	0
Cytomegalovirus Test Positive	4 (0.8)	0	2 (0.5)	0	0	0
Drug Level Changed	0	1 (0.8)	0	0	0	0

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Drug Level Increased	2 (0.4)	0	2 (0.5)	0	0	0
Ejection Fraction Decreased	1 (0.2)	0	0	0	0	0
Electrocardiogram Abnormal	1 (0.2)	0	0	0	0	0
Electrocardiogram Qt Prolonged	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Electrocardiogram T Wave Abnormal	1 (0.2)	0	0	0	0	0
Electroencephalogram Abnormal	1 (0.2)	0	0	0	0	0
Gamma-Glutamyltransferase Abnormal	0	0	1 (0.2)	0	0	0
Gamma-Glutamyltransferase Increased	15 (3.1)	5 (4.0)	14 (3.3)	8 (7.2)	0	0
Haematocrit Decreased	0	0	1 (0.2)	0	0	0
Haemoglobin Decreased	1 (0.2)	1 (0.8)	1 (0.2)	0	1 (2.0)	0
Heart Sounds Abnormal	1 (0.2)	0	0	0	0	0
Hepatic Enzyme Abnormal	0	1 (0.8)	2 (0.5)	0	0	0
Hepatic Enzyme Increased	2 (0.4)	2 (1.6)	2 (0.5)	1 (0.9)	0	0
Liver Function Test Abnormal	1 (0.2)	0	2 (0.5)	0	0	0
Liver Function Test Increased	5 (1.0)	1 (0.8)	5 (1.2)	1 (0.9)	0	0
Lymphocyte Count Decreased	0	0	1 (0.2)	0	0	0
Lymphocyte Count Increased	0	0	1 (0.2)	0	0	0
Neutrophil Count Abnormal	0	1 (0.8)	0	0	0	0
Neutrophil Count Decreased	1 (0.2)	0	1 (0.2)	0	0	0
Nutritional Condition Abnormal	0	0	1 (0.2)	0	0	0
Occult Blood Positive	1 (0.2)	0	0	0	0	0
Oxygen Saturation Decreased	5 (1.0)	0	2 (0.5)	0	0	0
Platelet Count Decreased	3 (0.6)	0	1 (0.2)	0	0	0

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Protein Total Decreased	1 (0.2)	0	0	0	0	0
Prothrombin Time Prolonged	0	0	0	1 (0.9)	0	0
Pulse Absent	0	0	0	1 (0.9)	0	0
Red Blood Cell Count Decreased	1 (0.2)	0	0	0	0	0
Respiratory Rate Increased	1 (0.2)	0	0	0	0	0
Salmonella Test Positive	1 (0.2)	0	0	0	0	0
Serum Ferritin Increased	1 (0.2)	0	0	0	0	0
Transaminases Increased	7 (1.5)	2 (1.6)	3 (0.7)	2 (1.8)	0	0
Troponin I Increased	0	0	0	1 (0.9)	0	0
Troponin Increased	1 (0.2)	0	0	0	0	0
Urine Output Decreased	1 (0.2)	0	0	0	0	0
Weight Decreased	6 (1.3)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Weight Increased	0	0	1 (0.2)	0	0	0
White Blood Cell Count Abnormal	0	1 (0.8)	0	0	0	0
Metabolism And Nutrition Disorders	**78 (16.3)**	**14 (11 1)**	**55 (12.9)**	**14 (12.6)**	**6 (12.2)**	**4 (44.4)**
Acidosis	3 (0.6)	3 (2.4)	1 (0.2)	0	2 (4.1)	0
Cachexia	1 (0.2)	0	0	0	0	0
Decreased Appetite	6 (1.3)	1 (0.8)	9 (2.1)	2 (1.8)	0	0
Dehydration	6 (1.3)	1 (0.8)	4 (0.9)	0	0	0
Diabetes Mellitus	4 (0.8)	0	2 (0.5)	0	0	0
Electrolyte Depletion	0	1 (0.8)	0	0	0	0
Electrolyte Imbalance	1 (0.2)	1 (0.8)	0	1 (0.9)	0	0

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Failure To Thrive	1 (0.2)	0	0	0	0	0
Feeding Disorder	0	0	1 (0.2)	0	0	0
Fluid Overload	0	0	4 (0.9)	1 (0.9)	1 (2.0)	0
Fluid Retention	1 (0.2)	0	3 (0.7)	0	0	0
Gout	1 (0.2)	0	0	0	0	0
Hypercholesterolaemia	1 (0.2)	0	0	0	0	0
Hyperglycaemia	12 (2.5)	5 (4.0)	14 (3.3)	3 (2.7)	0	0
Hyperinsulinaemic Hypoglycaemia	1 (0.2)	0	0	0	0	0
Hyperkalaemia	4 (0.8)	0	3 (0.7)	2 (1.8)	0	0
Hypermagnesaemia	2 (0.4)	0	0	0	0	0
Hypernatraemia	1 (0.2)	0	0	0	0	1 (11.1)
Hyperphosphataemia	0	0	1 (0.2)	0	0	0
Hypertriglyceridaemia	1 (0.2)	0	0	1 (0.9)	0	0
Hyperuricaemia	1 (0.2)	0	0	0	0	0
Hypoalbuminaemia	5 (1.0)	0	2 (0.5)	0	0	1 (11.1)
Hypocalcaemia	6 (1.3)	2 (1.6)	2 (0.5)	0	0	1 (11.1)
Hypoglycaemia	4 (0.8)	0	0	0	0	0
Hypokalaemia	23 (4.8)	4 (3 2)	13 (3.0)	5 (4.5)	3 (6.1)	2 (22.2)
Hypomagnesaemia	7 (1.5)	1 (0.8)	3 (0.7)	0	0	0
Hyponatraemia	3 (0.6)	1 (0.8)	3 (0.7)	1 (0.9)	1 (2.0)	0
Hypophagia	2 (0.4)	1 (0.8)	0	0	0	0
Hypophosphataemia	4 (0.8)	3 (2.4)	3 (0.7)	0	0	1 (11.1)
Hypoproteinaemia	1 (0.2)	0	0	0	0	0

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Hypovolaemia	0	0	2 (0.5)	0	0	0
Malnutrition	4 (0.8)	0	4 (0.9)	0	0	0
Metabolic Acidosis	4 (0.8)	1 (0.8)	1 (0.2)	3 (2.7)	1 (2.0)	1 (11.1)
Metabolic Alkalosis	0	0	1 (0.2)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**26 (5.4)**	**7 (5.6)**	**19 (4.4)**	**3 (2.7)**	**1 (2.0)**	**1 (11.1)**
Arthralgia	3 (0.6)	2 (1.6)	4 (0.9)	0	0	0
Back Pain	6 (1.3)	2 (1.6)	2 (0.5)	2 (1.8)	1 (2.0)	0
Bone Pain	6 (1.3)	0	0	2 (1.8)	0	0
Flank Pain	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Intervertebral Disc Degeneration	0	0	1 (0.2)	0	0	0
Intervertebral Disc Protrusion	0	0	1 (0.2)	0	0	0
Muscle Contracture	1 (0.2)	0	0	0	0	0
Muscle Spasms	1 (0.2)	1 (0.8)	1 (0.2)	0	0	0
Muscular Weakness	4 (0.8)	1 (0.8)	3 (0.7)	0	0	1 (11.1)
Musculoskeletal Pain	0	0	2 (0.5)	0	0	0
Musculoskeletal Stiffness	0	0	1 (0.2)	0	0	0
Myalgia	2 (0.4)	1 (0.8)	3 (0.7)	0	0	0
Myopathy	7 (1.5)	1 (0.8)	1 (0.2)	0	0	0
Neck Pain	1 (0.2)	0	1 (0.2)	0	0	0
Osteonecrosis	0	0	1 (0.2)	0	0	0
Pain In Extremity	3 (0.6)	0	0	2 (1.8)	0	1 (11.1)
Pathological Fracture	0	0	1 (0.2)	0	0	0

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Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**33 (6.9)**	**11 (8.7)**	**33 (7.7)**	**6 (5.4)**	**0**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	3 (0.7)	2 (1.8)	0	0
Acute Myeloid Leukaemia	7 (1.5)	6 (4.8)	8 (1.9)	1 (0.9)	0	0
Acute Myeloid Leukaemia Recurrent	10 (2.1)	2 (1.6)	4 (0.9)	2 (1.8)	0	0
Adult T-Cell Lymphoma/Leukaemia	0	0	1 (0.2)	0	0	0
B-Cell Lymphoma	0	0	1 (0.2)	0	0	0
Chronic Myeloid Leukaemia	1 (0.2)	0	0	0	0	0
Hodgkin's Disease	0	0	1 (0.2)	0	0	0
Hodgkin's Disease Recurrent	0	0	1 (0.2)	0	0	0
Leukaemia	1 (0.2)	1 (0.8)	2 (0.5)	0	0	0
Leukaemia Recurrent	4 (0.8)	1 (0.8)	3 (0.7)	0	0	0
Lymphoma	5 (1.0)	0	2 (0.5)	0	0	0
Meningioma	1 (0.2)	0	0	0	0	0
Metastases To Kidney	0	0	1 (0.2)	0	0	0
Metastases To Liver	0	0	1 (0.2)	0	0	0
Metastatic Neoplasm	1 (0.2)	0	0	0	0	0
Myelodysplastic Syndrome	1 (0.2)	0	0	0	0	0
Neoplasm Malignant	1 (0.2)	0	3 (0.7)	0	0	0
Non-Hodgkin's Lymphoma	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Non-Hodgkin's Lymphoma Recurrent	0	0	2 (0.5)	0	0	0
Plasma Cell Myeloma	0	0	1 (0.2)	0	0	0

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Post Transplant Lymphoproliferative Disorder	1 (0.2)	0	0	0	0	0
Renal Cancer	1 (0.2)	0	0	0	0	0
Squamous Cell Carcinoma	0	0	0	1 (0.9)	0	0
Tumour Pain	1 (0.2)	0	0	0	0	0
Uterine Leiomyoma	0	1 (0.8)	0	0	0	0
Nervous System Disorders	**47 (9.8)**	**17 (13 5)**	**39 (9.1)**	**16 (14.4)**	**3 (6.1)**	**1 (11.1)**
Amnesia	1 (0.2)	0	0	0	0	0
Ataxia	1 (0.2)	0	0	0	0	0
Balance Disorder	0	0	1 (0.2)	0	0	0
Brain Compression	0	0	0	0	1 (2.0)	0
Brain Oedema	1 (0.2)	2 (1.6)	0	2 (1.8)	0	0
Central Nervous System Lesion	0	1 (0.8)	1 (0.2)	0	0	0
Cerebellar Haemorrhage	2 (0.4)	0	0	0	1 (2.0)	0
Cerebral Haemorrhage	3 (0.6)	2 (1.6)	2 (0.5)	3 (2.7)	0	0
Cerebral Hypoperfusion	0	0	1 (0.2)	0	0	0
Cerebral Infarction	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Cerebrovascular Accident	1 (0.2)	0	1 (0.2)	0	0	0
Cognitive Disorder	2 (0.4)	0	0	0	0	0
Coma	2 (0.4)	1 (0.8)	4 (0.9)	1 (0.9)	0	0
Demyelination	1 (0.2)	0	0	0	0	0
Depressed Level Of Consciousness	3 (0.6)	0	2 (0.5)	0	0	0
Dizziness	1 (0.2)	1 (0.8)	2 (0.5)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Encephalopathy	4 (0.8)	0	1 (0.2)	1 (0.9)	0	0
Facial Paresis	0	0	1 (0.2)	0	0	0
Generalised Tonic-Clonic Seizure	0	0	1 (0.2)	1 (0.9)	0	0
Guillain-Barre Syndrome	0	0	0	1 (0.9)	0	0
Haemorrhage Intracranial	0	2 (1.6)	3 (0.7)	2 (1.8)	0	0
Haemorrhagic Stroke	1 (0.2)	0	1 (0.2)	0	0	0
Headache	10 (2.1)	5 (4.0)	9 (2.1)	3 (2.7)	2 (4.1)	0
Hemiparesis	0	0	2 (0.5)	2 (1.8)	0	0
Hemiplegia	1 (0.2)	0	2 (0.5)	0	0	0
Hydrocephalus	0	0	0	0	1 (2.0)	0
Hypoglycaemic Coma	1 (0.2)	0	0	0	0	0
Hypokinesia	0	0	1 (0.2)	0	0	0
Hyporeflexia	1 (0.2)	0	0	0	0	0
Intensive Care Unit Acquired Weakness	0	0	0	0	0	1 (11.1)
Lethargy	2 (0.4)	1 (0.8)	0	0	0	1 (11.1)
Leukoencephalopathy	1 (0.2)	0	0	0	0	0
Loss Of Consciousness	1 (0.2)	3 (2.4)	2 (0.5)	3 (2.7)	1 (2.0)	0
Meningism	1 (0.2)	0	0	0	0	0
Metabolic Encephalopathy	1 (0.2)	0	0	0	0	0
Migraine	1 (0.2)	0	0	0	0	0
Myoclonus	0	1 (0.8)	0	0	0	0
Nervous System Disorder	1 (0.2)	0	0	0	0	0
Neuropathy Peripheral	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 Severe/Life Threatening Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Neurotoxicity	0	0	1 (0.2)	0	0	0
Nystagmus	0	0	0	0	1 (2.0)	0
Paralysis	1 (0.2)	0	0	0	0	0
Paresis	0	0	1 (0.2)	0	0	0
Peroneal Nerve Palsy	1 (0.2)	0	0	0	0	0
Post Herpetic Neuralgia	0	2 (1.6)	0	1 (0.9)	0	0
Psychomotor Hyperactivity	1 (0.2)	0	0	0	0	0
Seizure	7 (1.5)	2 (1.6)	4 (0.9)	1 (0.9)	0	0
Sensory Loss	1 (0.2)	0	0	0	0	0
Somnolence	2 (0.4)	0	2 (0.5)	1 (0.9)	0	0
Stupor	1 (0.2)	1 (0.8)	1 (0.2)	1 (0.9)	0	0
Syncope	9 (1.9)	0	2 (0.5)	0	1 (2.0)	0
Tonic Convulsion	0	1 (0.8)	0	0	0	0
Transient Ischaemic Attack	0	1 (0.8)	0	0	0	0
Tremor	0	0	1 (0.2)	1 (0.9)	0	0
Trigeminal Neuralgia	0	0	1 (0.2)	0	0	0
Unresponsive To Stimuli	1 (0.2)	0	2 (0.5)	1 (0.9)	0	0
Visual Field Defect	0	0	1 (0.2)	0	0	0
Product Issues	**0**	**0**	**0**	**1 (0 9)**	**0**	**0**
Device Breakage	0	0	0	1 (0.9)	0	0
Psychiatric Disorders	**21 (4.4)**	**3 (2.4)**	**16 (3.7)**	**4 (3.6)**	**0**	**1 (11.1)**

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

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Abnormal Behaviour	0	0	1 (0.2)	0	0	0
Agitation	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Anxiety	1 (0.2)	0	2 (0.5)	2 (1.8)	0	0
Confusional State	4 (0.8)	2 (1.6)	4 (0.9)	0	0	1 (11.1)
Delirium	0	1 (0.8)	0	0	0	0
Depression	5 (1.0)	0	3 (0.7)	2 (1.8)	0	0
Depression Suicidal	0	0	1 (0.2)	0	0	0
Disorientation	0	0	0	1 (0.9)	0	0
Eating Disorder	0	0	1 (0.2)	0	0	0
Fear	0	0	1 (0.2)	0	0	0
Flat Affect	1 (0.2)	0	0	0	0	0
Hallucination	1 (0.2)	0	2 (0.5)	0	0	0
Hallucination, Visual	1 (0.2)	0	0	0	0	0
Hypomania	1 (0.2)	0	0	0	0	0
Insomnia	1 (0.2)	0	0	1 (0.9)	0	0
Mental Status Changes	5 (1.0)	0	4 (0.9)	1 (0.9)	0	0
Mood Altered	0	0	1 (0.2)	0	0	0
Stress	1 (0.2)	0	1 (0.2)	0	0	0
Suicidal Ideation	1 (0.2)	0	0	1 (0.9)	0	0
Renal And Urinary Disorders	**34 (7.1)**	**9 (7.1)**	**37 (8.6)**	**6 (5.4)**	**1 (2.0)**	**0**
Acute Kidney Injury	9 (1.9)	0	7 (1.6)	1 (0.9)	1 (2.0)	0
Anuria	3 (0.6)	0	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Azotaemia	0	0	1 (0.2)	0	0	0
Bladder Spasm	2 (0.4)	0	0	0	0	0
Choluria	1 (0.2)	0	0	0	0	0
Cystitis Haemorrhagic	3 (0.6)	0	1 (0.2)	2 (1.8)	0	0
Dysuria	1 (0.2)	1 (0.8)	1 (0.2)	2 (1.8)	0	0
Haematuria	7 (1.5)	1 (0.8)	6 (1.4)	1 (0.9)	0	0
Hydronephrosis	1 (0.2)	1 (0.8)	0	0	0	0
Obstructive Nephropathy	0	0	1 (0.2)	0	0	0
Oliguria	4 (0.8)	1 (0.8)	1 (0.2)	0	0	0
Polyuria	1 (0.2)	0	0	0	0	0
Renal Failure	12 (2.5)	5 (4.0)	19 (4.4)	3 (2.7)	0	0
Renal Haematoma	1 (0.2)	0	0	0	0	0
Renal Impairment	2 (0.4)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Renal Tubular Necrosis	0	0	2 (0.5)	0	0	0
Tubulointerstitial Nephritis	0	0	0	1 (0.9)	0	0
Urethral Discharge	0	0	0	1 (0.9)	0	0
Urinary Incontinence	1 (0.2)	0	2 (0.5)	0	0	0
Urinary Retention	1 (0.2)	0	0	0	0	0
Reproductive System And Breast Disorders	**8 (1.7)**	**4 (3.2)**	**4 (0.9)**	**4 (3.6)**	**0**	**0**
Erectile Dysfunction	1 (0.2)	0	0	0	0	0
Menorrhagia	1 (0.2)	0	2 (0.5)	0	0	0
Menstrual Disorder	1 (0.2)	0	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Penile Pain	0	0	0	1 (0.9)	0	0
Prostatitis	0	1 (0.8)	0	0	0	0
Scrotal Oedema	1 (0.2)	0	0	0	0	0
Testicular Pain	0	0	1 (0.2)	0	0	0
Uterine Haemorrhage	0	0	1 (0.2)	0	0	0
Vaginal Haemorrhage	3 (0.6)	3 (2.4)	0	3 (2.7)	0	0
Vulval Oedema	1 (0.2)	0	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**81 (16.9)**	**20 (15 9)**	**89 (20.8)**	**19 (17.1)**	**10 (20.4)**	**4 (44.4)**
Acute Pulmonary Oedema	0	2 (1.6)	2 (0.5)	0	0	0
Acute Respiratory Distress Syndrome	6 (1.3)	0	5 (1.2)	2 (1.8)	1 (2.0)	0
Acute Respiratory Failure	4 (0.8)	1 (0.8)	1 (0.2)	0	0	0
Apnoea	1 (0.2)	1 (0.8)	0	0	0	0
Asthma	0	0	1 (0.2)	0	0	0
Atelectasis	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Bronchial Hyperreactivity	0	0	0	1 (0.9)	0	0
Bronchial Obstruction	0	0	1 (0.2)	1 (0.9)	0	0
Bronchopneumopathy	1 (0.2)	0	0	0	0	0
Bronchospasm	0	0	2 (0.5)	0	0	0
Chronic Obstructive Pulmonary Disease	0	0	1 (0.2)	0	0	0
Cough	3 (0.6)	0	2 (0.5)	1 (0.9)	0	0
Diffuse Alveolar Damage	0	0	1 (0.2)	0	0	0
Dyspnoea	25 (5.2)	6 (4.8)	26 (6.1)	3 (2.7)	3 (6.1)	1 (11.1)

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

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Emphysema	0	1 (0.8)	0	0	0	0
Epiglottis Ulcer	1 (0.2)	0	0	0	0	0
Epistaxis	8 (1.7)	1 (0.8)	2 (0.5)	3 (2.7)	0	0
Haemoptysis	2 (0.4)	2 (1.6)	3 (0.7)	0	0	0
Haemothorax	0	0	1 (0.2)	1 (0.9)	0	0
Hydrothorax	1 (0.2)	0	1 (0.2)	0	0	0
Hypercapnia	1 (0.2)	0	0	0	0	0
Hypoxia	7 (1.5)	2 (1.6)	19 (4.4)	1 (0.9)	4 (8.2)	3 (33.3)
Interstitial Lung Disease	2 (0.4)	2 (1.6)	1 (0.2)	0	0	0
Laryngeal Oedema	0	0	0	0	1 (2.0)	0
Lung Consolidation	0	0	1 (0.2)	0	0	1 (11.1)
Lung Disorder	2 (0.4)	0	0	1 (0.9)	0	0
Lung Infiltration	4 (0.8)	0	7 (1.6)	0	0	0
Nasal Congestion	1 (0.2)	0	0	0	0	0
Nasal Necrosis	0	0	0	1 (0.9)	0	0
Obliterative Bronchiolitis	0	0	1 (0.2)	0	0	0
Organising Pneumonia	2 (0.4)	0	0	0	0	0
Oropharyngeal Pain	0	0	3 (0.7)	1 (0.9)	0	0
Pleural Effusion	5 (1.0)	1 (0.8)	5 (1.2)	1 (0.9)	0	0
Pleurisy	0	0	1 (0.2)	0	0	0
Pleuritic Pain	2 (0.4)	0	1 (0.2)	0	0	0
Pneumonia Aspiration	2 (0.4)	1 (0.8)	3 (0.7)	0	0	0
Pneumonitis	3 (0.6)	1 (0.8)	1 (0.2)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Pneumothorax	3 (0.6)	0	0	2 (1.8)	0	0
Productive Cough	1 (0.2)	0	3 (0.7)	1 (0.9)	0	0
Pulmonary Alveolar Haemorrhage	1 (0.2)	2 (1.6)	1 (0.2)	0	1 (2.0)	0
Pulmonary Congestion	1 (0.2)	0	0	0	0	0
Pulmonary Embolism	3 (0.6)	0	2 (0.5)	0	0	0
Pulmonary Fibrosis	0	0	1 (0.2)	0	0	0
Pulmonary Haemorrhage	3 (0.6)	3 (2.4)	2 (0.5)	2 (1.8)	0	0
Pulmonary Haemosiderosis	0	0	1 (0.2)	0	0	0
Pulmonary Hypertension	2 (0.4)	0	0	0	0	0
Pulmonary Mass	3 (0.6)	0	3 (0.7)	1 (0.9)	0	0
Pulmonary Oedema	5 (1.0)	3 (2.4)	7 (1.6)	2 (1.8)	1 (2.0)	0
Rales	1 (0.2)	0	0	0	0	0
Respiratory Acidosis	0	1 (0.8)	1 (0.2)	0	0	0
Respiratory Arrest	1 (0.2)	0	0	0	0	0
Respiratory Disorder	1 (0.2)	0	1 (0.2)	0	1 (2.0)	0
Respiratory Distress	9 (1.9)	0	5 (1.2)	0	2 (4.1)	0
Respiratory Failure	18 (3.8)	6 (4.8)	31 (7.2)	6 (5.4)	2 (4.1)	0
Respiratory Tract Haemorrhage	1 (0.2)	0	0	0	0	0
Restrictive Pulmonary Disease	1 (0.2)	0	0	0	0	0
Rhinalgia	0	0	1 (0.2)	0	0	0
Sinus Congestion	0	0	1 (0.2)	0	0	0
Sinus Disorder	0	1 (0.8)	0	0	0	0
Tachypnoea	5 (1.0)	2 (1.6)	4 (0.9)	1 (0.9)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Tonsillar Disorder	1 (0.2)	0	0	0	0	0
Wheezing	0	0	0	1 (0.9)	0	0
Skin And Subcutaneous Tissue Disorders	**21 (4.4)**	**5 (4.0)**	**13 (3.0)**	**4 (3.6)**	**1 (2.0)**	**2 (22.2)**
Alopecia	1 (0.2)	0	1 (0.2)	1 (0.9)	0	0
Alopecia Totalis	1 (0.2)	0	0	0	0	0
Blister	2 (0.4)	0	1 (0.2)	0	0	0
Cold Sweat	1 (0.2)	0	0	0	0	0
Decubitus Ulcer	0	0	1 (0.2)	0	0	0
Dry Skin	1 (0.2)	0	1 (0.2)	0	0	0
Erythema	2 (0.4)	0	0	0	0	0
Exfoliative Rash	0	0	1 (0.2)	0	0	0
Hypersensitivity Vasculitis	0	1 (0.8)	0	0	0	0
Night Sweats	2 (0.4)	0	0	0	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome	1 (0.2)	0	0	0	0	0
Petechiae	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Pruritus	2 (0.4)	0	1 (0.2)	1 (0.9)	0	0
Rash	3 (0.6)	2 (1.6)	2 (0.5)	1 (0.9)	0	1 (11.1)
Rash Erythematous	0	1 (0.8)	0	0	0	0
Rash Generalised	0	0	0	0	1 (2.0)	1 (11.1)
Rash Maculo-Papular	2 (0.4)	1 (0.8)	0	0	0	0
Rash Pruritic	0	0	3 (0.7)	0	0	0
Skin Disorder	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 Severe/Life Threatening Treatment Emergent Adverse Events by Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Skin Exfoliation	0	0	1 (0.2)	0	0	0
Skin Hypopigmentation	0	1 (0.8)	0	0	0	0
Skin Lesion	0	0	1 (0.2)	1 (0.9)	0	0
Skin Oedema	1 (0.2)	0	0	0	0	0
Skin Ulcer	0	0	1 (0.2)	0	0	0
Subcutaneous Emphysema	1 (0.2)	0	0	0	0	0
Social Circumstances	**1 (0.2)**	**0**	**0**	**0**	**0**	**0**
Social Problem	1 (0.2)	0	0	0	0	0
Surgical And Medical Procedures	**2 (0.4)**	**1 (0.8)**	**1 (0.2)**	**0**	**1 (2.0)**	**0**
Bone Marrow Transplant	1 (0.2)	1 (0.8)	0	0	0	0
Chemotherapy	0	0	1 (0.2)	0	0	0
Stem Cell Transplant	1 (0.2)	0	0	0	0	0
Surgery	0	0	0	0	1 (2.0)	0
Vascular Disorders	**46 (9.6)**	**13 (10 3)**	**52 (12.1)**	**17 (15.3)**	**5 (10.2)**	**2 (22.2)**
Circulatory Collapse	1 (0.2)	0	1 (0.2)	3 (2.7)	0	0
Deep Vein Thrombosis	1 (0.2)	1 (0.8)	2 (0.5)	0	1 (2.0)	0
Embolism Arterial	0	0	1 (0.2)	0	0	0
Haemodynamic Instability	2 (0.4)	0	1 (0.2)	0	0	0
Haemorrhage	1 (0.2)	1 (0.8)	2 (0.5)	1 (0.9)	0	0
Haemorrhagic Infarction	0	0	1 (0.2)	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 Race
Number (%) of Subjects

	Posaconazole		Fluconazole		Itraconazole	
	Caucasian n = 479	Non-Caucasian n = 126	Caucasian n = 428	Non-Caucasian n = 111	Caucasian n = 49	Non-Caucasian n = 9
Hypertension	8 (1.7)	3 (2.4)	14 (3.3)	2 (1.8)	2 (4.1)	0
Hypertensive Crisis	1 (0.2)	0	1 (0.2)	0	0	0
Hypotension	31 (6.5)	7 (5.6)	29 (6.8)	11 (9 9)	3 (6.1)	2 (22.2)
Hypovolaemic Shock	0	2 (1.6)	3 (0.7)	0	0	0
Ischaemia	0	0	0	1 (0.9)	0	0
Microangiopathy	1 (0.2)	0	0	0	0	0
Orthostatic Hypotension	1 (0.2)	1 (0.8)	0	0	0	0
Pallor	1 (0.2)	0	0	0	0	0
Peripheral Circulatory Failure	1 (0.2)	0	0	0	0	0
Peripheral Vascular Disorder	1 (0.2)	0	0	0	0	0
Shock	0	0	3 (0.7)	1 (0.9)	0	0
Subclavian Vein Thrombosis	1 (0.2)	0	0	0	0	0
Vasodilatation	0	0	1 (0.2)	0	0	0
Vena Cava Embolism	0	0	1 (0.2)	0	0	0
Venous Thrombosis	0	0	1 (0.2)	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 2.7.4-174　　人種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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Subjects Reporting Any Adverse Event	**100 (97.1)**	**5 (100.0)**	**1 (100.0)**	**14 (100.0)**	**1 (100.0)**	**178 (95.7)**	**20 (90.9)**	**25 (96.2)**	**68 (97.1)**	**0**	**278 (96.2)**	**25 (92.6)**	**26 (96.3)**	**82 (97.6)**	**1 (100.0)**
Blood And Lymphatic System Disorders	**43 (41.7)**	**2 (40.0)**	**0**	**10 (71.4)**	**0**	**71 (38.2)**	**9 (40.9)**	**12 (46.2)**	**16 (22.9)**	**0**	**114 (39.4)**	**11 (40.7)**	**12 (44.4)**	**26 (31.0)**	**0**
Anaemia	17 (16.5)	1 (20.0)	0	3 (21.4)	0	36 (19.4)	5 (22.7)	9 (34.6)	10 (14.3)	0	53 (18.3)	6 (22.2)	9 (33.3)	13 (15 5)	0
Anaemia Megaloblastic	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Aplastic Anaemia	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Autoimmune Haemolytic Anaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bandaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Coagulopathy	3 (2.9)	0	0	0	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	5 (1.7)	1 (3.7)	0	1 (1.2)	0
Disseminated Intravascular Coagulation	1 (1.0)	0	0	0	0	3 (1.6)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	0
Eosinophilia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Febrile Neutropenia	5 (4.9)	0	0	0	0	13 (7.0)	1 (4.5)	0	3 (4.3)	0	18 (6 2)	1 (3.7)	0	3 (3.6)	0
Haemolysis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Haemolytic Anaemia	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Haemolytic Uraemic Syndrome	2 (1.9)	0	0	2 (14.3)	0	0	0	0	0	0	2 (0.7)	0	0	2 (2.4)	0
Hypercoagulation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Leukocytosis	0	0	0	1 (7.1)	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Leukopenia	3 (2.9)	0	0	1 (7.1)	0	7 (3.8)	0	0	0	0	10 (3 5)	0	0	1 (1.2)	0
Lymphadenopathy	1 (1.0)	0	0	1 (7.1)	0	3 (1.6)	1 (4.5)	2 (7.7)	1 (1.4)	0	4 (1.4)	1 (3.7)	2 (7.4)	2 (2.4)	0
Neutropenia	8 (7.8)	1 (20.0)	0	3 (21.4)	0	22 (11.8)	3 (13.6)	0	2 (2.9)	0	30 (10.4)	4 (14.8)	0	5 (6.0)	0
Pancytopenia	4 (3.9)	0	0	2 (14.3)	0	11 (5.9)	0	1 (3.8)	1 (1.4)	0	15 (5 2)	0	1 (3.7)	3 (3.6)	0
Polycythaemia	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Retroperitoneal Lymphadenopathy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Splenic Infarction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Splenic Lesion	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Splenomegaly	4 (3.9)	1 (20.0)	0	0	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	6 (2.1)	2 (7.4)	0	1 (1.2)	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Thrombocytopenia	17 (16.5)	1 (20.0)	0	4 (28.6)	0	29 (15.6)	4 (18.2)	1 (3.8)	9 (12.9)	0	46 (15.9)	5 (18.5)	1 (3.7)	13 (15 5)	0
Thrombocytosis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Thrombotic Thrombocytopenic Purpura	3 (2.9)	0	0	2 (14.3)	0	1 (0.5)	0	0	0	0	4 (1.4)	0	0	2 (2.4)	0
Cardiac Disorders	**47 (45.6)**	**2 (40.0)**	**0**	**7 (50.0)**	**0**	**55 (29.6)**	**7 (31.8)**	**5 (19.2)**	**12 (17.1)**	**0**	**102 (35.3)**	**9 (33.3)**	**5 (18.5)**	**19 (22.6)**	**0**
Angina Pectoris	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Aortic Valve Incompetence	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Aortic Valve Sclerosis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Arrhythmia	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Arrhythmia Supraventricular	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Arteriosclerosis Coronary Artery	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Atrial Fibrillation	6 (5.8)	0	0	1 (7.1)	0	9 (4.8)	0	1 (3.8)	1 (1.4)	0	15 (5 2)	0	1 (3.7)	2 (2.4)	0
Atrial Flutter	4 (3.9)	0	0	0	0	3 (1.6)	0	0	0	0	7 (2.4)	0	0	0	0
Atrioventricular Block	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	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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Atrioventricular Block First Degree	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Bradycardia	2 (1.9)	0	0	0	0	6 (3.2)	0	0	2 (2.9)	0	8 (2.8)	0	0	2 (2.4)	0
Bundle Branch Block	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Bundle Branch Block Left	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Bundle Branch Block Right	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Cardiac Arrest	1 (1.0)	0	0	1 (7.1)	0	5 (2.7)	0	0	1 (1.4)	0	6 (2.1)	0	0	2 (2.4)	0
Cardiac Failure	4 (3.9)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	5 (1.7)	0	0	1 (1.2)	0
Cardiac Failure Congestive	1 (1.0)	0	0	1 (7.1)	0	7 (3.8)	3 (13.6)	0	1 (1.4)	0	8 (2.8)	3 (11.1)	0	2 (2.4)	0
Cardiac Valve Disease	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cardio-Respiratory Arrest	7 (6.8)	1 (20.0)	0	0	0	8 (4.3)	0	1 (3.8)	0	0	15 (5 2)	1 (3.7)	1 (3.7)	0	0
Cardiogenic Shock	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cardiomegaly	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Cardiomyopathy	3 (2.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Cardiopulmonary Failure	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Coronary Artery Occlusion	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Cyanosis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0

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Defect Conduction Intraventricular	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Dilatation Atrial	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Extrasystoles	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Left Atrial Enlargement	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Left Ventricular Dysfunction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Left Ventricular Hypertrophy	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Mitral Valve Calcification	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Mitral Valve Incompetence	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Mitral Valve Stenosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Myocardial Infarction	0	0	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	1 (0.3)	1 (3.7)	0	1 (1.2)	0
Palpitations	3 (2.9)	0	0	0	0	3 (1.6)	0	0	0	0	6 (2.1)	0	0	0	0
Pericardial Effusion	8 (7.8)	0	0	1 (7.1)	0	2 (1.1)	1 (4.5)	0	2 (2.9)	0	10 (3 5)	1 (3.7)	0	3 (3.6)	0
Pericardial Rub	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Pericarditis	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Pulseless Electrical Activity	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Sinus Bradycardia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Sinus Tachycardia	4 (3.9)	0	0	1 (7.1)	0	3 (1.6)	1 (4.5)	0	0	0	7 (2.4)	1 (3.7)	0	1 (1.2)	0

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Number (%) of Subjects

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	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Supraventricular Tachycardia	6 (5.8)	0	0	0	0	7 (3.8)	1 (4.5)	0	0	0	13 (4 5)	1 (3.7)	0	0	0
Tachycardia	18 (17.5)	2 (40.0)	0	5 (35.7)	0	12 (6.5)	4 (18.2)	1 (3.8)	6 (8.6)	0	30 (10.4)	6 (22.2)	1 (3.7)	11 (13 1)	0
Tricuspid Valve Incompetence	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Ventricular Extrasystoles	0	0	0	1 (7.1)	0	4 (2.2)	1 (4.5)	0	0	0	4 (1.4)	1 (3.7)	0	1 (1.2)	0
Ventricular Fibrillation	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Ventricular Hypertrophy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Ventricular Tachycardia	2 (1.9)	0	0	0	0	2 (1.1)	0	0	2 (2.9)	0	4 (1.4)	0	0	2 (2.4)	0
Congenital, Familial And Genetic Disorders	**0**	**0**	**0**	**0**	**0**	**2 (1.1)**	**0**	**0**	**0**	**0**	**2 (0.7)**	**0**	**0**	**0**	**0**
Aplasia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Fanconi Syndrome	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Ear And Labyrinth Disorders	**13 (12.6)**	**0**	**0**	**0**	**0**	**12 (6.5)**	**1 (4.5)**	**4 (15.4)**	**3 (4.3)**	**0**	**25 (8.7)**	**1 (3.7)**	**4 (14.8)**	**3 (3.6)**	**0**
Cerumen Impaction	1 (1.0)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0
Conductive Deafness	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0

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Deafness	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Ear Discomfort	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Ear Pain	6 (5.8)	0	0	0	0	4 (2.2)	1 (4.5)	0	1 (1.4)	0	10 (3 5)	1 (3.7)	0	1 (1.2)	0
Ear Pruritus	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Excessive Cerumen Production	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
External Ear Inflammation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypoacusis	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Middle Ear Effusion	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Tinnitus	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Vertigo	1 (1.0)	0	0	0	0	3 (1.6)	0	2 (7.7)	0	0	4 (1.4)	0	2 (7.4)	0	0
Vertigo Labyrinthine	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Endocrine Disorders	**6 (5.8)**	**0**	**0**	**3 (21.4)**	**0**	**3 (1.6)**	**0**	**2 (7.7)**	**3 (4.3)**	**0**	**9 (3.1)**	**0**	**2 (7.4)**	**6 (7.1)**	**0**
Adrenal Insufficiency	3 (2.9)	0	0	0	0	1 (0.5)	0	1 (3.8)	2 (2.9)	0	4 (1.4)	0	1 (3.7)	2 (2.4)	0
Adrenocortical Insufficiency Acute	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Cushingoid	2 (1.9)	0	0	0	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	3 (1.0)	0	1 (3.7)	1 (1.2)	0
Hyperthyroidism	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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Hypogonadism	0	0	0	1 (7.1)	0	0	0	0	1 (1.4)	0	0	0	0	2 (2.4)	0
Hypothyroidism	1 (1.0)	0	0	2 (14.3)	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	2 (2.4)	0
Eye Disorders	**27 (26.2)**	**1 (20.0)**	**0**	**7 (50.0)**	**0**	**31 (16.7)**	**3 (13.6)**	**10 (38.5)**	**11 (15.7)**	**0**	**58 (20.1)**	**4 (14.8)**	**10 (37.0)**	**18 (21.4)**	**0**
Blepharitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blindness	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Cataract	2 (1.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Conjunctival Haemorrhage	1 (1.0)	0	0	0	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	0	0
Conjunctival Hyperaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Conjunctival Irritation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Conjunctival Oedema	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Conjunctivitis Allergic	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Corneal Epithelium Defect	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Corneal Erosion	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Corneal Perforation	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Dacryostenosis Acquired	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Diplopia	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Dry Eye	4 (3.9)	1 (20.0)	0	1 (7.1)	0	0	0	0	2 (2.9)	0	4 (1.4)	1 (3.7)	0	3 (3.6)	0

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Number (%) of Subjects

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	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Erythema Of Eyelid	0	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Exophthalmos	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Eye Disorder	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Eye Irritation	2 (1.9)	0	0	0	0	4 (2.2)	0	3 (11.5)	0	0	6 (2.1)	0	3 (11.1)	0	0
Eye Movement Disorder	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Eye Oedema	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Eye Pain	1 (1.0)	0	0	2 (14.3)	0	2 (1.1)	0	1 (3.8)	2 (2.9)	0	3 (1.0)	0	1 (3.7)	4 (4.8)	0
Eye Pruritus	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Eye Swelling	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Eyelid Cyst	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Eyelid Oedema	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Eyelid Ptosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypoaesthesia Eye	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Iridocyclitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Keratopathy	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Lacrimation Increased	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Mydriasis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Myopia	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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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, Race
Number (%) of Subjects

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Ocular Hyperaemia	0	0	0	0	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Optic Atrophy	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Papilloedema	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Periorbital Oedema	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Photophobia	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Photopsia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pinguecula	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Pupillary Reflex Impaired	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pupils Unequal	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Retinal Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Retinal Exudates	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Scleral Discolouration	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Scleral Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Scleral Oedema	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Uveitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Vision Blurred	9 (8.7)	0	0	2 (14.3)	0	7 (3.8)	0	7 (26.9)	2 (2.9)	0	16 (5 5)	0	7 (25.9)	4 (4.8)	0
Visual Impairment	2 (1.9)	0	0	0	0	2 (1.1)	0	0	3 (4.3)	0	4 (1.4)	0	0	3 (3.6)	0
Gastrointestinal Disorders	**69 (67.0)**	**5 (100.0)**	**1 (100.0)**	**12 (85.7)**	**1 (100.0)**	**120 (64.5)**	**15 (68.2)**	**22 (84.6)**	**49 (70.0)**	**0**	**189 (65.4)**	**20 (74.1)**	**23 (85.2)**	**61 (72.6)**	**1 (100.0)**

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Abdominal Discomfort	1 (1.0)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Abdominal Distension	12 (11.7)	2 (40.0)	0	3 (21.4)	0	14 (7.5)	0	0	2 (2.9)	0	26 (9.0)	2 (7.4)	0	5 (6.0)	0
Abdominal Hernia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Abdominal Pain	22 (21.4)	2 (40.0)	0	3 (21.4)	0	17 (9.1)	6 (27.3)	5 (19.2)	6 (8.6)	0	39 (13.5)	8 (29.6)	5 (18.5)	9 (10.7)	0
Abdominal Pain Lower	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Abdominal Pain Upper	13 (12.6)	0	0	1 (7.1)	0	13 (7.0)	0	1 (3.8)	15 (21.4)	0	26 (9.0)	0	1 (3.7)	16 (19.0)	0
Abdominal Rigidity	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Abdominal Tenderness	1 (1.0)	0	1 (100.0)	0	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	3 (1.0)	1 (3.7)	1 (3.7)	1 (1.2)	0
Abdominal Wall Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Abnormal Faeces	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Anal Incontinence	1 (1.0)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Anorectal Discomfort	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Ascites	6 (5.8)	0	0	2 (14.3)	0	5 (2.7)	0	0	1 (1.4)	0	11 (3.8)	0	0	3 (3.6)	0
Barrett's Oesophagus	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Number (%) of Subjects

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Cheilitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Colitis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Constipation	11 (10.7)	3 (60.0)	0	3 (21.4)	1 (100.0)	26 (14.0)	1 (4.5)	8 (30.8)	4 (5.7)	0	37 (12.8)	4 (14.8)	8 (29.6)	7 (8.3)	1 (100.0)
Dental Caries	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Dental Discomfort	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Diarrhoea	34 (33.0)	2 (40.0)	0	6 (42.9)	1 (100.0)	40 (21.5)	6 (27.3)	13 (50.0)	18 (25.7)	0	74 (25.6)	8 (29.6)	13 (48.1)	24 (28.6)	1 (100.0)
Diarrhoea Haemorrhagic	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Dry Mouth	4 (3.9)	0	0	0	0	1 (0.5)	1 (4.5)	3 (11.5)	0	0	5 (1.7)	1 (3.7)	3 (11.1)	0	0
Duodenal Ulcer	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Duodenitis	2 (1.9)	0	0	1 (7.1)	0	0	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Dyspepsia	5 (4.9)	0	0	2 (14.3)	0	8 (4.3)	1 (4.5)	3 (11.5)	1 (1.4)	0	13 (4 5)	1 (3.7)	3 (11.1)	3 (3.6)	0
Dysphagia	2 (1.9)	2 (40.0)	0	0	0	11 (5.9)	1 (4.5)	0	0	0	13 (4 5)	3 (11.1)	0	0	0
Enteritis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Eructation	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Faecaloma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Faeces Discoloured	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Faeces Soft	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Flatulence	4 (3.9)	0	0	0	0	5 (2.7)	0	5 (19.2)	4 (5.7)	0	9 (3.1)	0	5 (18.5)	4 (4.8)	0
Food Poisoning	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Gastric Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gastric Haemorrhage	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Gastric Perforation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gastric Polyps	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gastric Ulcer	0	0	1 (100.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0
Gastritis	3 (2.9)	0	0	1 (7.1)	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	4 (1.4)	0	1 (3.7)	2 (2.4)	0
Gastrointestinal Haemorrhage	4 (3.9)	0	0	2 (14.3)	0	1 (0.5)	1 (4.5)	1 (3.8)	1 (1.4)	0	5 (1.7)	1 (3.7)	1 (3.7)	3 (3.6)	0
Gastrointestinal Hypermotility	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gastrointestinal Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Gastrointestinal Sounds Abnormal	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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Gastrooesophageal Reflux Disease	1 (1.0)	0	0	0	0	4 (2.2)	0	0	0	0	5 (1.7)	0	0	0	0
Gingival Bleeding	0	2 (40.0)	0	0	0	3 (1.6)	1 (4.5)	0	1 (1.4)	0	3 (1.0)	3 (11.1)	0	1 (1.2)	0
Gingival Hypertrophy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Gingival Pain	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Gingival Swelling	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Glossitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Glossodynia	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Haematemesis	1 (1.0)	2 (40.0)	0	1 (7.1)	0	0	1 (4.5)	1 (3.8)	1 (1.4)	0	1 (0.3)	3 (11.1)	1 (3.7)	2 (2.4)	0
Haematochezia	2 (1.9)	0	0	0	0	3 (1.6)	1 (4.5)	0	1 (1.4)	0	5 (1.7)	1 (3.7)	0	1 (1.2)	0
Haemorrhoidal Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Haemorrhoids	2 (1.9)	0	0	0	0	6 (3.2)	0	1 (3.8)	1 (1.4)	0	8 (2.8)	0	1 (3.7)	1 (1.2)	0
Hiatus Hernia	0	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Hypoaesthesia Oral	4 (3.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	5 (1.7)	1 (3.7)	0	0	0
Ileus	0	0	0	1 (7.1)	0	2 (1.1)	1 (4.5)	0	2 (2.9)	0	2 (0.7)	1 (3.7)	0	3 (3.6)	0
Ileus Paralytic	0	0	0	1 (7.1)	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	1 (1.2)	0
Intestinal Dilatation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Intestinal Infarction	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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Intestinal Ischaemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Intestinal Obstruction	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Intestinal Ulcer	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Irritable Bowel Syndrome	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Leukoplakia Oral	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Lip Dry	1 (1.0)	0	0	0	0	3 (1.6)	1 (4.5)	1 (3.8)	2 (2.9)	0	4 (1.4)	1 (3.7)	1 (3.7)	2 (2.4)	0
Lip Swelling	0	0	0	0	0	0	1 (4.5)	0	2 (2.9)	0	0	1 (3.7)	0	2 (2.4)	0
Mallory-Weiss Syndrome	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Melaena	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Mouth Haemorrhage	1 (1.0)	0	0	0	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	0	0
Mouth Ulceration	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	2 (2.4)	0
Nausea	29 (28.2)	0	1 (100.0)	5 (35.7)	1 (100.0)	51 (27.4)	5 (22.7)	13 (50.0)	22 (31.4)	0	80 (27.7)	5 (18.5)	14 (51.9)	27 (32 1)	1 (100.0)
Neutropenic Colitis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Obstruction Gastric	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Odynophagia	0	1 (20.0)	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	1 (3.7)	1 (3.7)	0	0
Oesophageal Pain	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Oesophageal Perforation	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0

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Oesophageal Stenosis	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Oesophageal Ulcer	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Oesophagitis	2 (1.9)	0	0	0	0	4 (2.2)	0	0	0	0	6 (2.1)	0	0	0	0
Oesophagitis Ulcerative	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Oral Discomfort	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Oral Disorder	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Oral Mucosal Blistering	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Oral Mucosal Erythema	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Oral Pain	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Palatal Swelling	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Pancreatic Atrophy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pancreatic Failure	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pancreatitis	1 (1.0)	0	0	0	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	3 (1.0)	1 (3.7)	0	1 (1.2)	0
Pancreatitis Acute	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Pancreatitis Haemorrhagic	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Pneumatosis Intestinalis	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Proctalgia	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Rectal Haemorrhage	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Rectal Lesion	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Retching	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Salivary Hypersecretion	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Stomatitis	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	1 (1.4)	0	3 (1.0)	0	1 (3.7)	1 (1.2)	0
Submaxillary Gland Enlargement	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Tongue Coated	3 (2.9)	0	0	0	0	0	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Tongue Oedema	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Tongue Ulceration	4 (3.9)	0	0	0	0	0	0	0	0	0	4 (1.4)	0	0	0	0
Tooth Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Toothache	1 (1.0)	0	0	0	0	0	0	1 (3.8)	1 (1.4)	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Umbilical Hernia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Upper Gastrointestinal Haemorrhage	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Vomiting	29 (28.2)	2 (40.0)	1 (100.0)	2 (14.3)	1 (100.0)	43 (23.1)	5 (22.7)	13 (50.0)	16 (22.9)	0	72 (24.9)	7 (25.9)	14 (51.9)	18 (21.4)	1 (100.0)

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
General Disorders And Administration Site Conditions	**73 (70.9)**	**4 (80.0)**	**1 (100.0)**	**13 (92.9)**	**1 (100.0)**	**124 (66.7)**	**19 (86.4)**	**21 (80.8)**	**37 (52.9)**	**0**	**197 (68.2)**	**23 (85.2)**	**22 (81.5)**	**50 (59 5)**	**1 (100.0)**
Asthenia	14 (13.6)	3 (60.0)	1 (100.0)	1 (7.1)	1 (100.0)	27 (14.5)	3 (13.6)	12 (46.2)	7 (10.0)	0	41 (14.2)	6 (22.2)	13 (48.1)	8 (9.5)	1 (100.0)
Brain Death	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Catheter Site Discharge	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Catheter Site Erythema	1 (1.0)	0	0	0	0	6 (3.2)	0	0	0	0	7 (2.4)	0	0	0	0
Catheter Site Haematoma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Catheter Site Haemorrhage	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Catheter Site Pain	2 (1.9)	0	0	0	0	3 (1.6)	0	1 (3.8)	1 (1.4)	0	5 (1.7)	0	1 (3.7)	1 (1.2)	0
Catheter Site Related Reaction	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Catheter Site Swelling	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Chest Discomfort	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Chest Pain	13 (12.6)	1 (20.0)	0	3 (21.4)	0	23 (12.4)	7 (31.8)	2 (7.7)	11 (15.7)	0	36 (12.5)	8 (29.6)	2 (7.4)	14 (16.7)	0
Chills	11 (10.7)	1 (20.0)	0	2 (14.3)	1 (100.0)	19 (10.2)	4 (18.2)	1 (3.8)	4 (5.7)	0	30 (10.4)	5 (18.5)	1 (3.7)	6 (7.1)	1 (100.0)

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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, Race
Number (%) of Subjects

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Crepitations	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Crying	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Cyst	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Death	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Discomfort	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Disease Progression	8 (7.8)	1 (20.0)	0	4 (28.6)	1 (100.0)	10 (5.4)	1 (4.5)	1 (3.8)	3 (4.3)	0	18 (6 2)	2 (7.4)	1 (3.7)	7 (8.3)	1 (100.0)
Drug Interaction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Drug Intolerance	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Early Satiety	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Face Oedema	2 (1.9)	1 (20.0)	0	0	1 (100.0)	0	0	0	2 (2.9)	0	2 (0.7)	1 (3.7)	0	2 (2.4)	1 (100.0)
Facial Pain	3 (2.9)	1 (20.0)	0	0	0	1 (0.5)	0	0	1 (1.4)	0	4 (1.4)	1 (3.7)	0	1 (1.2)	0
Fatigue	14 (13.6)	1 (20.0)	0	4 (28.6)	1 (100.0)	21 (11.3)	3 (13.6)	2 (7.7)	6 (8.6)	0	35 (12.1)	4 (14.8)	2 (7.4)	10 (11 9)	1 (100.0)
Feeling Cold	0	0	0	2 (14.3)	0	0	0	0	0	0	0	0	0	2 (2.4)	0
Feeling Jittery	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Gait Disturbance	1 (1.0)	0	0	1 (7.1)	0	5 (2.7)	2 (9.1)	1 (3.8)	1 (1.4)	0	6 (2.1)	2 (7.4)	1 (3.7)	2 (2.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
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Gait Inability	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
General Physical Health Deterioration	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Generalised Oedema	6 (5.8)	0	0	3 (21.4)	0	4 (2.2)	0	1 (3.8)	1 (1.4)	0	10 (3 5)	0	1 (3.7)	4 (4.8)	0
Granuloma	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hyperthermia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypothermia	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Inflammation	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Influenza Like Illness	0	0	0	0	0	2 (1.1)	0	3 (11.5)	0	0	2 (0.7)	0	3 (11.1)	0	0
Infusion Site Erythema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Infusion Site Inflammation	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Infusion Site Phlebitis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Injection Site Pain	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Localised Oedema	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Malaise	3 (2.9)	1 (20.0)	0	0	0	5 (2.7)	2 (9.1)	2 (7.7)	2 (2.9)	0	8 (2.8)	3 (11.1)	2 (7.4)	2 (2.4)	0
Mass	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Mucosal Dryness	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Mucosal Inflammation	6 (5.8)	0	0	0	0	15 (8.1)	3 (13.6)	3 (11.5)	3 (4.3)	0	21 (7 3)	3 (11.1)	3 (11.1)	3 (3.6)	0
Multi-Organ Disorder	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Multiple Organ Dysfunction Syndrome	7 (6.8)	0	0	2 (14.3)	0	4 (2.2)	0	0	2 (2.9)	0	11 (3.8)	0	0	4 (4.8)	0
Nodule	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	1 (1.4)	0	3 (1.0)	0	0	2 (2.4)	0
Oedema	5 (4.9)	0	0	0	0	12 (6.5)	0	1 (3.8)	1 (1.4)	0	17 (5 9)	0	1 (3.7)	1 (1.2)	0
Oedema Peripheral	18 (17.5)	1 (20.0)	1 (100.0)	4 (28.6)	0	24 (12.9)	5 (22.7)	2 (7.7)	7 (10.0)	0	42 (14.5)	6 (22.2)	3 (11.1)	11 (13 1)	0
Pain	5 (4.9)	0	0	0	0	7 (3.8)	2 (9.1)	3 (11.5)	2 (2.9)	0	12 (4 2)	2 (7.4)	3 (11.1)	2 (2.4)	0
Peripheral Swelling	6 (5.8)	0	0	0	0	7 (3.8)	1 (4.5)	1 (3.8)	4 (5.7)	0	13 (4 5)	1 (3.7)	1 (3.7)	4 (4.8)	0
Pseudocyst	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Puncture Site Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pyrexia	35 (34.0)	2 (40.0)	0	5 (35.7)	1 (100.0)	56 (30.1)	9 (40.9)	17 (65.4)	18 (25.7)	0	91 (31.5)	11 (40.7)	17 (63.0)	23 (27.4)	1 (100.0)
Secretion Discharge	0	0	0	0	0	0	1 (4.5)	0	1 (1.4)	0	0	1 (3.7)	0	1 (1.2)	0
Sluggishness	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Suprapubic Pain	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Swelling	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Vessel Puncture Site Haematoma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vessel Puncture Site Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hepatobiliary Disorders	**16 (15.5)**	**0**	**0**	**3 (21.4)**	**0**	**17 (9.1)**	**4 (18.2)**	**5 (19.2)**	**6 (8.6)**	**0**	**33 (11.4)**	**4 (14.8)**	**5 (18.5)**	**9 (10.7)**	**0**
Cholecystitis	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Cholelithiasis	3 (2.9)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	6 (2.1)	0	0	1 (1.2)	0
Cholestasis	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Deficiency Of Bile Secretion	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Gallbladder Enlargement	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Gallbladder Polyp	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hepatic Cyst	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hepatic Failure	1 (1.0)	0	0	0	0	3 (1.6)	1 (4.5)	0	1 (1.4)	0	4 (1.4)	1 (3.7)	0	1 (1.2)	0
Hepatic Function Abnormal	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	1 (1.2)	0
Hepatic Lesion	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Hepatic Necrosis	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Hepatic Steatosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hepatitis Acute	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Hepatocellular Injury	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hepatomegaly	2 (1.9)	0	0	0	0	2 (1.1)	1 (4.5)	2 (7.7)	0	0	4 (1.4)	1 (3.7)	2 (7.4)	0	0
Hepatosplenomegaly	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Hepatotoxicity	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Hyperbilirubinaemia	2 (1.9)	0	0	2 (14.3)	0	2 (1.1)	1 (4.5)	0	2 (2.9)	0	4 (1.4)	1 (3.7)	0	4 (4.8)	0
Jaundice	3 (2.9)	0	0	1 (7.1)	0	3 (1.6)	0	2 (7.7)	2 (2.9)	0	6 (2.1)	0	2 (7.4)	3 (3.6)	0
Liver Disorder	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Ocular Icterus	3 (2.9)	0	0	0	0	4 (2.2)	1 (4.5)	0	0	0	7 (2.4)	1 (3.7)	0	0	0
Immune System Disorders	**34 (33.0)**	**1 (20.0)**	**0**	**5 (35.7)**	**1 (100.0)**	**14 (7.5)**	**1 (4.5)**	**2 (7.7)**	**3 (4.3)**	**0**	**48 (16.6)**	**2 (7.4)**	**2 (7.4)**	**8 (9.5)**	**1 (100.0)**
Acute Graft Versus Host Disease In Intestine	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Acute Graft Versus Host Disease In Liver	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Graft Versus Host Disease	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Drug Hypersensitivity	2 (1.9)	0	0	0	1 (100.0)	2 (1.1)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	1 (100.0)

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Graft Versus Host Disease	11 (10.7)	1 (20.0)	0	4 (28.6)	0	2 (1.1)	1 (4.5)	0	0	0	13 (4 5)	2 (7.4)	0	4 (4.8)	0
Graft Versus Host Disease In Gastrointestinal Tract	7 (6.8)	0	0	0	0	1 (0.5)	0	0	0	0	8 (2.8)	0	0	0	0
Graft Versus Host Disease In Liver	6 (5.8)	0	0	0	0	0	0	0	0	0	6 (2.1)	0	0	0	0
Graft Versus Host Disease In Lung	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Graft Versus Host Disease In Skin	17 (16.5)	1 (20.0)	0	1 (7.1)	1 (100.0)	3 (1.6)	0	0	0	0	20 (6 9)	1 (3.7)	0	1 (1.2)	1 (100.0)
Hypersensitivity	1 (1.0)	0	0	0	0	5 (2.7)	0	0	1 (1.4)	0	6 (2.1)	0	0	1 (1.2)	0
Hypogammaglobulinaemia	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Iodine Allergy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Kidney Transplant Rejection	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Seasonal Allergy	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Transplant Rejection	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Infections And Infestations	**77 (74.8)**	**4 (80.0)**	**0**	**11 (78.6)**	**1 (100.0)**	**114 (61.3)**	**11 (50.0)**	**17 (65.4)**	**45 (64.3)**	**0**	**191 (66.1)**	**15 (55.6)**	**17 (63.0)**	**56 (66.7)**	**1 (100.0)**
Abdominal Abscess	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Abdominal Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Abscess	0	0	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	1 (0.3)	1 (3.7)	0	1 (1.2)	0
Abscess Limb	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Abscess Neck	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Abscess Of Eyelid	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Abscess Oral	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Acarodermatitis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Acid Fast Bacilli Infection	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Acinetobacter Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Acquired Immunodeficiency Syndrome	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Actinomycosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Adenovirus Infection	1 (1.0)	0	0	2 (14.3)	0	0	0	0	0	0	1 (0.3)	0	0	2 (2.4)	0
Aids Related Complication	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Alpha Haemolytic Streptococcal Infection	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Anal Abscess	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Arthritis Bacterial	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Arthritis Infective	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Aspergilloma	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Aspergillus Infection	3 (2.9)	0	0	1 (7.1)	0	2 (1.1)	0	1 (3.8)	0	0	5 (1.7)	0	1 (3.7)	1 (1.2)	0
Atypical Pneumonia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Bacteraemia	8 (7.8)	1 (20.0)	0	0	1 (100.0)	8 (4.3)	0	1 (3.8)	2 (2.9)	0	16 (5 5)	1 (3.7)	1 (3.7)	2 (2.4)	1 (100.0)
Bacterial Disease Carrier	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bacterial Infection	4 (3.9)	1 (20.0)	0	1 (7.1)	0	8 (4.3)	0	2 (7.7)	1 (1.4)	0	12 (4 2)	1 (3.7)	2 (7.4)	2 (2.4)	0
Brain Abscess	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Bronchiolitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bronchitis	4 (3.9)	0	0	0	0	5 (2.7)	0	1 (3.8)	5 (7.1)	0	9 (3.1)	0	1 (3.7)	5 (6.0)	0
Bronchitis Bacterial	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Bronchitis Viral	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Bronchopulmonary Aspergillosis	1 (1.0)	0	0	0	0	5 (2.7)	0	0	0	0	6 (2.1)	0	0	0	0
Candida Infection	4 (3.9)	0	0	0	0	1 (0.5)	0	0	0	0	5 (1.7)	0	0	0	0
Catheter Site Cellulitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Catheter Site Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Cellulitis	3 (2.9)	0	0	0	0	8 (4.3)	1 (4.5)	0	2 (2.9)	0	11 (3.8)	1 (3.7)	0	2 (2.4)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Cellulitis Of Male External Genital Organ	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Cellulitis Orbital	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Cerebral Aspergillosis	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Cerebral Toxoplasmosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Sinusitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Clostridium Difficile Colitis	2 (1.9)	0	0	1 (7.1)	0	3 (1.6)	1 (4.5)	0	0	0	5 (1.7)	1 (3.7)	0	1 (1.2)	0
Clostridium Difficile Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Conjunctivitis	3 (2.9)	0	0	1 (7.1)	0	5 (2.7)	0	1 (3.8)	4 (5.7)	0	8 (2.8)	0	1 (3.7)	5 (6.0)	0
Corynebacterium Infection	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Corynebacterium Sepsis	1 (1.0)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Cystitis Bacterial	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Cytomegalovirus Chorioretinitis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Cytomegalovirus Colitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cytomegalovirus Duodenitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Cytomegalovirus Infection	9 (8.7)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	12 (4 2)	0	0	1 (1.2)	0
Dacryocystitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
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Device Related Infection	4 (3.9)	0	0	0	0	5 (2.7)	2 (9.1)	0	0	0	9 (3.1)	2 (7.4)	0	0	0
Disseminated Tuberculosis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Diverticulitis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Ear Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Empyema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Encephalitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
End Stage Aids	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Endocarditis Bacterial	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Endophthalmitis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Enterobacter Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Enterococcal Bacteraemia	0	0	0	0	0	4 (2.2)	0	0	1 (1.4)	0	4 (1.4)	0	0	1 (1.2)	0
Enterococcal Infection	11 (10.7)	0	0	3 (21.4)	0	7 (3.8)	1 (4.5)	0	0	0	18 (6 2)	1 (3.7)	0	3 (3.6)	0
Enterococcal Sepsis	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Escherichia Bacteraemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Escherichia Infection	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Escherichia Sepsis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Escherichia Urinary Tract Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Eye Infection Staphylococcal	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
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Eyelid Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Folliculitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Fungaemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Fungal Infection	1 (1.0)	0	0	0	0	2 (1.1)	2 (9.1)	0	0	0	3 (1.0)	2 (7.4)	0	0	0
Fungal Rhinitis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Fungal Sepsis	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Fungal Skin Infection	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Furuncle	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Fusarium Infection	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Gastroenteritis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Gastroenteritis Viral	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Genital Herpes	0	0	0	0	0	0	1 (4.5)	1 (3.8)	0	0	0	1 (3.7)	1 (3.7)	0	0
Gingival Abscess	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gingivitis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Helicobacter Gastritis	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Hepatic Candidiasis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Hepatosplenic Candidiasis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Herpes Simplex	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Herpes Simplex Pneumonia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Herpes Zoster	3 (2.9)	0	0	0	0	5 (2.7)	0	1 (3.8)	0	0	8 (2.8)	0	1 (3.7)	0	0

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All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Race
Number (%) of Subjects

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Hiv Wasting Syndrome	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hordeolum	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Human Polyomavirus Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Infection Parasitic	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Influenza	0	0	0	0	0	2 (1.1)	1 (4.5)	0	3 (4.3)	0	2 (0.7)	1 (3.7)	0	3 (3.6)	0
Infusion Site Cellulitis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Intervertebral Discitis	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Klebsiella Bacteraemia	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Klebsiella Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Klebsiella Sepsis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Localised Infection	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Lower Respiratory Tract Infection	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Lung Abscess	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Lung Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Lung Infection Pseudomonal	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Mastoiditis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Meningitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	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 Cryptococcal	0	0	0	0	0	1 (0.5)	0	4 (15.4)	3 (4.3)	0	1 (0.3)	0	4 (14.8)	3 (3.6)	0
Meningitis Tuberculous	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Molluscum Contagiosum	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Mucormycosis	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Mycobacterial Infection	0	0	0	0	0	4 (2.2)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	0
Mycobacterium Avium Complex Infection	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Mycobacterium Kansasii Infection	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Mycoplasma Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nasopharyngitis	0	0	0	0	0	4 (2.2)	0	1 (3.8)	2 (2.9)	0	4 (1.4)	0	1 (3.7)	2 (2.4)	0
Neurosyphilis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Nocardiosis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Oesophageal Candidiasis	0	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Onychomycosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Oral Candidiasis	8 (7.8)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	10 (3 5)	0	0	1 (1.2)	0
Oral Fungal Infection	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Oral Hairy Leukoplakia	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Oral Herpes	3 (2.9)	1 (20.0)	0	0	0	6 (3.2)	2 (9.1)	0	0	0	9 (3.1)	3 (11.1)	0	0	0
Orchitis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Osteomyelitis	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Otitis Media	1 (1.0)	0	0	0	0	0	1 (4.5)	1 (3.8)	0	0	1 (0.3)	1 (3.7)	1 (3.7)	0	0
Parainfluenzae Virus Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Paronychia	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Pelvic Abscess	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Periorbital Infection	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Peritonitis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Pharyngitis	2 (1.9)	0	0	0	0	0	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Pharyngotonsillitis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Plague	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pleural Infection Bacterial	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pneumococcal Sepsis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pneumocystis Jirovecii Pneumonia	0	0	0	0	0	2 (1.1)	1 (4.5)	0	3 (4.3)	0	2 (0.7)	1 (3.7)	0	3 (3.6)	0
Pneumonia	10 (9.7)	3 (60.0)	0	3 (21.4)	1 (100.0)	24 (12.9)	3 (13.6)	1 (3.8)	4 (5.7)	0	34 (11.8)	6 (22.2)	1 (3.7)	7 (8.3)	1 (100.0)

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Pneumonia Bacterial	3 (2.9)	1 (20.0)	0	0	0	1 (0.5)	0	0	0	0	4 (1.4)	1 (3.7)	0	0	0
Pneumonia Cytomegaloviral	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pneumonia Escherichia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Pneumonia Fungal	6 (5.8)	0	0	1 (7.1)	0	5 (2.7)	0	1 (3.8)	1 (1.4)	0	11 (3.8)	0	1 (3.7)	2 (2.4)	0
Pneumonia Klebsiella	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Pneumonia Pseudomonal	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Pneumonia Staphylococcal	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Postoperative Wound Infection	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Proctitis Herpes	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pseudallescheria Infection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pseudomembranous Colitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pseudomonas Infection	3 (2.9)	0	0	0	0	2 (1.1)	0	0	0	0	5 (1.7)	0	0	0	0
Pulmonary Mycosis	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Pulmonary Tuberculosis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Purulent Discharge	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Pyelonephritis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
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Respiratory Syncytial Virus Infection	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Respiratory Tract Infection	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Retinitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Rhinitis	1 (1.0)	0	0	0	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	0	0
Salmonella Sepsis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Sepsis	6 (5.8)	0	0	3 (21.4)	0	9 (4.8)	0	1 (3.8)	2 (2.9)	0	15 (5 2)	0	1 (3.7)	5 (6.0)	0
Septic Embolus	3 (2.9)	0	0	0	1 (100.0)	0	0	0	0	0	3 (1.0)	0	0	0	1 (100.0)
Septic Shock	6 (5.8)	0	0	0	0	2 (1.1)	0	0	0	0	8 (2.8)	0	0	0	0
Serratia Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Sinusitis	7 (6.8)	1 (20.0)	0	1 (7.1)	1 (100.0)	11 (5.9)	1 (4.5)	1 (3.8)	2 (2.9)	0	18 (6 2)	2 (7.4)	1 (3.7)	3 (3.6)	1 (100.0)
Sinusitis Aspergillus	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Sinusitis Bacterial	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Sinusitis Fungal	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Skin Bacterial Infection	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Skin Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Staphylococcal Bacteraemia	7 (6.8)	1 (20.0)	0	2 (14.3)	0	5 (2.7)	1 (4.5)	1 (3.8)	1 (1.4)	0	12 (4 2)	2 (7.4)	1 (3.7)	3 (3.6)	0
Staphylococcal Infection	6 (5.8)	0	0	1 (7.1)	0	11 (5.9)	1 (4.5)	1 (3.8)	0	0	17 (5 9)	1 (3.7)	1 (3.7)	1 (1.2)	0
Staphylococcal Sepsis	2 (1.9)	0	0	0	0	2 (1.1)	3 (13.6)	0	1 (1.4)	0	4 (1.4)	3 (11.1)	0	1 (1.2)	0
Staphylococcal Skin Infection	0	0	0	0	0	0	1 (4.5)	0	1 (1.4)	0	0	1 (3.7)	0	1 (1.2)	0
Stenotrophomonas Infection	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Stenotrophomonas Sepsis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Subcutaneous Abscess	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Superinfection Fungal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Syphilis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Systemic Candida	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Tooth Abscess	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Tooth Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Torulopsis Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Tracheitis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Trichosporon Infection	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Tuberculosis	0	0	0	0	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0

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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, Race
Number (%) of Subjects

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	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Upper Respiratory Tract Infection	6 (5.8)	0	0	2 (14.3)	0	3 (1.6)	1 (4.5)	6 (23.1)	1 (1.4)	0	9 (3.1)	1 (3.7)	6 (22.2)	3 (3.6)	0
Urinary Tract Infection	4 (3.9)	0	0	0	1 (100.0)	4 (2.2)	1 (4.5)	0	9 (12.9)	0	8 (2.8)	1 (3.7)	0	9 (10.7)	1 (100.0)
Urinary Tract Infection Staphylococcal	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Varicella	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Varicella Zoster Virus Infection	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Viral Infection	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	3 (1.0)	1 (3.7)	0	2 (2.4)	0
Viral Sinusitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Wound Infection	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Wound Infection Fungal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Injury, Poisoning And Procedural Complications	**25 (24.3)**	**2 (40.0)**	**0**	**3 (21.4)**	**0**	**33 (17.7)**	**4 (18.2)**	**5 (19.2)**	**11 (15.7)**	**0**	**58 (20.1)**	**6 (22.2)**	**5 (18.5)**	**14 (16.7)**	**0**
Arthropod Bite	0	0	0	0	0	0	1 (4.5)	1 (3.8)	0	0	0	1 (3.7)	1 (3.7)	0	0
Barotitis Media	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Contusion	6 (5.8)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	8 (2.8)	0	0	1 (1.2)	0
Corneal Abrasion	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0

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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, Race
Number (%) of Subjects

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Eschar	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Excoriation	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Eye Burns	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Eye Contusion	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Fall	6 (5.8)	1 (20.0)	0	1 (7.1)	0	6 (3.2)	2 (9.1)	0	0	0	12 (4 2)	3 (11.1)	0	1 (1.2)	0
Femur Fracture	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Foot Fracture	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Graft Complication	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Haemolytic Transfusion Reaction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Head Injury	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hip Fracture	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hyphaema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Incision Site Haematoma	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Incision Site Pain	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Infusion Related Reaction	2 (1.9)	0	0	0	0	4 (2.2)	0	0	0	0	6 (2.1)	0	0	0	0
Injury	2 (1.9)	0	0	0	0	0	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Joint Injury	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Laceration	1 (1.0)	0	0	1 (7.1)	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	1 (1.2)	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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Limb Injury	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Muscle Strain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Overdose	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Post Lumbar Puncture Syndrome	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Post Procedural Haemorrhage	2 (1.9)	1 (20.0)	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	1 (3.7)	0	0	0
Procedural Complication	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Procedural Pain	3 (2.9)	0	0	1 (7.1)	0	4 (2.2)	0	1 (3.8)	2 (2.9)	0	7 (2.4)	0	1 (3.7)	3 (3.6)	0
Procedural Site Reaction	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Scratch	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Skin Abrasion	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Spinal Compression Fracture	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Spinal Cord Injury	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Stress Fracture	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Subarachnoid Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Sunburn	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Toxicity To Various Agents	0	1 (20.0)	0	0	0	4 (2.2)	0	1 (3.8)	0	0	4 (1.4)	1 (3.7)	1 (3.7)	0	0
Tracheal Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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Number (%) of Subjects

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Transfusion Reaction	1 (1.0)	0	0	0	0	4 (2.2)	1 (4.5)	0	2 (2.9)	0	5 (1.7)	1 (3.7)	0	2 (2.4)	0
Wound	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Wound Complication	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Wound Decomposition	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Wound Necrosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Investigations	**56 (54.4)**	**5 (100.0)**	**1 (100.0)**	**10 (71.4)**	**1 (100.0)**	**85 (45.7)**	**11 (50.0)**	**16 (61.5)**	**28 (40.0)**	**0**	**141 (48.8)**	**16 (59.3)**	**17 (63.0)**	**38 (45.2)**	**1 (100.0)**
Activated Partial Thromboplastin Time Prolonged	1 (1.0)	0	0	0	0	0	1 (4.5)	1 (3.8)	0	0	1 (0.3)	1 (3.7)	1 (3.7)	0	0
Alanine Aminotransferase	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Alanine Aminotransferase Increased	9 (8.7)	0	0	1 (7.1)	0	6 (3.2)	2 (9.1)	5 (19.2)	3 (4.3)	0	15 (5 2)	2 (7.4)	5 (18.5)	4 (4.8)	0
Ammonia Increased	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Amylase	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Amylase Increased	1 (1.0)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0
Anticoagulation Drug Level Above Therapeutic	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Aspartate Aminotransferase Increased	2 (1.9)	0	0	1 (7.1)	0	6 (3.2)	0	7 (26.9)	4 (5.7)	0	8 (2.8)	0	7 (25.9)	5 (6.0)	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Aspiration Pleural Cavity	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Atrial Pressure Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bacterial Test Positive	1 (1.0)	0	0	0	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	0	0
Bilirubin Conjugated Increased	1 (1.0)	0	0	0	0	0	0	0	2 (2.9)	0	1 (0.3)	0	0	2 (2.4)	0
Biopsy Brain	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Biopsy Skin	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Biopsy Skin Abnormal	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Blast Cell Count Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Albumin Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Alkaline Phosphatase Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Alkaline Phosphatase Increased	7 (6.8)	1 (20.0)	0	1 (7.1)	0	4 (2.2)	1 (4.5)	5 (19.2)	5 (7.1)	0	11 (3.8)	2 (7.4)	5 (18.5)	6 (7.1)	0
Blood Bilirubin Increased	6 (5.8)	1 (20.0)	0	1 (7.1)	0	4 (2.2)	1 (4.5)	0	3 (4.3)	0	10 (3 5)	2 (7.4)	0	4 (4.8)	0
Blood Cholesterol Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Blood Creatinine Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Creatinine Increased	10 (9.7)	0	0	3 (21.4)	0	10 (5.4)	0	1 (3.8)	2 (2.9)	0	20 (6 9)	0	1 (3.7)	5 (6.0)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Emergent Adverse Events by Risk Group, Race
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Blood Culture Positive	1 (1.0)	0	0	0	0	6 (3.2)	0	0	1 (1.4)	0	7 (2.4)	0	0	1 (1.2)	0
Blood Electrolytes Decreased	0	0	0	0	1 (100.0)	0	0	0	0	0	0	0	0	0	1 (100.0)
Blood Fibrinogen Decreased	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Blood Gases Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Glucose Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Glucose Increased	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Blood Immunoglobulin G Decreased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Lactate Dehydrogenase Increased	2 (1.9)	1 (20.0)	0	1 (7.1)	0	3 (1.6)	1 (4.5)	0	2 (2.9)	0	5 (1.7)	2 (7.4)	0	3 (3.6)	0
Blood Lactic Acid Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Magnesium Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Phosphorus Increased	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Blood Potassium Decreased	0	0	0	0	0	4 (2.2)	0	0	0	0	4 (1.4)	0	0	0	0
Blood Potassium Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Pressure Decreased	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Blood Pressure Increased	3 (2.9)	0	0	0	0	4 (2.2)	0	0	1 (1.4)	0	7 (2.4)	0	0	1 (1.2)	0
Blood Pressure Orthostatic	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0

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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, Race
Number (%) of Subjects

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Blood Pressure Systolic Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Sodium Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Sodium Increased	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Blood Triglycerides Increased	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Blood Urea Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Urea Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Blood Urea Increased	3 (2.9)	1 (20.0)	0	3 (21.4)	0	2 (1.1)	1 (4.5)	0	0	0	5 (1.7)	2 (7.4)	0	3 (3.6)	0
Blood Uric Acid	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Blood Uric Acid Increased	0	0	0	0	0	1 (0.5)	0	0	3 (4.3)	0	1 (0.3)	0	0	3 (3.6)	0
Blood Urine Present	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Body Temperature	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Body Temperature Increased	0	0	0	1 (7.1)	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	2 (2.4)	0
Breath Sounds Abnormal	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	4 (1.4)	1 (3.7)	0	2 (2.4)	0
Carbon Dioxide Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Cardiac Murmur	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Cardioactive Drug Level Decreased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	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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	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Cardioactive Drug Level Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Chest X-Ray Abnormal	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Clostridium Test	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Clostridium Test Positive	3 (2.9)	0	0	0	0	6 (3.2)	0	0	0	0	9 (3.1)	0	0	0	0
Computerised Tomogram Abnormal	0	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Csf Protein Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Culture Urine Positive	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cytomegalovirus Test	1 (1.0)	0	0	0	0	4 (2.2)	0	0	0	0	5 (1.7)	0	0	0	0
Cytomegalovirus Test Positive	2 (1.9)	0	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	0	0
Drug Level Changed	3 (2.9)	0	0	0	0	0	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Drug Level Increased	3 (2.9)	1 (20.0)	0	0	1 (100.0)	3 (1.6)	0	0	0	0	6 (2.1)	1 (3.7)	0	0	1 (100.0)
Ejection Fraction Decreased	0	1 (20.0)	0	1 (7.1)	0	2 (1.1)	0	0	0	0	2 (0.7)	1 (3.7)	0	1 (1.2)	0
Electrocardiogram Abnormal	2 (1.9)	0	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	0	0
Electrocardiogram Change	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Electrocardiogram Qrs Complex Prolonged	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Electrocardiogram Qt Interval Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Electrocardiogram Qt Prolonged	0	0	0	0	0	5 (2.7)	1 (4.5)	4 (15.4)	1 (1.4)	0	5 (1.7)	1 (3.7)	4 (14.8)	1 (1.2)	0
Electrocardiogram St Segment Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Electrocardiogram St Segment Elevation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Electrocardiogram T Wave Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Electrocardiogram T Wave Inversion	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Electrocardiogram T Wave Peaked	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Electroencephalogram Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Eosinophil Count Increased	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Fundoscopy Abnormal	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0

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Fungal Test Positive	2 (1.9)	0	0	0	0	4 (2.2)	0	0	0	0	6 (2.1)	0	0	0	0
Gamma-Glutamyltransferase Increased	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
General Physical Condition Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Glucocorticoids Decreased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Haemoglobin Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Haemoglobin Decreased	2 (1.9)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	5 (1.7)	0	0	1 (1.2)	0
Heart Rate Irregular	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	2 (0.7)	0	1 (3.7)	2 (2.4)	0
Hepatic Enzyme Increased	4 (3.9)	0	0	1 (7.1)	0	3 (1.6)	1 (4.5)	0	0	0	7 (2.4)	1 (3.7)	0	1 (1.2)	0
Hepatitis A Antibody Positive	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hepatitis C Virus Test Positive	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Herpes Simplex Test Positive	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
International Normalised Ratio Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
International Normalised Ratio Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Laboratory Test Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Lipase	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lipase Abnormal	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lipase Increased	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Liver Function Test Abnormal	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Liver Function Test Increased	7 (6.8)	1 (20.0)	1 (100.0)	1 (7.1)	0	7 (3.8)	0	0	1 (1.4)	0	14 (4.8)	1 (3.7)	1 (3.7)	2 (2.4)	0
Medical Observation Normal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Myocardial Necrosis Marker Increased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Neutrophil Count Decreased	1 (1.0)	0	0	0	0	1 (0.5)	0	2 (7.7)	0	0	2 (0.7)	0	2 (7.4)	0	0
Nuclear Magnetic Resonance Imaging Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nutritional Condition Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Occult Blood Positive	1 (1.0)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Oxygen Saturation Decreased	5 (4.9)	1 (20.0)	0	1 (7.1)	0	1 (0.5)	0	0	0	0	6 (2.1)	1 (3.7)	0	1 (1.2)	0

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Pancreatic Enzymes Increased	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Platelet Count Decreased	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	2 (7.7)	0	0	2 (0.7)	0	2 (7.4)	1 (1.2)	0
Platelet Count Increased	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Prostatic Specific Antigen Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Prothrombin Level Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Prothrombin Time Prolonged	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	1 (4.5)	1 (3.8)	1 (1.4)	0	2 (0.7)	1 (3.7)	1 (3.7)	2 (2.4)	0
Prothrombin Time Shortened	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Pulmonary Function Test Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pupillary Light Reflex Tests Abnormal	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Qrs Axis Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Renal Scan	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Respiratory Rate Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Right Ventricular Systolic Pressure Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Serum Ferritin Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Spleen Palpable	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Sputum Culture Positive	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Transaminases Increased	0	0	0	0	0	0	0	1 (3.8)	1 (1.4)	0	0	0	1 (3.7)	1 (1.2)	0
Troponin Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Urine Output Decreased	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Viral Load Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Weight Decreased	6 (5.8)	0	0	1 (7.1)	0	8 (4.3)	3 (13.6)	2 (7.7)	6 (8.6)	0	14 (4.8)	3 (11.1)	2 (7.4)	7 (8.3)	0
Weight Increased	0	0	0	0	0	0	0	1 (3.8)	1 (1.4)	0	0	0	1 (3.7)	1 (1.2)	0
White Blood Cell Count Decreased	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
White Blood Cell Count Increased	2 (1.9)	0	0	0	0	6 (3.2)	0	0	0	0	8 (2.8)	0	0	0	0
White Blood Cells Urine Positive	0	0	1 (100.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0
X-Ray Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Metabolism And Nutrition Disorders	**64 (62.1)**	**3 (60.0)**	**1 (100.0)**	**12 (85.7)**	**1 (100.0)**	**80 (43.0)**	**11 (50.0)**	**11 (42.3)**	**24 (34.3)**	**0**	**144 (49.8)**	**14 (51.9)**	**12 (44.4)**	**36 (42.9)**	**1 (100.0)**
Acidosis	0	1 (20.0)	0	0	0	0	0	0	1 (1.4)	0	0	1 (3.7)	0	1 (1.2)	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Cachexia	0	0	0	1 (7.1)	0	1 (0.5)	0	2 (7.7)	0	0	1 (0.3)	0	2 (7.4)	1 (1.2)	0
Decreased Appetite	18 (17.5)	1 (20.0)	1 (100.0)	2 (14.3)	1 (100.0)	22 (11.8)	5 (22.7)	7 (26.9)	9 (12.9)	0	40 (13.8)	6 (22.2)	8 (29.6)	11 (13 1)	1 (100.0)
Dehydration	4 (3.9)	2 (40.0)	1 (100.0)	4 (28.6)	0	12 (6.5)	0	2 (7.7)	5 (7.1)	0	16 (5 5)	2 (7.4)	3 (11.1)	9 (10.7)	0
Diabetes Mellitus	2 (1.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Diabetes Mellitus Inadequate Control	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Electrolyte Imbalance	2 (1.9)	0	0	0	0	2 (1.1)	1 (4.5)	0	1 (1.4)	0	4 (1.4)	1 (3.7)	0	1 (1.2)	0
Failure To Thrive	4 (3.9)	0	0	0	0	3 (1.6)	0	0	0	0	7 (2.4)	0	0	0	0
Fluid Overload	5 (4.9)	0	0	2 (14.3)	0	5 (2.7)	2 (9.1)	0	1 (1.4)	0	10 (3 5)	2 (7.4)	0	3 (3.6)	0
Fluid Retention	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	1 (1.2)	0
Hypercalcaemia	5 (4.9)	1 (20.0)	0	1 (7.1)	0	2 (1.1)	1 (4.5)	0	0	0	7 (2.4)	2 (7.4)	0	1 (1.2)	0
Hypercholesterolaemia	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Hypercreatininaemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hyperglycaemia	15 (14.6)	0	0	6 (42.9)	0	9 (4.8)	0	2 (7.7)	3 (4.3)	0	24 (8 3)	0	2 (7.4)	9 (10.7)	0

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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, Race
Number (%) of Subjects

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Hyperkalaemia	12 (11.7)	0	0	1 (7.1)	0	10 (5.4)	1 (4.5)	1 (3.8)	3 (4.3)	0	22 (7.6)	1 (3.7)	1 (3.7)	4 (4.8)	0
Hyperlipidaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hypernatraemia	2 (1.9)	0	0	2 (14.3)	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	2 (2.4)	0
Hyperphosphataemia	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Hypertriglyceridaemia	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Hyperuricaemia	2 (1.9)	0	0	2 (14.3)	0	0	0	1 (3.8)	2 (2.9)	0	2 (0.7)	0	1 (3.7)	4 (4.8)	0
Hypervolaemia	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Hypoalbuminaemia	2 (1.9)	1 (20.0)	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	1 (3.7)	0	0	0
Hypocalcaemia	9 (8.7)	1 (20.0)	0	4 (28.6)	0	8 (4.3)	2 (9.1)	1 (3.8)	3 (4.3)	0	17 (5 9)	3 (11.1)	1 (3.7)	7 (8.3)	0
Hypoglycaemia	1 (1.0)	0	0	0	0	5 (2.7)	1 (4.5)	0	0	0	6 (2.1)	1 (3.7)	0	0	0
Hypokalaemia	14 (13.6)	0	1 (100.0)	3 (21.4)	0	27 (14.5)	2 (9.1)	1 (3.8)	8 (11.4)	0	41 (14.2)	2 (7.4)	2 (7.4)	11 (13 1)	0
Hypomagnesaemia	9 (8.7)	1 (20.0)	0	1 (7.1)	0	14 (7.5)	2 (9.1)	0	2 (2.9)	0	23 (8.0)	3 (11.1)	0	3 (3.6)	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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Hyponatraemia	6 (5.8)	0	0	0	0	5 (2.7)	0	2 (7.7)	1 (1.4)	0	11 (3.8)	0	2 (7.4)	1 (1.2)	0
Hypophagia	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Hypophosphataemia	4 (3.9)	0	0	0	0	3 (1.6)	1 (4.5)	1 (3.8)	1 (1.4)	0	7 (2.4)	1 (3.7)	1 (3.7)	1 (1.2)	0
Hypoproteinaemia	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Hypovolaemia	0	0	0	0	0	5 (2.7)	1 (4.5)	0	1 (1.4)	0	5 (1.7)	1 (3.7)	0	1 (1.2)	0
Iron Overload	2 (1.9)	0	0	1 (7.1)	0	0	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Lactic Acidosis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Malnutrition	2 (1.9)	0	0	1 (7.1)	0	7 (3.8)	0	0	1 (1.4)	0	9 (3.1)	0	0	2 (2.4)	0
Metabolic Acidosis	7 (6.8)	0	0	3 (21.4)	1 (100.0)	7 (3.8)	1 (4.5)	1 (3.8)	0	0	14 (4.8)	1 (3.7)	1 (3.7)	3 (3.6)	1 (100.0)
Metabolic Alkalosis	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Metabolic Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Polydipsia	0	0	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	1 (0.3)	1 (3.7)	0	1 (1.2)	0
Tumour Lysis Syndrome	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Vitamin K Deficiency	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders	**43 (41.7)**	**2 (40.0)**	**0**	**10 (71.4)**	**0**	**67 (36.0)**	**11 (50.0)**	**15 (57.7)**	**25 (35.7)**	**0**	**110 (38.1)**	**13 (48.1)**	**15 (55.6)**	**35 (41.7)**	**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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Amyotrophy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Arthralgia	10 (9.7)	0	0	2 (14.3)	0	15 (8.1)	1 (4.5)	1 (3.8)	2 (2.9)	0	25 (8.7)	1 (3.7)	1 (3.7)	4 (4.8)	0
Arthritis	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Back Pain	13 (12.6)	1 (20.0)	0	4 (28.6)	0	10 (5.4)	5 (22.7)	2 (7.7)	5 (7.1)	0	23 (8.0)	6 (22.2)	2 (7.4)	9 (10.7)	0
Bone Lesion	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Bone Pain	4 (3.9)	0	0	0	0	5 (2.7)	1 (4.5)	0	2 (2.9)	0	9 (3.1)	1 (3.7)	0	2 (2.4)	0
Bursitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chest Wall Mass	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Compartment Syndrome	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Dactylitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Fistula	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Fistula Discharge	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Flank Pain	1 (1.0)	1 (20.0)	0	1 (7.1)	0	5 (2.7)	0	0	2 (2.9)	0	6 (2.1)	1 (3.7)	0	3 (3.6)	0
Groin Pain	0	0	0	0	0	0	1 (4.5)	0	1 (1.4)	0	0	1 (3.7)	0	1 (1.2)	0
Haemarthrosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypercreatinaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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All Randomized Subjects
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Number (%) of Subjects

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Joint Range Of Motion Decreased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Joint Stiffness	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Joint Swelling	1 (1.0)	0	0	1 (7.1)	0	4 (2.2)	0	0	0	0	5 (1.7)	0	0	1 (1.2)	0
Mobility Decreased	2 (1.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Muscle Atrophy	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Muscle Contracture	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Muscle Rigidity	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Muscle Spasms	2 (1.9)	0	0	0	0	10 (5.4)	1 (4.5)	2 (7.7)	0	0	12 (4 2)	1 (3.7)	2 (7.4)	0	0
Muscle Twitching	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Muscular Weakness	8 (7.8)	0	0	2 (14.3)	0	5 (2.7)	2 (9.1)	3 (11.5)	4 (5.7)	0	13 (4 5)	2 (7.4)	3 (11.1)	6 (7.1)	0
Musculoskeletal Chest Pain	3 (2.9)	0	0	0	0	4 (2.2)	1 (4.5)	0	0	0	7 (2.4)	1 (3.7)	0	0	0
Musculoskeletal Discomfort	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Musculoskeletal Pain	7 (6.8)	0	0	0	0	14 (7.5)	2 (9.1)	0	2 (2.9)	0	21 (7 3)	2 (7.4)	0	2 (2.4)	0
Musculoskeletal Stiffness	3 (2.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	4 (1.4)	1 (3.7)	0	1 (1.2)	0
Myalgia	3 (2.9)	0	0	0	0	5 (2.7)	0	1 (3.8)	7 (10.0)	0	8 (2.8)	0	1 (3.7)	7 (8.3)	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Myopathy	3 (2.9)	0	0	2 (14.3)	0	1 (0.5)	0	0	0	0	4 (1.4)	0	0	2 (2.4)	0
Myositis	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Neck Pain	2 (1.9)	0	0	0	0	6 (3.2)	1 (4.5)	2 (7.7)	0	0	8 (2.8)	1 (3.7)	2 (7.4)	0	0
Nuchal Rigidity	0	0	0	0	0	0	0	7 (26.9)	0	0	0	0	7 (25.9)	0	0
Osteoarthritis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Osteonecrosis	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Pain In Extremity	21 (20.4)	1 (20.0)	0	1 (7.1)	0	19 (10.2)	3 (13.6)	0	8 (11.4)	0	40 (13.8)	4 (14.8)	0	9 (10.7)	0
Pain In Jaw	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Pathological Fracture	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Psoriatic Arthropathy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Rhabdomyolysis	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Rheumatoid Arthritis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Rotator Cuff Syndrome	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Soft Tissue Mass	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Spinal Osteoarthritis	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0

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Synovitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Systemic Lupus Erythematosus	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Tendon Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vertebral Lesion	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**22 (21.4)**	**1 (20.0)**	**0**	**5 (35.7)**	**0**	**38 (20.4)**	**3 (13.6)**	**2 (7.7)**	**6 (8.6)**	**0**	**60 (20.8)**	**4 (14.8)**	**2 (7.4)**	**11 (13.1)**	**0**
Acute Lymphocytic Leukaemia Recurrent	0	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Acute Myeloid Leukaemia	8 (7.8)	1 (20.0)	0	1 (7.1)	0	16 (8.6)	2 (9.1)	1 (3.8)	2 (2.9)	0	24 (8 3)	3 (11.1)	1 (3.7)	3 (3.6)	0
Acute Myeloid Leukaemia Recurrent	1 (1.0)	0	0	1 (7.1)	0	7 (3.8)	1 (4.5)	0	1 (1.4)	0	8 (2.8)	1 (3.7)	0	2 (2.4)	0
Anogenital Warts	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Blast Cell Crisis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Blast Crisis In Myelogenous Leukaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Central Nervous System Lymphoma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chloroma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Lymphocytic Leukaemia	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Chronic Lymphocytic Leukaemia Recurrent	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Myeloid Leukaemia	3 (2.9)	0	0	1 (7.1)	0	4 (2.2)	0	0	0	0	7 (2.4)	0	0	1 (1.2)	0
Fibroadenoma Of Breast	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hepatic Cancer	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hepatic Neoplasm	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Kaposi's Sarcoma	0	0	0	0	0	1 (0.5)	0	0	2 (2.9)	0	1 (0.3)	0	0	2 (2.4)	0
Leukaemia	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Leukaemia Cutis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Leukaemic Retinopathy	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lipoma Of Breast	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Lung Neoplasm	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Lymphocytic Leukaemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Lymphoma	1 (1.0)	0	0	0	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	0	0
Metastases To Bone	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Metastases To Meninges	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Myelodysplastic Syndrome	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Neoplasm	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Neoplasm Malignant	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Non-Hodgkin's Lymphoma	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Plasma Cell Myeloma	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Respiratory Tract Neoplasm	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
T-Cell Lymphoma	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nervous System Disorders	**58 (56.3)**	**4 (80.0)**	**1 (100.0)**	**10 (71.4)**	**1 (100.0)**	**85 (45.7)**	**15 (68.2)**	**23 (88.5)**	**40 (57.1)**	**0**	**143 (49.5)**	**19 (70.4)**	**24 (88.9)**	**50 (59.5)**	**1 (100.0)**
Ageusia	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Amnesia	0	0	0	1 (7.1)	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	2 (2.4)	0
Aphasia	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Arachnoiditis	0	0	0	0	1 (100.0)	0	0	0	0	0	0	0	0	0	1 (100.0)
Asterixis	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Ataxia	0	0	0	0	0	2 (1.1)	0	1 (3.8)	1 (1.4)	0	2 (0.7)	0	1 (3.7)	1 (1.2)	0
Balance Disorder	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Brain Oedema	2 (1.9)	0	0	0	0	0	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Brain Stem Syndrome	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0

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Number (%) of Subjects

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Cauda Equina Syndrome	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Central Nervous System Inflammation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Central Nervous System Lesion	0	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Cerebral Atrophy	2 (1.9)	0	0	0	0	0	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Cerebral Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Cerebral Haematoma	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Cerebral Haemorrhage	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Cerebral Infarction	2 (1.9)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Cerebrovascular Accident	2 (1.9)	0	0	0	0	0	0	1 (3.8)	1 (1.4)	0	2 (0.7)	0	1 (3.7)	1 (1.2)	0
Choreoathetosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cognitive Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Coma	5 (4.9)	1 (20.0)	0	1 (7.1)	0	1 (0.5)	0	0	0	0	6 (2.1)	1 (3.7)	0	1 (1.2)	0
Coordination Abnormal	1 (1.0)	0	0	0	0	1 (0.5)	0	0	2 (2.9)	0	2 (0.7)	0	0	2 (2.4)	0
Cranial Nerve Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Demyelination	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Depressed Level Of Consciousness	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0

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Number (%) of Subjects

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Dizziness	11 (10.7)	2 (40.0)	1 (100.0)	4 (28.6)	0	14 (7.5)	1 (4.5)	12 (46.2)	3 (4.3)	0	25 (8.7)	3 (11.1)	13 (48.1)	7 (8.3)	0
Dizziness Postural	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Dysarthria	2 (1.9)	0	0	0	0	3 (1.6)	1 (4.5)	1 (3.8)	0	0	5 (1.7)	1 (3.7)	1 (3.7)	0	0
Dysgeusia	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Dyskinesia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Dystonia	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Embolic Stroke	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Encephalomalacia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Encephalopathy	2 (1.9)	0	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	0	0
Facial Paralysis	0	0	0	0	0	1 (0.5)	1 (4.5)	1 (3.8)	0	0	1 (0.3)	1 (3.7)	1 (3.7)	0	0
Facial Paresis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Haemorrhage Intracranial	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Haemorrhagic Cerebral Infarction	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Head Titubation	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Headache	19 (18.4)	2 (40.0)	0	3 (21.4)	0	44 (23.7)	8 (36.4)	14 (53.8)	22 (31.4)	0	63 (21.8)	10 (37.0)	14 (51.9)	25 (29.8)	0
Hemianopia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hemianopia Homonymous	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0

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Hemiparesis	3 (2.9)	0	0	1 (7.1)	0	0	0	1 (3.8)	2 (2.9)	0	3 (1.0)	0	1 (3.7)	3 (3.6)	0
Hemiplegia	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Hyperreflexia	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Hypoaesthesia	6 (5.8)	0	0	1 (7.1)	0	3 (1.6)	0	1 (3.8)	6 (8.6)	0	9 (3.1)	0	1 (3.7)	7 (8.3)	0
Hypokinesia	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Hyporeflexia	1 (1.0)	0	0	0	0	0	1 (4.5)	0	2 (2.9)	0	1 (0.3)	1 (3.7)	0	2 (2.4)	0
Hypotonia	0	0	0	0	0	2 (1.1)	2 (9.1)	0	0	0	2 (0.7)	2 (7.4)	0	0	0
IIIrd Nerve Paralysis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Intellectual Disability	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Intention Tremor	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Intracranial Pressure Increased	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Intraventricular Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Ischaemic Stroke	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Lethargy	8 (7.8)	2 (40.0)	0	2 (14.3)	0	5 (2.7)	0	1 (3.8)	1 (1.4)	0	13 (4 5)	2 (7.4)	1 (3.7)	3 (3.6)	0
Loss Of Consciousness	3 (2.9)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	0
Memory Impairment	2 (1.9)	0	0	0	0	2 (1.1)	0	1 (3.8)	2 (2.9)	0	4 (1.4)	0	1 (3.7)	2 (2.4)	0
Mental Impairment	0	0	0	0	0	3 (1.6)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0

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Metabolic Encephalopathy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Migraine	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Mononeuropathy Multiplex	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Motor Dysfunction	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Myoclonus	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Nervous System Disorder	0	0	0	1 (7.1)	0	0	0	2 (7.7)	0	0	0	0	2 (7.4)	1 (1.2)	0
Neurological Decompensation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Neuropathy Peripheral	1 (1.0)	0	0	0	0	4 (2.2)	0	0	0	0	5 (1.7)	0	0	0	0
Nystagmus	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Occipital Neuralgia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Paraesthesia	6 (5.8)	0	0	0	0	5 (2.7)	0	3 (11.5)	5 (7.1)	0	11 (3.8)	0	3 (11.1)	5 (6.0)	0
Parkinsonism	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Peroneal Nerve Palsy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Post Herpetic Neuralgia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Postural Tremor	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Presyncope	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Psychomotor Skills Impaired	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Restless Legs Syndrome	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0

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Sciatica	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Sedation	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Seizure	7 (6.8)	0	0	0	0	4 (2.2)	0	2 (7.7)	4 (5.7)	0	11 (3.8)	0	2 (7.4)	4 (4.8)	0
Sensory Loss	1 (1.0)	0	0	0	0	4 (2.2)	1 (4.5)	0	0	0	5 (1.7)	1 (3.7)	0	0	0
Sinus Headache	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Slow Response To Stimuli	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Somnolence	7 (6.8)	0	0	1 (7.1)	1 (100.0)	5 (2.7)	3 (13.6)	2 (7.7)	2 (2.9)	0	12 (4 2)	3 (11.1)	2 (7.4)	3 (3.6)	1 (100.0)
Speech Disorder	1 (1.0)	0	0	0	1 (100.0)	2 (1.1)	2 (9.1)	0	1 (1.4)	0	3 (1.0)	2 (7.4)	0	1 (1.2)	1 (100.0)
Syncope	0	0	0	0	0	2 (1.1)	1 (4.5)	1 (3.8)	0	0	2 (0.7)	1 (3.7)	1 (3.7)	0	0
Tension Headache	0	0	0	0	0	1 (0.5)	0	3 (11.5)	0	0	1 (0.3)	0	3 (11.1)	0	0
Toxic Encephalopathy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Tremor	8 (7.8)	0	0	3 (21.4)	0	10 (5.4)	0	6 (23.1)	4 (5.7)	0	18 (6 2)	0	6 (22.2)	7 (8.3)	0
Unresponsive To Stimuli	7 (6.8)	0	0	3 (21.4)	0	2 (1.1)	2 (9.1)	0	1 (1.4)	0	9 (3.1)	2 (7.4)	0	4 (4.8)	0
Visual Field Defect	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Vocal Cord Paralysis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Product Issues	**0**	**0**	**0**	**0**	**0**	**2 (1.1)**	**0**	**0**	**0**	**0**	**2 (0.7)**	**0**	**0**	**0**	**0**
Device Occlusion	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Thrombosis In Device	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Psychiatric Disorders	**53 (51.5)**	**3 (60.0)**	**0**	**9 (64.3)**	**1 (100.0)**	**65 (34.9)**	**9 (40.9)**	**6 (23.1)**	**14 (20.0)**	**0**	**118 (40.8)**	**12 (44.4)**	**6 (22.2)**	**23 (27.4)**	**1 (100.0)**
Adjustment Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Aggression	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Agitation	3 (2.9)	0	0	4 (28.6)	0	9 (4.8)	0	0	1 (1.4)	0	12 (4 2)	0	0	5 (6.0)	0
Anxiety	13 (12.6)	2 (40.0)	0	2 (14.3)	0	27 (14.5)	2 (9.1)	1 (3.8)	2 (2.9)	0	40 (13.8)	4 (14.8)	1 (3.7)	4 (4.8)	0
Belligerence	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blunted Affect	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Confusional State	15 (14.6)	2 (40.0)	0	1 (7.1)	0	12 (6.5)	1 (4.5)	2 (7.7)	2 (2.9)	0	27 (9 3)	3 (11.1)	2 (7.4)	3 (3.6)	0
Delirium	1 (1.0)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0
Delusion	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Depressed Mood	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0

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Summary of Treatment Emergent Adverse Events by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Depression	20 (19.4)	2 (40.0)	0	1 (7.1)	0	20 (10.8)	2 (9.1)	1 (3.8)	4 (5.7)	0	40 (13.8)	4 (14.8)	1 (3.7)	5 (6.0)	0
Disorientation	2 (1.9)	0	0	0	0	2 (1.1)	1 (4.5)	0	0	0	4 (1.4)	1 (3.7)	0	0	0
Eating Disorder	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Echolalia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Flat Affect	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Hallucination	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Hallucination, Auditory	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hallucination, Visual	1 (1.0)	1 (20.0)	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Insomnia	17 (16.5)	3 (60.0)	0	2 (14.3)	0	19 (10.2)	3 (13.6)	0	9 (12.9)	0	36 (12.5)	6 (22.2)	0	11 (13.1)	0
Irritability	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Libido Decreased	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Mental Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Mental Status Changes	13 (12.6)	0	0	1 (7.1)	1 (100.0)	13 (7.0)	2 (9.1)	1 (3.8)	1 (1.4)	0	26 (9.0)	2 (7.4)	1 (3.7)	2 (2.4)	1 (100.0)
Mood Altered	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Mood Swings	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Nervousness	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Nightmare	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Organic Brain Syndrome	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Paranoia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Perseveration	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Posturing	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Psychomotor Retardation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Psychotic Disorder	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Restlessness	4 (3.9)	0	0	2 (14.3)	0	2 (1.1)	0	0	0	0	6 (2.1)	0	0	2 (2.4)	0
Sleep Disorder	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Staring	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Substance-Induced Psychotic Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Tearfulness	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Renal And Urinary Disorders	**50 (48.5)**	**3 (60.0)**	**0**	**9 (64.3)**	**1 (100.0)**	**42 (22.6)**	**6 (27.3)**	**4 (15.4)**	**8 (11.4)**	**0**	**92 (31.8)**	**9 (33.3)**	**4 (14.8)**	**17 (20 2)**	**1 (100.0)**
Acute Kidney Injury	7 (6.8)	0	0	2 (14.3)	0	3 (1.6)	1 (4.5)	1 (3.8)	0	0	10 (3 5)	1 (3.7)	1 (3.7)	2 (2.4)	0
Anuria	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	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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Azotaemia	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Bladder Pain	0	0	0	1 (7.1)	0	0	0	0	1 (1.4)	0	0	0	0	2 (2.4)	0
Bladder Spasm	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	2 (0.7)	1 (3.7)	0	1 (1.2)	0
Choluria	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Kidney Disease	2 (1.9)	0	0	0	0	1 (0.5)	0	0	0	0	3 (1.0)	0	0	0	0
Cystitis Haemorrhagic	3 (2.9)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	5 (1.7)	0	0	1 (1.2)	0
Dysuria	7 (6.8)	1 (20.0)	0	2 (14.3)	0	3 (1.6)	1 (4.5)	0	1 (1.4)	0	10 (3 5)	2 (7.4)	0	3 (3.6)	0
End Stage Renal Disease	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Haematuria	3 (2.9)	0	0	1 (7.1)	0	4 (2.2)	0	0	2 (2.9)	0	7 (2.4)	0	0	3 (3.6)	0
Hydronephrosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Incontinence	1 (1.0)	1 (20.0)	0	1 (7.1)	0	1 (0.5)	0	0	0	0	2 (0.7)	1 (3.7)	0	1 (1.2)	0
Micturition Urgency	2 (1.9)	1 (20.0)	0	0	0	0	0	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Nephritis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Nephrolithiasis	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Nephropathy Toxic	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	2 (2.4)	0
Nocturia	1 (1.0)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Oliguria	2 (1.9)	0	0	1 (7.1)	0	0	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0

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Number (%) of Subjects

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Pollakiuria	4 (3.9)	0	0	0	1 (100.0)	3 (1.6)	0	0	0	0	7 (2.4)	0	0	0	1 (100.0)
Polyuria	0	0	0	0	0	3 (1.6)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Renal Colic	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Renal Cyst	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Renal Disorder	1 (1.0)	0	0	0	0	1 (0.5)	0	1 (3.8)	2 (2.9)	0	2 (0.7)	0	1 (3.7)	2 (2.4)	0
Renal Failure	26 (25.2)	2 (40.0)	0	5 (35.7)	1 (100.0)	15 (8.1)	1 (4.5)	1 (3.8)	4 (5.7)	0	41 (14.2)	3 (11.1)	1 (3.7)	9 (10.7)	1 (100.0)
Renal Impairment	4 (3.9)	1 (20.0)	0	0	0	2 (1.1)	0	0	1 (1.4)	0	6 (2.1)	1 (3.7)	0	1 (1.2)	0
Renal Mass	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Renal Tubular Acidosis	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Renal Tubular Necrosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Urinary Hesitation	0	0	0	0	0	2 (1.1)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Urinary Incontinence	3 (2.9)	0	0	0	0	4 (2.2)	0	1 (3.8)	0	0	7 (2.4)	0	1 (3.7)	0	0
Urinary Retention	0	0	0	1 (7.1)	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Urine Flow Decreased	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Reproductive System And Breast Disorders	**8 (7.8)**	**0**	**0**	**3 (21.4)**	**0**	**14 (7.5)**	**4 (18.2)**	**0**	**5 (7.1)**	**0**	**22 (7.6)**	**4 (14.8)**	**0**	**8 (9.5)**	**0**

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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Amenorrhoea	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Benign Prostatic Hyperplasia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Breast Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Breast Swelling	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Breast Tenderness	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Dysmenorrhoea	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Erectile Dysfunction	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Hypomenorrhoea	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Menstruation Delayed	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Nipple Exudate Bloody	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Ovarian Cyst	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pelvic Fluid Collection	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Premature Menopause	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Prostatitis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pruritus Genital	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Scrotal Mass	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Scrotal Oedema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Scrotal Pain	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Scrotal Ulcer	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Testicular Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Uterine Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Vaginal Discharge	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vaginal Haemorrhage	3 (2.9)	0	0	2 (14.3)	0	3 (1.6)	2 (9.1)	0	1 (1.4)	0	6 (2.1)	2 (7.4)	0	3 (3.6)	0
Vulvovaginal Pain	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Vulvovaginal Pruritus	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**75 (72.8)**	**5 (100.0)**	**0**	**12 (85.7)**	**1 (100.0)**	**111 (59.7)**	**10 (45.5)**	**14 (53.8)**	**29 (41.4)**	**0**	**186 (64.4)**	**15 (55.6)**	**14 (51.9)**	**41 (48.8)**	**1 (100.0)**
Acute Respiratory Distress Syndrome	4 (3.9)	0	0	2 (14.3)	0	1 (0.5)	0	0	0	0	5 (1.7)	0	0	2 (2.4)	0
Acute Respiratory Failure	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Allergic Sinusitis	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Apnoea	0	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Asthma	1 (1.0)	0	0	0	0	1 (0.5)	0	0	2 (2.9)	0	2 (0.7)	0	0	2 (2.4)	0
Atelectasis	4 (3.9)	0	0	0	0	2 (1.1)	0	0	0	0	6 (2.1)	0	0	0	0
Bronchial Obstruction	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Bronchial Wall Thickening	0	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Bronchiectasis	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Bronchospasm	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	0	0	1 (1.4)	0	3 (1.0)	0	0	2 (2.4)	0

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Cheyne-Stokes Respiration	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Chronic Obstructive Pulmonary Disease	0	0	0	0	0	5 (2.7)	0	0	1 (1.4)	0	5 (1.7)	0	0	1 (1.2)	0
Cough	20 (19.4)	2 (40.0)	0	4 (28.6)	1 (100.0)	32 (17.2)	4 (18.2)	9 (34.6)	13 (18.6)	0	52 (18.0)	6 (22.2)	9 (33.3)	17 (20 2)	1 (100.0)
Dysphonia	0	1 (20.0)	0	0	0	3 (1.6)	0	0	1 (1.4)	0	3 (1.0)	1 (3.7)	0	1 (1.2)	0
Dyspnoea	27 (26.2)	2 (40.0)	0	4 (28.6)	0	45 (24.2)	5 (22.7)	5 (19.2)	11 (15.7)	0	72 (24.9)	7 (25.9)	5 (18.5)	15 (17 9)	0
Dyspnoea Exertional	4 (3.9)	1 (20.0)	0	0	0	3 (1.6)	0	1 (3.8)	0	0	7 (2.4)	1 (3.7)	1 (3.7)	0	0
Emphysema	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Epistaxis	16 (15.5)	1 (20.0)	0	7 (50.0)	0	19 (10.2)	2 (9.1)	1 (3.8)	2 (2.9)	0	35 (12.1)	3 (11.1)	1 (3.7)	9 (10.7)	0
Haemoptysis	16 (15.5)	2 (40.0)	0	3 (21.4)	0	11 (5.9)	0	0	7 (10.0)	0	27 (9 3)	2 (7.4)	0	10 (11 9)	0
Haemothorax	2 (1.9)	0	0	1 (7.1)	0	0	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	1 (1.2)	0
Hiccups	2 (1.9)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	0
Hypercapnia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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Hypopnoea	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hypoxia	8 (7.8)	1 (20.0)	0	1 (7.1)	1 (100.0)	8 (4.3)	0	1 (3.8)	1 (1.4)	0	16 (5 5)	1 (3.7)	1 (3.7)	2 (2.4)	1 (100.0)
Interstitial Lung Disease	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Lower Respiratory Tract Congestion	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Lung Consolidation	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lung Disorder	2 (1.9)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Lung Infiltration	6 (5.8)	1 (20.0)	0	2 (14.3)	0	11 (5.9)	1 (4.5)	0	0	0	17 (5 9)	2 (7.4)	0	2 (2.4)	0
Mediastinal Haematoma	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Nasal Congestion	6 (5.8)	0	0	1 (7.1)	0	8 (4.3)	0	0	1 (1.4)	0	14 (4.8)	0	0	2 (2.4)	0
Nasal Disorder	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Nasal Dryness	0	0	0	1 (7.1)	0	4 (2.2)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Nasal Obstruction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nasal Oedema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nasal Septum Perforation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nasal Ulcer	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1 2)	0
Obliterative Bronchiolitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Obstructive Airways Disorder	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Organising Pneumonia	3 (2.9)	0	0	0	0	0	0	0	0	0	3 (1.0)	0	0	0	0
Oropharyngeal Pain	8 (7.8)	0	0	2 (14.3)	0	12 (6.5)	1 (4.5)	3 (11.5)	6 (8.6)	0	20 (6 9)	1 (3.7)	3 (11.1)	8 (9.5)	0
Oropharyngeal Plaque	1 (1.0)	0	0	0	0	0	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Orthopnoea	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Painful Respiration	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Paranasal Sinus Hypersecretion	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Pharyngeal Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pharyngeal Erythema	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pharyngeal Ulceration	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pleural Effusion	13 (12.6)	1 (20.0)	0	3 (21.4)	0	15 (8.1)	3 (13.6)	1 (3.8)	1 (1.4)	0	28 (9.7)	4 (14.8)	1 (3.7)	4 (4.8)	0
Pleural Fibrosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pleuritic Pain	5 (4.9)	0	0	2 (14.3)	0	8 (4.3)	0	1 (3.8)	0	0	13 (4 5)	0	1 (3.7)	2 (2.4)	0
Pneumomediastinum	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pneumonia Aspiration	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Pneumonitis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pneumothorax	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	1 (1.4)	0	4 (1.4)	0	0	2 (2.4)	0
Productive Cough	3 (2.9)	0	0	2 (14.3)	0	5 (2.7)	0	2 (7.7)	2 (2.9)	0	8 (2.8)	0	2 (7.4)	4 (4.8)	0
Pulmonary Alveolar Haemorrhage	1 (1.0)	0	0	1 (7.1)	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	1 (1.2)	0
Pulmonary Congestion	0	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Pulmonary Fibrosis	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Pulmonary Haemorrhage	1 (1.0)	1 (20.0)	0	2 (14.3)	0	3 (1.6)	0	0	0	0	4 (1.4)	1 (3.7)	0	2 (2.4)	0
Pulmonary Hypertension	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Pulmonary Infarction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pulmonary Mass	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Pulmonary Oedema	4 (3.9)	0	0	1 (7.1)	0	9 (4.8)	0	0	1 (1.4)	0	13 (4 5)	0	0	2 (2.4)	0
Rales	2 (1.9)	3 (60.0)	0	0	0	4 (2.2)	2 (9.1)	1 (3.8)	1 (1.4)	0	6 (2.1)	5 (18.5)	1 (3.7)	1 (1.2)	0
Respiratory Acidosis	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	1 (1.2)	0
Respiratory Alkalosis	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Respiratory Arrest	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Respiratory Disorder	1 (1.0)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	2 (0.7)	0	0	1 (1.2)	0
Respiratory Distress	8 (7.8)	0	0	1 (7.1)	0	9 (4.8)	0	0	3 (4.3)	0	17 (5 9)	0	0	4 (4.8)	0
Respiratory Failure	17 (16.5)	1 (20.0)	0	4 (28.6)	1 (100.0)	17 (9.1)	0	1 (3.8)	3 (4.3)	0	34 (11.8)	1 (3.7)	1 (3.7)	7 (8.3)	1 (100.0)
Respiratory Tract Congestion	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	0	0	2 (2.9)	0	3 (1.0)	0	0	3 (3.6)	0
Rhinitis Allergic	1 (1.0)	0	0	0	0	4 (2.2)	0	0	2 (2.9)	0	5 (1.7)	0	0	2 (2.4)	0
Rhinorrhoea	10 (9.7)	0	0	0	0	2 (1.1)	0	3 (11.5)	4 (5.7)	0	12 (4 2)	0	3 (11.1)	4 (4.8)	0
Rhonchi	1 (1.0)	0	0	0	0	3 (1.6)	0	0	2 (2.9)	0	4 (1.4)	0	0	2 (2.4)	0
Sinus Congestion	6 (5.8)	1 (20.0)	0	0	0	4 (2.2)	0	0	1 (1.4)	0	10 (3 5)	1 (3.7)	0	1 (1.2)	0
Sinus Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Sneezing	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Sputum Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Tachypnoea	1 (1.0)	3 (60.0)	0	2 (14.3)	0	6 (3.2)	3 (13.6)	0	3 (4.3)	0	7 (2.4)	6 (22.2)	0	5 (6.0)	0
Throat Irritation	1 (1.0)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Throat Tightness	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
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Upper-Airway Cough Syndrome	4 (3.9)	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	5 (1.7)	0	1 (3.7)	0	0
Vocal Cord Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Wheezing	4 (3.9)	1 (20.0)	0	1 (7.1)	0	9 (4.8)	2 (9.1)	0	2 (2.9)	0	13 (4 5)	3 (11.1)	0	3 (3.6)	0
Skin And Subcutaneous Tissue Disorders	**49 (47.6)**	**1 (20.0)**	**1 (100.0)**	**7 (50.0)**	**1 (100.0)**	**85 (45.7)**	**7 (31.8)**	**14 (53.8)**	**19 (27.1)**	**0**	**134 (46.4)**	**8 (29.6)**	**15 (55.6)**	**26 (31.0)**	**1 (100.0)**
Acne	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Alopecia	1 (1.0)	0	0	0	0	7 (3.8)	0	4 (15.4)	3 (4.3)	0	8 (2.8)	0	4 (14.8)	3 (3.6)	0
Blister	2 (1.9)	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0
Blood Blister	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Cold Sweat	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cutaneous Lupus Erythematosus	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Decubitus Ulcer	1 (1.0)	1 (20.0)	0	1 (7.1)	0	6 (3.2)	0	0	0	0	7 (2.4)	1 (3.7)	0	1 (1.2)	0
Dermal Cyst	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Dermatitis Allergic	1 (1.0)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0

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Dermatitis Atopic	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Dermatosis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Drug Eruption	0	0	0	0	0	1 (0.5)	0	1 (3.8)	1 (1.4)	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Dry Skin	4 (3.9)	0	0	0	0	3 (1.6)	2 (9.1)	3 (11.5)	0	0	7 (2.4)	2 (7.4)	3 (11.1)	0	0
Ecchymosis	6 (5.8)	0	0	1 (7.1)	0	5 (2.7)	1 (4.5)	0	0	0	11 (3.8)	1 (3.7)	0	1 (1.2)	0
Erythema	8 (7.8)	0	0	0	0	9 (4.8)	0	0	0	0	17 (5 9)	0	0	0	0
Hyperhidrosis	2 (1.9)	0	0	0	0	2 (1.1)	2 (9.1)	3 (11.5)	1 (1.4)	0	4 (1.4)	2 (7.4)	3 (11.1)	1 (1.2)	0
Ingrowing Nail	1 (1.0)	0	0	0	0	4 (2.2)	0	0	0	0	5 (1.7)	0	0	0	0
Lipodystrophy Acquired	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Livedo Reticularis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Macule	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Miliaria	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Neutrophilic Dermatosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Night Sweats	3 (2.9)	0	0	0	0	8 (4.3)	1 (4.5)	0	1 (1.4)	0	11 (3.8)	1 (3.7)	0	1 (1.2)	0
Onychoclasis	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0

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Palmar Erythema	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Petechiae	5 (4.9)	0	0	1 (7.1)	0	7 (3.8)	0	0	1 (1.4)	0	12 (4 2)	0	0	2 (2.4)	0
Photosensitivity Reaction	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Pigmentation Disorder	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Prurigo	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Pruritus	13 (12.6)	0	1 (100.0)	0	1 (100.0)	10 (5.4)	1 (4.5)	2 (7.7)	1 (1.4)	0	23 (8.0)	1 (3.7)	3 (11.1)	1 (1.2)	1 (100.0)
Pruritus Allergic	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pruritus Generalised	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Psoriasis	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Purpura	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Rash	15 (14.6)	0	0	1 (7.1)	1 (100.0)	24 (12.9)	1 (4.5)	2 (7.7)	2 (2.9)	0	39 (13.5)	1 (3.7)	2 (7.4)	3 (3.6)	1 (100.0)
Rash Erythematous	2 (1.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	1 (1.4)	0	4 (1.4)	0	0	2 (2.4)	0
Rash Generalised	2 (1.9)	0	0	0	0	6 (3.2)	0	0	0	0	8 (2.8)	0	0	0	0
Rash Macular	2 (1.9)	0	0	1 (7.1)	0	1 (0.5)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	1 (1.2)	0
Rash Maculo-Papular	2 (1.9)	0	0	0	0	6 (3.2)	0	0	0	0	8 (2.8)	0	0	0	0
Rash Papular	0	0	0	0	0	0	0	2 (7.7)	0	0	0	0	2 (7.4)	0	0

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Rash Pruritic	0	0	0	0	0	3 (1.6)	0	4 (15.4)	1 (1.4)	0	3 (1.0)	0	4 (14.8)	1 (1.2)	0
Rash Vesicular	1 (1.0)	0	0	0	0	0	0	2 (7.7)	0	0	1 (0.3)	0	2 (7.4)	0	0
Scab	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Skin Burning Sensation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Skin Discolouration	0	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (3.7)	0	0	0
Skin Disorder	3 (2.9)	0	0	0	0	1 (0.5)	0	0	0	0	4 (1.4)	0	0	0	0
Skin Exfoliation	1 (1.0)	0	0	0	0	2 (1.1)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Skin Haemorrhage	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Skin Hyperpigmentation	0	0	0	1 (7.1)	0	0	0	1 (3.8)	1 (1.4)	0	0	0	1 (3.7)	2 (2.4)	0
Skin Irritation	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Skin Lesion	6 (5.8)	0	0	2 (14.3)	0	8 (4.3)	1 (4.5)	0	2 (2.9)	0	14 (4.8)	1 (3.7)	0	4 (4.8)	0
Skin Mass	4 (3.9)	1 (20.0)	0	0	0	1 (0.5)	0	0	2 (2.9)	0	5 (1.7)	1 (3.7)	0	2 (2.4)	0
Skin Ulcer	0	0	0	1 (7.1)	0	2 (1.1)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	1 (1.2)	0
Skin Ulcer Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Stevens-Johnson Syndrome	0	0	0	0	0	0	0	1 (3.8)	1 (1.4)	0	0	0	1 (3.7)	1 (1.2)	0
Subcutaneous Emphysema	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0

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Swelling Face	2 (1.9)	1 (20.0)	0	0	0	1 (0.5)	1 (4.5)	0	1 (1.4)	0	3 (1.0)	2 (7.4)	0	1 (1.2)	0
Urticaria	2 (1.9)	0	0	0	0	5 (2.7)	0	1 (3.8)	1 (1.4)	0	7 (2.4)	0	1 (3.7)	1 (1.2)	0
Urticaria Papular	0	0	0	0	0	0	0	4 (15.4)	0	0	0	0	4 (14.8)	0	0
Social Circumstances	**0**	**0**	**0**	**0**	**0**	**1 (0.5)**	**0**	**0**	**0**	**0**	**1 (0.3)**	**0**	**0**	**0**	**0**
Treatment Noncompliance	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Surgical And Medical Procedures	**15 (14.6)**	**1 (20.0)**	**0**	**3 (21.4)**	**0**	**30 (16.1)**	**1 (4.5)**	**0**	**10 (14.3)**	**0**	**45 (15.6)**	**2 (7.4)**	**0**	**13 (15.5)**	**0**
Abdominal Cavity Drainage	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Autologous Bone Marrow Transplantation Therapy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bone Marrow Transplant	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cataract Operation	2 (1.9)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	4 (1.4)	0	0	1 (1.2)	0
Catheter Removal	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Central Venous Catheter Removal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chemotherapy	0	0	0	0	0	5 (2.7)	0	0	0	0	5 (1.7)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Choledocholithotomy	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Corneal Transplant	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Debridement	0	0	0	0	0	3 (1.6)	1 (4.5)	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Endotracheal Intubation	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Exploratory Operation	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Eye Laser Surgery	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Eye Operation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Gastrostomy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Haemofiltration	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Laparotomy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Lung Lobectomy	1 (1.0)	0	0	1 (7.1)	0	0	0	0	0	0	1 (0.3)	0	0	1 (1.2)	0
Lung Operation	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Lung Transplant	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Maxillofacial Operation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Medical Device Implantation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Metabolic Abnormality Management	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Nail Operation	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Omentectomy	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Orthopaedic Procedure	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Photopheresis	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Plastic Surgery To The Face	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Pneumonectomy	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Polypectomy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pulmonary Resection	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Sinus Operation	3 (2.9)	1 (20.0)	0	0	0	5 (2.7)	0	0	2 (2.9)	0	8 (2.8)	1 (3.7)	0	2 (2.4)	0
Skin Graft	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Splenectomy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Stem Cell Transplant	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Surgery	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Therapeutic Procedure	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Thoracotomy	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Tooth Extraction	1 (1.0)	0	0	0	0	2 (1.1)	0	0	1 (1.4)	0	3 (1.0)	0	0	1 (1.2)	0
Transfusion	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Transplant	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Wisdom Teeth Removal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Wound Drainage	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vascular Disorders	**49 (47.6)**	**3 (60.0)**	**1 (100.0)**	**6 (42.9)**	**1 (100.0)**	**61 (32.8)**	**8 (36.4)**	**5 (19.2)**	**12 (17.1)**	**0**	**110 (38.1)**	**11 (40.7)**	**6 (22.2)**	**18 (21.4)**	**1 (100.0)**

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Aneurysm	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Angiopathy	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0	1 (1.2)	0
Aortic Aneurysm	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Arterial Insufficiency	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Arteriosclerosis	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Circulatory Collapse	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Deep Vein Thrombosis	3 (2.9)	0	0	1 (7.1)	0	2 (1.1)	0	0	0	0	5 (1.7)	0	0	1 (1.2)	0
Flushing	5 (4.9)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	7 (2.4)	0	1 (3.7)	0	0
Haematoma	3 (2.9)	0	0	1 (7.1)	0	5 (2.7)	0	0	2 (2.9)	0	8 (2.8)	0	0	3 (3.6)	0
Haemodynamic Instability	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Haemorrhage	0	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Hot Flush	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hypertension	20 (19.4)	0	0	4 (28.6)	0	23 (12.4)	4 (18.2)	1 (3.8)	3 (4.3)	0	43 (14.9)	4 (14.8)	1 (3.7)	7 (8.3)	0
Hypoperfusion	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypotension	22 (21.4)	3 (60.0)	0	3 (21.4)	1 (100.0)	24 (12.9)	3 (13.6)	2 (7.7)	5 (7.1)	0	46 (15.9)	6 (22.2)	2 (7.4)	8 (9.5)	1 (100.0)
Hypovolaemic Shock	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Infarction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Intermittent Claudication	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Ischaemia	2 (1.9)	0	0	0	0	2 (1.1)	0	0	0	0	4 (1.4)	0	0	0	0
Orthostatic Hypertension	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Orthostatic Hypotension	3 (2.9)	0	1 (100.0)	0	0	2 (1.1)	1 (4.5)	0	0	0	5 (1.7)	1 (3.7)	1 (3.7)	0	0
Pallor	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Peripheral Artery Thrombosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Peripheral Ischaemia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Peripheral Venous Disease	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Phlebitis	1 (1.0)	0	0	0	0	1 (0.5)	2 (9.1)	0	1 (1.4)	0	2 (0.7)	2 (7.4)	0	1 (1.2)	0
Poor Peripheral Circulation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Raynaud's Phenomenon	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Shock Haemorrhagic	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Thrombophlebitis	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Thrombophlebitis Superficial	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Thrombosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vasodilatation	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Venous Thrombosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	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 2.7.4-175　　人種別の副作用の発現例数（%）（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, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Subjects Reporting Any Adverse Event	**31 (30.1)**	**1 (20.0)**	**1 (100.0)**	**4 (28.6)**	**0**	**66 (35.5)**	**12 (54.5)**	**16 (61.5)**	**33 (47.1)**	**0**	**97 (33.6)**	**13 (48.1)**	**17 (63.0)**	**37 (44.0)**	**0**
Blood And Lymphatic System Disorders	**0**	**0**	**0**	**0**	**0**	**3 (1.6)**	**1 (4.5)**	**1 (3.8)**	**3 (4.3)**	**0**	**3 (1.0)**	**1 (3.7)**	**1 (3.7)**	**3 (3.6)**	**0**
Anaemia	0	0	0	0	0	0	1 (4.5)	1 (3.8)	2 (2.9)	0	0	1 (3.7)	1 (3.7)	2 (2.4)	0
Eosinophilia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Pancytopenia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Thrombocytopenia	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Cardiac Disorders	**4 (3.9)**	**0**	**0**	**0**	**0**	**9 (4.8)**	**0**	**1 (3.8)**	**0**	**0**	**13 (4 5)**	**0**	**1 (3.7)**	**0**	**0**
Aortic Valve Sclerosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Arteriosclerosis Coronary Artery	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Atrial Fibrillation	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Atrial Flutter	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Bundle Branch Block	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cardio-Respiratory Arrest	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Extrasystoles	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	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

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Left Ventricular Hypertrophy	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Mitral Valve Stenosis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Myocardial Infarction	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Supraventricular Tachycardia	1 (1.0)	0	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	0	0	0	0
Tachycardia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Ventricular Extrasystoles	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Ventricular Hypertrophy	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Ventricular Tachycardia	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Ear And Labyrinth Disorders	**1 (1.0)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (1.4)**	**0**	**1 (0.3)**	**0**	**0**	**1 (1.2)**	**0**
Ear Pain	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hypoacusis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Tinnitus	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Endocrine Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (1.4)**	**0**	**0**	**0**	**0**	**1 (1.2)**	**0**
Adrenal Insufficiency	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	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

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Adrenocortical Insufficiency Acute	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hypogonadism	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Eye Disorders	**0**	**0**	**0**	**1 (7.1)**	**0**	**3 (1.6)**	**0**	**1 (3.8)**	**2 (2.9)**	**0**	**3 (1.0)**	**0**	**1 (3.7)**	**3 (3.6)**	**0**
Conjunctival Hyperaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Erythema Of Eyelid	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Eye Irritation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Eye Pain	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Vision Blurred	0	0	0	1 (7.1)	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	1 (1.2)	0
Gastrointestinal Disorders	**16 (15.5)**	**0**	**1 (100.0)**	**2 (14.3)**	**0**	**29 (15.6)**	**5 (22.7)**	**8 (30.8)**	**20 (28.6)**	**0**	**45 (15.6)**	**5 (18.5)**	**9 (33.3)**	**22 (26.2)**	**0**
Abdominal Discomfort	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Abdominal Distension	0	0	0	0	0	3 (1.6)	0	0	0	0	3 (1.0)	0	0	0	0
Abdominal Pain	1 (1.0)	0	0	1 (7.1)	0	2 (1.1)	2 (9.1)	0	1 (1.4)	0	3 (1.0)	2 (7.4)	0	2 (2.4)	0
Abdominal Pain Upper	1 (1.0)	0	0	0	0	1 (0.5)	0	0	10 (14.3)	0	2 (0.7)	0	0	10 (11 9)	0
Abdominal Tenderness	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Abnormal Faeces	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Constipation	1 (1.0)	0	0	0	0	0	0	2 (7.7)	0	0	1 (0.3)	0	2 (7.4)	0	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 by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Diarrhoea	3 (2.9)	0	0	0	0	4 (2.2)	2 (9.1)	1 (3.8)	5 (7.1)	0	7 (2.4)	2 (7.4)	1 (3.7)	5 (6.0)	0
Dry Mouth	0	0	0	0	0	1 (0.5)	0	3 (11.5)	0	0	1 (0.3)	0	3 (11.1)	0	0
Dyspepsia	0	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	2 (0.7)	0	1 (3.7)	0	0
Dysphagia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Eructation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Faeces Soft	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Flatulence	0	0	0	0	0	0	0	1 (3.8)	2 (2.9)	0	0	0	1 (3.7)	2 (2.4)	0
Gastrointestinal Haemorrhage	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Gastrooesophageal Reflux Disease	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hypoaesthesia Oral	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Ileus	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lip Dry	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Lip Swelling	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Nausea	8 (7.8)	0	1 (100.0)	1 (7.1)	0	13 (7.0)	2 (9.1)	2 (7.7)	8 (11.4)	0	21 (7 3)	2 (7.4)	3 (11.1)	9 (10.7)	0
Oesophageal Ulcer	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Oral Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	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 by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Pancreatitis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Retching	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Vomiting	7 (6.8)	0	1 (100.0)	0	0	10 (5.4)	2 (9.1)	1 (3.8)	5 (7.1)	0	17 (5 9)	2 (7.4)	2 (7.4)	5 (6.0)	0
General Disorders And Administration Site Conditions	**2 (1.9)**	**0**	**0**	**2 (14.3)**	**0**	**8 (4.3)**	**1 (4.5)**	**0**	**6 (8.6)**	**0**	**10 (3 5)**	**1 (3.7)**	**0**	**8 (9.5)**	**0**
Asthenia	1 (1.0)	0	0	0	0	3 (1.6)	0	0	1 (1.4)	0	4 (1.4)	0	0	1 (1.2)	0
Chest Pain	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Chills	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Death	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Fatigue	2 (1.9)	0	0	2 (14.3)	0	2 (1.1)	0	0	1 (1.4)	0	4 (1.4)	0	0	3 (3.6)	0
Malaise	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Mucosal Inflammation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Oedema Peripheral	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Pyrexia	1 (1.0)	0	0	0	0	0	0	0	2 (2.9)	0	1 (0.3)	0	0	2 (2.4)	0
Hepatobiliary Disorders	**2 (1.9)**	**0**	**0**	**0**	**0**	**1 (0.5)**	**2 (9.1)**	**1 (3.8)**	**1 (1.4)**	**0**	**3 (1.0)**	**2 (7.4)**	**1 (3.7)**	**1 (1.2)**	**0**

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
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Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Cholestasis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hepatic Failure	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hepatic Function Abnormal	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Hepatocellular Injury	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hepatomegaly	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Hepatosplenomegaly	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Hyperbilirubinaemia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Jaundice	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Immune System Disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.5)**	**0**	**0**	**0**	**0**	**1 (0.3)**	**0**	**0**	**0**	**0**
Drug Hypersensitivity	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Infections And Infestations	**0**	**0**	**0**	**0**	**0**	**3 (1.6)**	**0**	**0**	**1 (1.4)**	**0**	**3 (1.0)**	**0**	**0**	**1 (1.2)**	**0**
Conjunctivitis	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Meningitis Cryptococcal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Oesophageal Candidiasis	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Injury, Poisoning And Procedural Complications	**1 (1.0)**	**0**	**0**	**0**	**0**	**2 (1.1)**	**0**	**1 (3.8)**	**1 (1.4)**	**0**	**3 (1.0)**	**0**	**1 (3.7)**	**1 (1.2)**	**0**
Excoriation	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	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

	BMT					Non-BMT					Overall rIFI Pool				
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Overdose	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Toxicity To Various Agents	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Transfusion Reaction	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Investigations	**6 (5.8)**	**1 (20.0)**	**0**	**2 (14.3)**	**0**	**20 (10.8)**	**4 (18.2)**	**12 (46.2)**	**7 (10.0)**	**0**	**26 (9.0)**	**5 (18.5)**	**12 (44.4)**	**9 (10.7)**	**0**
Alanine Aminotransferase Increased	2 (1.9)	0	0	0	0	1 (0.5)	2 (9.1)	5 (19.2)	1 (1.4)	0	3 (1.0)	2 (7.4)	5 (18.5)	1 (1.2)	0
Amylase	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Aspartate Aminotransferase Increased	0	0	0	1 (7.1)	0	2 (1.1)	0	4 (15.4)	2 (2.9)	0	2 (0.7)	0	4 (14.8)	3 (3.6)	0
Bilirubin Conjugated Increased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Blood Alkaline Phosphatase Abnormal	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Blood Alkaline Phosphatase Increased	0	0	0	0	0	0	1 (4.5)	3 (11.5)	1 (1.4)	0	0	1 (3.7)	3 (11.1)	1 (1.2)	0
Blood Bilirubin Increased	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Blood Creatinine Increased	0	0	0	0	0	4 (2.2)	0	1 (3.8)	0	0	4 (1.4)	0	1 (3.7)	0	0
Blood Gases Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
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Number (%) of Subjects

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Blood Triglycerides Increased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Blood Urea Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Cardioactive Drug Level Decreased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Cardioactive Drug Level Increased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Drug Level Changed	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Drug Level Increased	1 (1.0)	1 (20.0)	0	0	0	2 (1.1)	0	0	0	0	3 (1.0)	1 (3.7)	0	0	0
Electrocardiogram Change	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Electrocardiogram Qrs Complex Prolonged	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Electrocardiogram Qt Prolonged	0	0	0	0	0	2 (1.1)	0	3 (11.5)	1 (1.4)	0	2 (0.7)	0	3 (11.1)	1 (1.2)	0
Gamma-Glutamyltransferase Increased	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Glucocorticoids Decreased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hepatic Enzyme Increased	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Laboratory Test Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Lipase	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lipase Abnormal	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Liver Function Test Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Liver Function Test Increased	1 (1.0)	0	0	1 (7.1)	0	3 (1.6)	0	0	0	0	4 (1.4)	0	0	1 (1.2)	0
Pancreatic Enzymes Increased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Platelet Count Decreased	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Qrs Axis Abnormal	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Weight Decreased	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Weight Increased	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Metabolism And Nutrition Disorders	**2 (1.9)**	**0**	**1 (100.0)**	**0**	**0**	**4 (2.2)**	**2 (9.1)**	**0**	**5 (7.1)**	**0**	**6 (2.1)**	**2 (7.4)**	**1 (3.7)**	**5 (6.0)**	**0**
Decreased Appetite	1 (1.0)	0	1 (100.0)	0	0	2 (1.1)	1 (4.5)	0	3 (4.3)	0	3 (1.0)	1 (3.7)	1 (3.7)	3 (3.6)	0
Electrolyte Imbalance	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Hyperkalaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hyperphosphataemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0

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Hyperuricaemia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Hypokalaemia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Metabolic Acidosis	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Polydipsia	0	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**4 (3.9)**	**0**	**0**	**0**	**0**	**4 (2.2)**	**1 (4.5)**	**1 (3.8)**	**2 (2.9)**	**0**	**8 (2.8)**	**1 (3.7)**	**1 (3.7)**	**2 (2.4)**	**0**
Arthralgia	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Back Pain	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Bone Pain	1 (1.0)	0	0	0	0	1 (0.5)	0	0	0	0	2 (0.7)	0	0	0	0
Fistula	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Mobility Decreased	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Muscular Weakness	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Musculoskeletal Chest Pain	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Myalgia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Nuchal Rigidity	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Pain In Extremity	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Pain In Jaw	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0

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Nervous System Disorders	**6 (5.8)**	**0**	**0**	**1 (7.1)**	**0**	**16 (8.6)**	**3 (13.6)**	**3 (11.5)**	**10 (14.3)**	**0**	**22 (7.6)**	**3 (11.1)**	**3 (11.1)**	**11 (13 1)**	**0**
Balance Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Dizziness	0	0	0	1 (7.1)	0	3 (1.6)	1 (4.5)	1 (3.8)	1 (1.4)	0	3 (1.0)	1 (3.7)	1 (3.7)	2 (2.4)	0
Dysgeusia	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Headache	3 (2.9)	0	0	0	0	7 (3.8)	2 (9.1)	1 (3.8)	7 (10.0)	0	10 (3 5)	2 (7.4)	1 (3.7)	7 (8.3)	0
Hyperreflexia	0	0	0	0	0	0	0	0	2 (2.9)	0	0	0	0	2 (2.4)	0
Hypoaesthesia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hypotonia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Memory Impairment	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Mental Impairment	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Mononeuropathy Multiplex	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Neuropathy Peripheral	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Paraesthesia	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	2 (2.9)	0	3 (1.0)	0	1 (3.7)	2 (2.4)	0
Seizure	2 (1.9)	0	0	0	0	0	0	0	0	0	2 (0.7)	0	0	0	0
Somnolence	0	0	0	0	0	2 (1.1)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Speech Disorder	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Tremor	0	0	0	0	0	1 (0.5)	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0

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	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Psychiatric Disorders	**0**	**0**	**0**	**0**	**0**	**5 (2.7)**	**1 (4.5)**	**0**	**0**	**0**	**5 (1.7)**	**1 (3.7)**	**0**	**0**	**0**
Anxiety	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Confusional State	0	0	0	0	0	2 (1.1)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Delirium	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Mental Status Changes	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Renal And Urinary Disorders	**2 (1.9)**	**0**	**0**	**0**	**0**	**4 (2.2)**	**2 (9.1)**	**1 (3.8)**	**0**	**0**	**6 (2.1)**	**2 (7.4)**	**1 (3.7)**	**0**	**0**
Acute Kidney Injury	0	0	0	0	0	0	1 (4.5)	1 (3.8)	0	0	0	1 (3.7)	1 (3.7)	0	0
Choluria	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Chronic Kidney Disease	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Nephropathy Toxic	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Nocturia	0	0	0	0	0	2 (1.1)	0	0	0	0	2 (0.7)	0	0	0	0
Renal Failure	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Renal Tubular Acidosis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Urinary Hesitation	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Reproductive System And Breast Disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.5)**	**1 (4.5)**	**0**	**1 (1.4)**	**0**	**1 (0.3)**	**1 (3.7)**	**0**	**1 (1.2)**	**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 by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Breast Swelling	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Breast Tenderness	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Hypomenorrhoea	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Menstruation Delayed	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	**0**	**0**	**0**	**0**	**0**	**2 (1.1)**	**1 (4.5)**	**1 (3.8)**	**0**	**0**	**2 (0.7)**	**1 (3.7)**	**1 (3.7)**	**0**	**0**
Dyspnoea	0	0	0	0	0	1 (0.5)	0	1 (3.8)	0	0	1 (0.3)	0	1 (3.7)	0	0
Epistaxis	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Lung Infiltration	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Skin And Subcutaneous Tissue Disorders	**5 (4.9)**	**0**	**0**	**0**	**0**	**10 (5.4)**	**2 (9.1)**	**8 (30.8)**	**4 (5.7)**	**0**	**15 (5 2)**	**2 (7.4)**	**8 (29.6)**	**4 (4.8)**	**0**
Alopecia	0	0	0	0	0	1 (0.5)	0	1 (3.8)	2 (2.9)	0	1 (0.3)	0	1 (3.7)	2 (2.4)	0
Dermatitis Atopic	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Dermatosis	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0	1 (1.2)	0
Dry Skin	1 (1.0)	0	0	0	0	1 (0.5)	1 (4.5)	0	0	0	2 (0.7)	1 (3.7)	0	0	0
Hyperhidrosis	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Pruritus	1 (1.0)	0	0	0	0	2 (1.1)	0	1 (3.8)	0	0	3 (1.0)	0	1 (3.7)	0	0
Rash	2 (1.9)	0	0	0	0	4 (2.2)	0	0	1 (1.4)	0	6 (2.1)	0	0	1 (1.2)	0

Refractory Invasive Fungal Infections (rIFI) Pool (ISS): P00041 and P01893
All Randomized Subjects
Summary of Treatment Related Treatment Emergent Adverse Events by Risk Group, Race
Number (%) of Subjects

	BMT					Non-BMT					Overall rIFI Pool				
	Caucasian n = 103	Black n = 5	Asian n = 1	Hispanic n = 14	Other n = 1	Caucasian n = 186	Black n = 22	Asian n = 26	Hispanic n = 70	Other n = 0	Caucasian n = 289	Black n = 27	Asian n = 27	Hispanic n = 84	Other n = 1
Rash Macular	0	0	0	0	0	0	1 (4.5)	0	0	0	0	1 (3.7)	0	0	0
Rash Maculo-Papular	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Rash Papular	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Rash Pruritic	0	0	0	0	0	1 (0.5)	0	2 (7.7)	0	0	1 (0.3)	0	2 (7.4)	0	0
Rash Vesicular	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Urticaria	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Urticaria Papular	0	0	0	0	0	0	0	1 (3.8)	0	0	0	0	1 (3.7)	0	0
Surgical And Medical Procedures	**0**	**0**	**0**	**0**	**0**	**1 (0.5)**	**0**	**0**	**0**	**0**	**1 (0.3)**	**0**	**0**	**0**	**0**
Therapeutic Procedure	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	0	0	0	0
Vascular Disorders	**3 (2.9)**	**0**	**0**	**0**	**0**	**1 (0.5)**	**1 (4.5)**	**0**	**1 (1.4)**	**0**	**4 (1.4)**	**1 (3.7)**	**0**	**1 (1.2)**	**0**
Haematoma	1 (1.0)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	0	0	0
Hypertension	1 (1.0)	0	0	0	0	0	1 (4.5)	0	0	0	1 (0.3)	1 (3.7)	0	0	0
Hypotension	1 (1.0)	0	0	0	0	0	0	0	1 (1.4)	0	1 (0.3)	0	0	1 (1.2)	0
Ischaemia	0	0	0	0	0	1 (0.5)	0	0	0	0	1 (0.3)	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 2.7.4-176　　体重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 by Weight (kg) (Incidence > 0% in Any Column)
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 events	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	**2**	**(7.1)**	**2**	**(7.1)**	**4**	**(19.0)**	**1**	**(6.7)**	**2**	**(13 3)**	**1**	**(12.5)**
Anaemia	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	1	(6.7)	1	(12.5)
Eosinophilia	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	0	(0.0)	1	(3.6)	3	(14.3)	1	(6.7)	0	(0.0)	0	(0.0)
Hypochromic anaemia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Iron deficiency anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Thrombocytopenia	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(7.1)**	**4**	**(14.3)**	**2**	**(9.5)**	**1**	**(6.7)**	**2**	**(13 3)**	**1**	**(12.5)**
Atrioventricular block first degree	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Bundle branch block right	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Cardiac failure	1	(3.6)	1	(3.6)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure congestive	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cor pulmonale	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Eye disorders	**4**	**(14.3)**	**5**	**(17.9)**	**3**	**(14.3)**	**7**	**(46.7)**	**10**	**(66.7)**	**6**	**(75.0)**

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**4**	**(14.3)**	**5**	**(17.9)**	**3**	**(14.3)**	**7**	**(46.7)**	**10**	**(66.7)**	**6**	**(75.0)**
Blepharitis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Colour blindness acquired	0	(0.0)	0	(0.0)	0	(0.0)	3	(20.0)	1	(6.7)	1	(12.5)
Conjunctival hyperaemia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diplopia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Dyschromatopsia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Ocular hyperaemia	0	(0.0)	2	(7.1)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Ocular hypertension	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Photophobia	2	(7.1)	1	(3.6)	2	(9.5)	4	(26.7)	5	(33 3)	2	(25.0)
Vision blurred	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	1	(6.7)	2	(25.0)
Visual impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(26.7)	1	(12.5)
Gastrointestinal disorders	**11**	**(39.3)**	**13**	**(46.4)**	**6**	**(28.6)**	**8**	**(53.3)**	**7**	**(46.7)**	**2**	**(25.0)**
Abdominal discomfort	1	(3.6)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Abdominal pain upper	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Cheilitis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Constipation	5	(17.9)	6	(21.4)	2	(9.5)	4	(26.7)	1	(6.7)	1	(12.5)
Dental caries	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Diarrhoea	4	(14.3)	2	(7.1)	0	(0.0)	3	(20.0)	0	(0.0)	1	(12.5)
Enterocolitis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Faeces hard	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Faeces soft	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Gastrointestinal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Haemorrhoidal haemorrhage	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**11**	**(39.3)**	**13**	**(46.4)**	**6**	**(28.6)**	**8**	**(53.3)**	**7**	**(46.7)**	**2**	**(25.0)**
Haemorrhoids	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	1	(6.7)	0	(0.0)
Hypoaesthesia oral	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lip dry	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	2	(13 3)	0	(0.0)
Melaena	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	2	(7.1)	4	(14.3)	1	(4.8)	1	(6.7)	0	(0.0)	0	(0.0)
Oral discomfort	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Oral dysaesthesia	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	2	(7.1)	0	(0.0)	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Trichoglossia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	2	(7.1)	0	(0.0)	1	(4.8)	2	(13.3)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**17**	**(60.7)**	**13**	**(46.4)**	**8**	**(38.1)**	**5**	**(33.3)**	**2**	**(13 3)**	**2**	**(25.0)**
Catheter site erythema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Chest discomfort	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Chest pain	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chills	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)	1	(6.7)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Malaise	2	(7.1)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Mucosal inflammation	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	5	(17.9)	1	(3.6)	1	(4.8)	1	(6.7)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**17**	**(60.7)**	**13**	**(46.4)**	**8**	**(38.1)**	**5**	**(33.3)**	**2**	**(13 3)**	**2**	**(25.0)**
Peripheral swelling	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	10	(35.7)	11	(39.3)	4	(19.0)	1	(6.7)	1	(6.7)	0	(0.0)
Thirst	2	(7.1)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	1	(12.5)
Hepatobiliary disorders	**5**	**(17.9)**	**8**	**(28.6)**	**1**	**(4.8)**	**2**	**(13.3)**	**4**	**(26.7)**	**2**	**(25.0)**
Hepatic function abnormal	5	(17.9)	8	(28.6)	1	(4.8)	1	(6.7)	4	(26.7)	1	(12.5)
Hepatobiliary disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	1	(12.5)
Immune system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(9.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cytokine release syndrome	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Graft versus host disease in gastrointestinal tract	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**14**	**(50.0)**	**17**	**(60.7)**	**13**	**(61.9)**	**3**	**(20.0)**	**7**	**(46.7)**	**2**	**(25.0)**
Angular cheilitis	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	0	(0.0)	1	(12.5)
Bacterial sepsis	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Blister infected	0	(0.0)	1	(3.6)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Bronchiolitis	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchitis	0	(0.0)	1	(3.6)	1	(4.8)	1	(6.7)	0	(0.0)	0	(0.0)
Bronchopulmonary aspergillosis	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Cellulitis	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	2	(7.1)	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Conjunctivitis bacterial	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis viral	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**14**	**(50.0)**	**17**	**(60.7)**	**13**	**(61.9)**	**3**	**(20.0)**	**7**	**(46.7)**	**2**	**(25.0)**
Cytomegalovirus infection	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Device related infection	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Enterocolitis viral	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroenteritis bacterial	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gingivitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Infected dermal cyst	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Influenza	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(3.6)	1	(3.6)	1	(4.8)	1	(6.7)	5	(33.3)	1	(12.5)
Oral herpes	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Osteomyelitis	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Paronychia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Periodontitis	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	1	(3.6)	1	(4.8)	1	(6.7)	0	(0.0)	0	(0.0)
Pneumonia	3	(10.7)	4	(14.3)	5	(23.8)	1	(6.7)	0	(0.0)	1	(12.5)
Pneumonia bacterial	3	(10.7)	2	(7.1)	1	(4.8)	0	(0.0)	1	(6.7)	0	(0.0)
Pneumonia fungal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Pyelonephritis	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sepsis	1	(3.6)	1	(3.6)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcal bacteraemia	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Upper respiratory tract infection	3	(10.7)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**6**	**(21.4)**	**5**	**(17.9)**	**2**	**(9.5)**	**1**	**(6.7)**	**1**	**(6.7)**	**1**	**(12.5)**
Accidental overdose	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Allergic transfusion reaction	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Arthropod bite	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Complications of bone marrow transplant	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Fall	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Laceration	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ligament sprain	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Limb injury	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Post procedural complication	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Postoperative fever	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin abrasion	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal compression fracture	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Thermal burn	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Transplantation complication	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Wound	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**10**	**(35.7)**	**14**	**(50.0)**	**6**	**(28.6)**	**6**	**(40.0)**	**7**	**(46.7)**	**2**	**(25.0)**
Alanine aminotransferase increased	6	(21.4)	2	(7.1)	1	(4.8)	1	(6.7)	0	(0.0)	1	(12.5)
Aspartate aminotransferase increased	6	(21.4)	2	(7.1)	2	(9.5)	2	(13.3)	1	(6.7)	1	(12.5)
Blood alkaline phosphatase increased	3	(10.7)	0	(0.0)	0	(0.0)	2	(13.3)	2	(13 3)	1	(12.5)
Blood creatinine increased	1	(3.6)	2	(7.1)	0	(0.0)	1	(6.7)	1	(6.7)	1	(12.5)
Blood glucose increased	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood lactate dehydrogenase increased	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**10**	**(35.7)**	**14**	**(50.0)**	**6**	**(28.6)**	**6**	**(40.0)**	**7**	**(46.7)**	**2**	**(25.0)**
Blood potassium decreased	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood pressure increased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood urea decreased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(3.6)	2	(7.1)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Cytomegalovirus test positive	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Electrocardiogram QT prolonged	1	(3.6)	5	(17.9)	1	(4.8)	1	(6.7)	1	(6.7)	0	(0.0)
Electrocardiogram ST segment elevation	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eosinophil count increased	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	2	(13 3)	1	(12.5)
Liver function test increased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	2	(13 3)	0	(0.0)
Neutrophil count decreased	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Platelet count decreased	0	(0.0)	3	(10.7)	2	(9.5)	0	(0.0)	1	(6.7)	1	(12.5)
Renal function test abnormal	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Weight decreased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	1	(6.7)	0	(0.0)
Metabolism and nutrition disorders	**15**	**(53.6)**	**11**	**(39.3)**	**5**	**(23.8)**	**3**	**(20.0)**	**1**	**(6.7)**	**1**	**(12.5)**
Decreased appetite	8	(28.6)	3	(10.7)	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hyperkalaemia	0	(0.0)	1	(3.6)	0	(0.0)	2	(13.3)	1	(6.7)	0	(0.0)
Hyperuricaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	3	(10.7)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycaemia	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypokalaemia	8	(28.6)	6	(21.4)	2	(9.5)	0	(0.0)	0	(0.0)	1	(12.5)
Hyponatraemia	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	1	(12.5)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**5**	**(17.9)**	**4**	**(14.3)**	**4**	**(19.0)**	**0**	**(0.0)**	**3**	**(20.0)**	**1**	**(12.5)**
Arthralgia	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Chondrocalcinosis pyrophosphate	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cytarabine syndrome	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Flank pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Joint effusion	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Muscular weakness	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Osteoporosis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pain in extremity	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	1	(12.5)
Periarthritis	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**2**	**(7.1)**	**2**	**(9.5)**	**1**	**(6.7)**	**0**	**(0.0)**	**1**	**(12.5)**
Acute myeloid leukaemia	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cancer pain	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastric cancer	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Lung cancer metastatic	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin papilloma	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Squamous cell carcinoma of lung	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tumour associated fever	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**2**	**(7.1)**	**2**	**(9.5)**	**1**	**(6.7)**	**0**	**(0.0)**	**1**	**(12.5)**
Tumour inflammation	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**2**	**(7.1)**	**3**	**(10.7)**	**3**	**(14.3)**	**4**	**(26.7)**	**3**	**(20.0)**	**1**	**(12.5)**
Dizziness	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	0	(0.0)	1	(3.6)	0	(0.0)	1	(6.7)	1	(6.7)	1	(12.5)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Headache	0	(0.0)	1	(3.6)	2	(9.5)	1	(6.7)	0	(0.0)	0	(0.0)
Hypoaesthesia	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hypogeusia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Loss of consciousness	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Neuropathy peripheral	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Parosmia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Psychiatric disorders	**2**	**(7.1)**	**3**	**(10.7)**	**0**	**(0.0)**	**7**	**(46.7)**	**5**	**(33 3)**	**0**	**(0.0)**
Anxiety	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Delirium	0	(0.0)	0	(0.0)	0	(0.0)	2	(13.3)	1	(6.7)	0	(0.0)
Hallucination	0	(0.0)	0	(0.0)	0	(0.0)	2	(13.3)	1	(6.7)	0	(0.0)
Hallucination, auditory	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Insomnia	2	(7.1)	1	(3.6)	0	(0.0)	3	(20.0)	3	(20.0)	0	(0.0)
Mental disorder	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**0**	**(0.0)**	**4**	**(14.3)**	**2**	**(9.5)**	**3**	**(20.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Acute kidney injury	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonic bladder	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neurogenic bladder	0	(0.0)	0	(0.0)	1	(4.8)	1	(6.7)	0	(0.0)	0	(0.0)
Pollakiuria	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Renal impairment	0	(0.0)	2	(7.1)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Urethral pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Urinary incontinence	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	**1**	**(3.6)**	**2**	**(7.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Benign prostatic hyperplasia	1	(3.6)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**5**	**(17.9)**	**11**	**(39.3)**	**7**	**(33.3)**	**3**	**(20.0)**	**2**	**(13 3)**	**4**	**(50.0)**
Asthma	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	2	(25.0)
Bronchitis chronic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	0	(0.0)	2	(7.1)	1	(4.8)	0	(0.0)	1	(6.7)	0	(0.0)
Haemoptysis	2	(7.1)	2	(7.1)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hypercapnia	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Interstitial lung disease	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Laryngeal pain	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Oropharyngeal discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**5**	**(17.9)**	**11**	**(39.3)**	**7**	**(33.3)**	**3**	**(20.0)**	**2**	**(13 3)**	**4**	**(50.0)**
Oropharyngeal pain	0	(0.0)	2	(7.1)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia aspiration	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumothorax	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Pneumothorax spontaneous	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Upper respiratory tract inflammation	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	1	(12.5)
Skin and subcutaneous tissue disorders	**9**	**(32.1)**	**9**	**(32.1)**	**8**	**(38.1)**	**4**	**(26.7)**	**2**	**(13 3)**	**2**	**(25.0)**
Alopecia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Decubitus ulcer	0	(0.0)	1	(3.6)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis contact	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Drug eruption	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	0	(0.0)	1	(3.6)	3	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema asteatotic	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	2	(7.1)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema nodosum	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperhidrosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hyperkeratosis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Ingrowing nail	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Perivascular dermatitis	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Petechiae	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Photosensitivity reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(25.0)

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Subjects With Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**9**	**(32.1)**	**9**	**(32.1)**	**8**	**(38.1)**	**4**	**(26.7)**	**2**	**(13 3)**	**2**	**(25.0)**
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Rash	3	(10.7)	1	(3.6)	2	(9.5)	1	(6.7)	1	(6.7)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Rash pruritic	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin exfoliation	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Skin irritation	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**7**	**(25.0)**	**5**	**(17.9)**	**3**	**(14.3)**	**2**	**(13.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	6	(21.4)	5	(17.9)	3	(14.3)	1	(6.7)	0	(0.0)	0	(0.0)
Orthostatic hypotension	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombophlebitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	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]

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付録 2.7.4-177　　体重別の副作用の発現例数（%）（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 by Weight (kg) (Incidence > 0% in Any Column)
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 drug-related adverse events	24	(85.7)	22	(78.6)	10	(47.6)	13	(86.7)	13	(86.7)	8	(100.0)
with no drug-related adverse events	4	(14.3)	6	(21.4)	11	(52.4)	2	(13.3)	2	(13 3)	0	(0.0)
Blood and lymphatic system disorders	**1**	**(3.6)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**
Anaemia	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Thrombocytopenia	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**0**	**(0.0)**	**1**	**(3.6)**	**1**	**(4.8)**	**0**	**(0.0)**	**2**	**(13 3)**	**0**	**(0.0)**
Bundle branch block right	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.7)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Eye disorders	**1**	**(3.6)**	**1**	**(3.6)**	**0**	**(0.0)**	**7**	**(46.7)**	**10**	**(66.7)**	**6**	**(75.0)**
Colour blindness acquired	0	(0.0)	0	(0.0)	0	(0.0)	3	(20.0)	1	(6.7)	1	(12.5)
Diplopia	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dyschromatopsia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Photophobia	0	(0.0)	0	(0.0)	0	(0.0)	4	(26.7)	5	(33 3)	2	(25.0)
Vision blurred	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	1	(6.7)	2	(25.0)
Visual impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(26.7)	1	(12.5)
Gastrointestinal disorders	**5**	**(17.9)**	**4**	**(14.3)**	**0**	**(0.0)**	**3**	**(20.0)**	**3**	**(20.0)**	**1**	**(12.5)**

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Subjects With Drug-Related Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**5**	**(17.9)**	**4**	**(14.3)**	**0**	**(0.0)**	**3**	**(20.0)**	**3**	**(20.0)**	**1**	**(12.5)**
Abdominal discomfort	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Constipation	2	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	2	(7.1)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Lip dry	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(13 3)	0	(0.0)
Nausea	2	(7.1)	2	(7.1)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Oral discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Oral dysaesthesia	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**13**	**(46.4)**	**9**	**(32.1)**	**2**	**(9.5)**	**3**	**(20.0)**	**1**	**(6.7)**	**0**	**(0.0)**
Chest pain	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	0	(0.0)	0	(0.0)	2	(9.5)	0	(0.0)	1	(6.7)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Injection site hypoaesthesia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Malaise	2	(7.1)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Oedema	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	3	(10.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	8	(28.6)	9	(32.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Thirst	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**4**	**(14.3)**	**5**	**(17.9)**	**1**	**(4.8)**	**2**	**(13.3)**	**4**	**(26.7)**	**2**	**(25.0)**
Hepatic function abnormal	4	(14.3)	5	(17.9)	1	(4.8)	1	(6.7)	4	(26.7)	1	(12.5)

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Subjects With Drug-Related Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**4**	**(14.3)**	**5**	**(17.9)**	**1**	**(4.8)**	**2**	**(13.3)**	**4**	**(26.7)**	**2**	**(25.0)**
Hepatobiliary disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	1	(12.5)
Infections and infestations	**0**	**(0.0)**	**2**	**(7.1)**	**2**	**(9.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cellulitis	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	1	(3.6)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**6**	**(21.4)**	**7**	**(25.0)**	**2**	**(9.5)**	**4**	**(26.7)**	**5**	**(33 3)**	**1**	**(12.5)**
Alanine aminotransferase increased	5	(17.9)	1	(3.6)	1	(4.8)	1	(6.7)	0	(0.0)	1	(12.5)
Aspartate aminotransferase increased	5	(17.9)	1	(3.6)	1	(4.8)	2	(13.3)	0	(0.0)	1	(12.5)
Blood alkaline phosphatase increased	2	(7.1)	0	(0.0)	0	(0.0)	1	(6.7)	2	(13 3)	1	(12.5)
Blood creatinine increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Blood lactate dehydrogenase increased	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Blood potassium decreased	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
C-reactive protein increased	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Electrocardiogram QT prolonged	1	(3.6)	4	(14.3)	1	(4.8)	1	(6.7)	1	(6.7)	0	(0.0)
Electrocardiogram ST segment elevation	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	2	(13 3)	1	(12.5)
Liver function test increased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Platelet count decreased	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**10**	**(35.7)**	**6**	**(21.4)**	**2**	**(9.5)**	**1**	**(6.7)**	**1**	**(6.7)**	**0**	**(0.0)**
Decreased appetite	5	(17.9)	2	(7.1)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	1	(6.7)	0	(0.0)
Hypokalaemia	6	(21.4)	4	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**2**	**(7.1)**	**0**	**(0.0)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Arthralgia	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Limb mass	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**1**	**(3.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.7)**	**2**	**(13 3)**	**1**	**(12.5)**
Dizziness	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	1	(12.5)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Hypogeusia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Mental impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Psychiatric disorders	**2**	**(7.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(40.0)**	**3**	**(20.0)**	**0**	**(0.0)**
Delirium	0	(0.0)	0	(0.0)	0	(0.0)	2	(13.3)	0	(0.0)	0	(0.0)
Hallucination	0	(0.0)	0	(0.0)	0	(0.0)	2	(13.3)	1	(6.7)	0	(0.0)
Hallucination, auditory	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Hallucination, visual	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)
Insomnia	2	(7.1)	0	(0.0)	0	(0.0)	2	(13.3)	1	(6.7)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(3.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertonic bladder	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(3.6)**	**2**	**(7.1)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Epistaxis	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Drug-Related Adverse Events by Weight (kg) (Incidence > 0% in Any Column)
Cohort 1 and 2 (ASaT)

	MK-5592						Voriconazole					
	<= 50		> 50 to 60		> 60		<= 50		> 50 to 60		> 60	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**1**	**(3.6)**	**2**	**(7.1)**	**1**	**(4.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Oropharyngeal pain	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**4**	**(14.3)**	**2**	**(7.1)**	**4**	**(19.0)**	**1**	**(6.7)**	**1**	**(6.7)**	**1**	**(12.5)**
Dermatitis acneiform	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	0	(0.0)	1	(3.6)	2	(9.5)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(3.6)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperhidrosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.7)	0	(0.0)	0	(0.0)
Photosensitivity reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Rash	3	(10.7)	0	(0.0)	1	(4.8)	0	(0.0)	1	(6.7)	0	(0.0)
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**5**	**(17.9)**	**4**	**(14.3)**	**2**	**(9.5)**	**1**	**(6.7)**	**0**	**(0.0)**	**0**	**(0.0)**
Hypertension	5	(17.9)	4	(14.3)	2	(9.5)	1	(6.7)	0	(0.0)	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]

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付録 2.7.4-178　　年齢・体重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）
Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1		29		6		41	
with one or more adverse events	1	(100.0)	29	(100.0)	6	(100.0)	41	(100.0)
with no adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	**0**	**(0.0)**	**2**	**(6.9)**	**0**	**(0.0)**	**6**	**(14.6)**
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.9)
Eosinophilia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Febrile neutropenia	0	(0.0)	2	(6.9)	0	(0.0)	2	(4 9)
Hypochromic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Cardiac disorders	**0**	**(0.0)**	**2**	**(6.9)**	**0**	**(0.0)**	**6**	**(14.6)**
Cardiac failure	0	(0.0)	1	(3.4)	0	(0.0)	3	(7 3)
Cardiac failure congestive	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Cor pulmonale	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Eye disorders	**1**	**(100.0)**	**5**	**(17.2)**	**0**	**(0.0)**	**6**	**(14.6)**
Blepharitis	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctival hyperaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Diplopia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Ocular hyperaemia	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)
Ocular hypertension	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Photophobia	0	(0.0)	4	(13.8)	0	(0.0)	1	(2.4)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**1**	**(100.0)**	**5**	**(17.2)**	**0**	**(0.0)**	**6**	**(14.6)**
Vision blurred	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**1**	**(100.0)**	**11**	**(37.9)**	**2**	**(33.3)**	**16**	**(39.0)**
Abdominal discomfort	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)
Cheilitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Constipation	0	(0.0)	5	(17.2)	2	(33.3)	6	(14.6)
Dental caries	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Diarrhoea	1	(100.0)	0	(0.0)	0	(0.0)	5	(12.2)
Enterocolitis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Faeces soft	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Haemorrhoidal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Haemorrhoids	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Hypoaesthesia oral	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Lip dry	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Melaena	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Nausea	1	(100.0)	3	(10.3)	1	(16.7)	2	(4 9)
Oral discomfort	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oral dysaesthesia	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)
Stomatitis	0	(0.0)	2	(6.9)	0	(0.0)	3	(7 3)
Trichoglossia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Vomiting	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**0**	**(0.0)**	**13**	**(44.8)**	**4**	**(66.7)**	**21**	**(51 2)**
Chest discomfort	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Chest pain	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Fatigue	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Malaise	0	(0.0)	0	(0.0)	1	(16.7)	1	(2.4)
Mucosal inflammation	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oedema peripheral	0	(0.0)	1	(3.4)	1	(16.7)	5	(12 2)
Peripheral swelling	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pyrexia	0	(0.0)	9	(31.0)	3	(50.0)	13	(31.7)
Thirst	0	(0.0)	1	(3.4)	1	(16.7)	1	(2.4)
Hepatobiliary disorders	**0**	**(0.0)**	**4**	**(13.8)**	**1**	**(16.7)**	**9**	**(22.0)**
Hepatic function abnormal	0	(0.0)	4	(13.8)	1	(16.7)	9	(22.0)
Immune system disorders	**0**	**(0.0)**	**2**	**(6.9)**	**0**	**(0.0)**	**0**	**(0.0)**
Cytokine release syndrome	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Graft versus host disease in gastrointestinal tract	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Infections and infestations	**1**	**(100.0)**	**19**	**(65.5)**	**2**	**(33.3)**	**22**	**(53.7)**

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**1**	**(100.0)**	**19**	**(65.5)**	**2**	**(33.3)**	**22**	**(53.7)**
Angular cheilitis	0	(0.0)	2	(6.9)	0	(0.0)	0	(0.0)
Bacterial sepsis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Blister infected	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Bronchiolitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Bronchitis	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Bronchopulmonary aspergillosis	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cellulitis	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Conjunctivitis	0	(0.0)	1	(3.4)	1	(16.7)	1	(2.4)
Conjunctivitis bacterial	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Cystitis viral	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Cytomegalovirus infection	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Device related infection	1	(100.0)	0	(0.0)	0	(0.0)	1	(2.4)
Enterocolitis viral	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Gastroenteritis bacterial	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Infected dermal cyst	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Influenza	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Lower respiratory tract infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Nasopharyngitis	0	(0.0)	3	(10.3)	0	(0.0)	0	(0.0)
Oral herpes	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Osteomyelitis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Paronychia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Periodontitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**1**	**(100.0)**	**19**	**(65.5)**	**2**	**(33.3)**	**22**	**(53.7)**
Pneumonia	1	(100.0)	4	(13.8)	0	(0.0)	7	(17 1)
Pneumonia bacterial	0	(0.0)	1	(3.4)	1	(16.7)	4	(9.8)
Pyelonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Sepsis	0	(0.0)	1	(3.4)	1	(16.7)	1	(2.4)
Staphylococcal bacteraemia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	2	(6.9)	0	(0.0)	2	(4 9)
Urinary tract infection	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**5**	**(17.2)**	**0**	**(0.0)**	**8**	**(19 5)**
Allergic transfusion reaction	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Arthropod bite	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Complications of bone marrow transplant	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Fall	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Laceration	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Ligament sprain	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Limb injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Post procedural complication	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Postoperative fever	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Skin abrasion	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Spinal compression fracture	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**5**	**(17.2)**	**0**	**(0.0)**	**8**	**(19 5)**
Transplantation complication	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Wound	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Investigations	**0**	**(0.0)**	**11**	**(37.9)**	**1**	**(16.7)**	**18**	**(43 9)**
Alanine aminotransferase increased	0	(0.0)	5	(17.2)	0	(0.0)	4	(9.8)
Aspartate aminotransferase increased	0	(0.0)	5	(17.2)	0	(0.0)	5	(12 2)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	3	(7 3)
Blood creatinine increased	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)
Blood glucose increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Blood lactate dehydrogenase increased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Blood potassium decreased	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Blood pressure increased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Blood urea decreased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
C-reactive protein increased	0	(0.0)	0	(0.0)	0	(0.0)	5	(12 2)
Electrocardiogram QT prolonged	0	(0.0)	2	(6.9)	1	(16.7)	4	(9.8)
Electrocardiogram ST segment elevation	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)
Eosinophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Liver function test increased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Neutrophil count decreased	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Platelet count decreased	0	(0.0)	2	(6.9)	0	(0.0)	3	(7 3)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**0**	**(0.0)**	**11**	**(37.9)**	**1**	**(16.7)**	**18**	**(43 9)**
Weight decreased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
White blood cell count decreased	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Metabolism and nutrition disorders	**1**	**(100.0)**	**9**	**(31.0)**	**3**	**(50.0)**	**18**	**(43 9)**
Decreased appetite	1	(100.0)	3	(10.3)	2	(33.3)	8	(19 5)
Hyperkalaemia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Hypoalbuminaemia	0	(0.0)	1	(3.4)	1	(16.7)	2	(4.9)
Hypoglycaemia	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Hypokalaemia	0	(0.0)	5	(17.2)	2	(33.3)	9	(22.0)
Hyponatraemia	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**6**	**(20.7)**	**0**	**(0.0)**	**7**	**(17 1)**
Arthralgia	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Back pain	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Chondrocalcinosis pyrophosphate	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Cytarabine syndrome	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Joint effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Limb mass	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Muscular weakness	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Osteoporosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**6**	**(20.7)**	**0**	**(0.0)**	**7**	**(17 1)**
Pain in extremity	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Periarthritis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(3.4)**	**0**	**(0.0)**	**3**	**(7 3)**
Acute myeloid leukaemia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Cancer pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Lung cancer metastatic	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Squamous cell carcinoma of lung	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Tumour associated fever	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Tumour inflammation	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Nervous system disorders	**0**	**(0.0)**	**1**	**(3.4)**	**0**	**(0.0)**	**7**	**(17 1)**
Dizziness	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Dysgeusia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Headache	0	(0.0)	0	(0.0)	0	(0.0)	3	(7 3)
Hypoaesthesia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Loss of consciousness	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Neuropathy peripheral	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Parosmia	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(6.9)**	**1**	**(16.7)**	**2**	**(4 9)**

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(6.9)**	**1**	**(16.7)**	**2**	**(4 9)**
Anxiety	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(16.7)	2	(4 9)
Mental disorder	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(3.4)**	**0**	**(0.0)**	**5**	**(12 2)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Hypertonic bladder	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Neurogenic bladder	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Renal impairment	0	(0.0)	1	(3.4)	0	(0.0)	2	(4.9)
Reproductive system and breast disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(7 3)**
Benign prostatic hyperplasia	0	(0.0)	0	(0.0)	0	(0.0)	3	(7 3)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**10**	**(34.5)**	**1**	**(16.7)**	**12**	**(29 3)**
Asthma	0	(0.0)	1	(3.4)	1	(16.7)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Cough	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Epistaxis	0	(0.0)	3	(10.3)	0	(0.0)	0	(0.0)
Haemoptysis	0	(0.0)	3	(10.3)	1	(16.7)	0	(0.0)
Hypercapnia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**10**	**(34.5)**	**1**	**(16.7)**	**12**	**(29 3)**
Interstitial lung disease	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Laryngeal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oropharyngeal pain	0	(0.0)	1	(3.4)	0	(0.0)	3	(7.3)
Pleural effusion	0	(0.0)	2	(6.9)	0	(0.0)	0	(0.0)
Pneumonia aspiration	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pneumothorax spontaneous	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Upper respiratory tract inflammation	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Skin and subcutaneous tissue disorders	**1**	**(100.0)**	**7**	**(24.1)**	**3**	**(50.0)**	**15**	**(36.6)**
Alopecia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Decubitus ulcer	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Dermatitis acneiform	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Dermatitis contact	0	(0.0)	0	(0.0)	1	(16.7)	1	(2.4)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Dry skin	0	(0.0)	2	(6.9)	0	(0.0)	2	(4 9)
Eczema asteatotic	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Erythema	0	(0.0)	2	(6.9)	1	(16.7)	0	(0.0)
Erythema nodosum	0	(0.0)	2	(6.9)	0	(0.0)	0	(0.0)
Hyperkeratosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Ingrowing nail	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

Subjects With Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**1**	**(100.0)**	**7**	**(24.1)**	**3**	**(50.0)**	**15**	**(36.6)**
Perivascular dermatitis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Petechiae	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.9)
Rash	0	(0.0)	2	(6.9)	1	(16.7)	3	(7 3)
Rash maculo-papular	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Rash pruritic	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Skin irritation	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**6**	**(20.7)**	**0**	**(0.0)**	**9**	**(22.0)**
Hypertension	0	(0.0)	6	(20.7)	0	(0.0)	8	(19.5)
Orthostatic hypotension	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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 2.7.4-179　　年齢・体重別の副作用の発現例数（%）（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）
ポサコナゾール群（ASaT）

Subjects With Drug-Related Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1		29		6		41	
with one or more drug-related adverse events	1	(100.0)	18	(62.1)	5	(83.3)	32	(78.0)
with no drug-related adverse events	0	(0.0)	11	(37.9)	1	(16.7)	9	(22.0)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(4 9)**
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(4 9)**
Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Eye disorders	**0**	**(0.0)**	**1**	**(3.4)**	**0**	**(0.0)**	**1**	**(2.4)**
Diplopia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Vision blurred	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**1**	**(100.0)**	**1**	**(3.4)**	**2**	**(33.3)**	**5**	**(12 2)**
Abdominal discomfort	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Constipation	0	(0.0)	0	(0.0)	1	(16.7)	1	(2.4)
Diarrhoea	1	(100.0)	0	(0.0)	0	(0.0)	2	(4.9)
Nausea	1	(100.0)	1	(3.4)	1	(16.7)	1	(2.4)
Oral dysaesthesia	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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Subjects With Drug-Related Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**0**	**(0.0)**	**9**	**(31.0)**	**3**	**(50.0)**	**12**	**(29 3)**
Chest pain	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Fatigue	0	(0.0)	1	(3.4)	0	(0.0)	1	(2.4)
Malaise	0	(0.0)	0	(0.0)	1	(16.7)	1	(2.4)
Oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oedema peripheral	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)
Pyrexia	0	(0.0)	6	(20.7)	3	(50.0)	8	(19.5)
Thirst	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**3**	**(10.3)**	**1**	**(16.7)**	**6**	**(14.6)**
Hepatic function abnormal	0	(0.0)	3	(10.3)	1	(16.7)	6	(14.6)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(9 8)**
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	3	(7 3)
Investigations	**0**	**(0.0)**	**6**	**(20.7)**	**1**	**(16.7)**	**8**	**(19 5)**
Alanine aminotransferase increased	0	(0.0)	4	(13.8)	0	(0.0)	3	(7 3)
Aspartate aminotransferase increased	0	(0.0)	4	(13.8)	0	(0.0)	3	(7 3)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Blood lactate dehydrogenase increased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Blood potassium decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

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Subjects With Drug-Related Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**0**	**(0.0)**	**6**	**(20.7)**	**1**	**(16.7)**	**8**	**(19 5)**
C-reactive protein increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(4 9)
Electrocardiogram QT prolonged	0	(0.0)	2	(6.9)	1	(16.7)	3	(7 3)
Electrocardiogram ST segment elevation	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Liver function test increased	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Platelet count decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Metabolism and nutrition disorders	**1**	**(100.0)**	**3**	**(10.3)**	**1**	**(16.7)**	**13**	**(31.7)**
Decreased appetite	1	(100.0)	1	(3.4)	1	(16.7)	6	(14.6)
Hypokalaemia	0	(0.0)	2	(6.9)	1	(16.7)	7	(17.1)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(3.4)**	**0**	**(0.0)**	**2**	**(4 9)**
Arthralgia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Limb mass	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.4)**
Dizziness	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(16.7)**	**1**	**(2.4)**
Insomnia	0	(0.0)	0	(0.0)	1	(16.7)	1	(2.4)

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Subjects With Drug-Related Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.4)**
Hypertonic bladder	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**2**	**(6.9)**	**0**	**(0.0)**	**2**	**(4 9)**
Epistaxis	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pleural effusion	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**4**	**(13.8)**	**1**	**(16.7)**	**5**	**(12 2)**
Dermatitis acneiform	0	(0.0)	1	(3.4)	0	(0.0)	0	(0.0)
Dry skin	0	(0.0)	1	(3.4)	0	(0.0)	2	(4 9)
Erythema	0	(0.0)	2	(6.9)	0	(0.0)	0	(0.0)
Rash	0	(0.0)	1	(3.4)	1	(16.7)	2	(4 9)
Rash maculo-papular	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Vascular disorders	**0**	**(0.0)**	**6**	**(20.7)**	**0**	**(0.0)**	**5**	**(12 2)**

Subjects With Drug-Related Adverse Events
by Age (< 65, >= 65: Years) and Weight (< 45, >= 45: kg) (Incidence > 0% in Any Column)
in MK-5592 Treatment Group
Cohort 1 and 2 (ASaT)

	< 65				>= 65			
	< 45		>= 45		< 45		>= 45	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**0**	**(0.0)**	**6**	**(20.7)**	**0**	**(0.0)**	**5**	**(12 2)**
Hypertension	0	(0.0)	6	(20.7)	0	(0.0)	5	(12.2)

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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CTD 第 2 部
2.7 臨床概要
2.7.5 参考文献

MSD 株式会社

2.7.5　参考文献

添付資料番号	タイトル	著者	掲載誌
[資料5.4: 002]	深在性真菌症の診断・治療ガイドライン2014	深在性真菌症のガイドライン作成委員会	協和企画
[資料5.4: 003]	造血細胞移植ガイドライン 真菌感染症の予防と治療（2017年9月）.	日本造血細胞移植学会ガイドライン委員会編.	https://www.jshct.com/uploads/files/guideline/01_04_shinkin.pdf
[資料5.4: 009]	Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial.	Walsh TJ, Raad I, Patterson TF, et al.	Clin Infect Dis. 2007; 44: 2-12.
[資料5.4: 010]	Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma.	Jang SH, Colangelo PM, Gobburu JVS.	Clin Pharmacol Ther. 2010; 88: 115-9.
[資料5.4: 012]	Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database.	Kontoyiannis DP, Marr KA, Park BJ, et al.	Clin Infect Dis. 2010; 50: 1091-100.
[資料5.4: 014]	Epidemiology of visceral mycoses in autopsy cases in Japan: the data from 1989 to 2009 in the Annual of Pathological Autopsy Cases in Japan.	Suzuki Y, Kume H, Togano T, et al.	Med Mycol. 2013; 51: 522-6.
[資料5.4: 015]	白血病死に占める深在性真菌症罹患者数の推計 －病理剖検輯報による疫学調査成績からの解析－.	栂野富輝、渋谷和俊、久米光.	Med Mycol J. 2012; 53: 53-8.
[資料5.4: 018]	Epidemiological study of *Fusarium* species causing invasive and superficial fusariosis in Japan.	Muraosa Y, Oguchi M, Yahiro M, et al.	Med Mycol J. 2017; 58: E5-E13.
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CTD 第 2 部
2.7 臨床概要
2.7.6 個々の試験のまとめ

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ール経口懸濁液予防投与の海外第Ⅲ相、無作為化、評価者盲検、実薬対照、並行群間、多施設共同試験（P01899試験）［評価資料］ 510
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略号及び用語の定義

略号	定義	
AC	Alveolar cell	肺胞上皮細胞
ACTH	Adrenocorticotropic hormone	副腎皮質刺激ホルモン
AIDS	Acquired immunodeficiency syndrome	後天性免疫不全症候群
ALP	Alkaline phosphatase	アルカリホスファターゼ
ALT	Alanine aminotransferase	アラニンアミノトランスフェラーゼ
AML	Acute myeloid leukemia	急性骨髄性白血病
ANC	Absolute neutrophil count	好中球絶対数
ASaT	All subjects as treated	治験薬を1回以上投与されたすべての被験者
AST	Aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
ATG	Antithymocyte globulin	抗胸腺細胞グロブリン
ATV	Atazanavir	アタザナビル
AUC	Area under the concentration-time curve	濃度－時間曲線下面積
$AUC_{0-\infty}$	Area under the concentration-time curve from 0 to infinity	投与後0時間から無限大時間までの濃度－時間曲線下面積
AUC_{0-last}	Area under the concentration-time curve from 0 to time of last quantifiable concentration	投与後0時間から最終測定可能時点までの濃度－時間曲線下面積
AUC_{0-t}	Area under the concentration-time curve from 0 to time t hours postdose	投与後0から t 時間までの濃度－時間曲線下面積
$AUC_{0-\tau}$	Area under the concentration-time curve for dosing interval	投与間隔の濃度－時間曲線下面積
$AUC_{0-12\ hr}$	Area under the concentration-time curve from 0 to 12 hours postdose	投与後0から12時間までの濃度－時間曲線下面積
$AUC_{0-24\ hr}$	Area under the concentration-time curve from 0 to 24 hours postdose	投与後0から24時間までの濃度－時間曲線下面積
$AUC_{0-72\ hr}$	Area under the concentration-time curve from 0 to 72 hours postdose	投与後0から72時間までの濃度－時間曲線下面積
$AUC_{12-24\ hr}$	Area under the concentration-time curve from 12 to 24 hours postdose	投与後12から24時間までの濃度－時間曲線下面積
AV	Atrioventricular	房室
BID	bis in die (twice daily)	1日2回
BMI	Body mass index	体格指数
BMT	Bone marrow transplant	骨髄移植 なお、1999年2月～2002年3月に実施された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（HSCT）であった。
bpm	Beats per minute	一分間の脈数の単位
BUN	Blood urea nitrogen	血中尿素窒素
$C_{12\ hr}$	Concentration at 12 hr postdose	投与後12時間の濃度
$C_{24\ hr}$	Concentration at 24 hr postdose	投与後24時間の濃度
Ca	Calcium	カルシウム
CAC	Clinical adjudication committee	臨床判定委員会
C_{avg}	Average concentration	平均濃度
CCr	Creatinine clearance (CL_{Cr})	クレアチニンクリアランス
CI	Confidence interval	信頼区間
CL	Clearance	クリアランス
CL/F	Apparent clearance	見かけのクリアランス
CL_{Cr}	Creatinine clearance	クレアチニンクリアランス
CL_r	Renal clearance	腎クリアランス

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略号	定義	
C_{last}	Concentration at time of last quantifible concentration	最終測定可能時点での濃度
C_{max}	Maximum concentration	最高濃度
C_{min}	Minimum concentration	最低濃度
CML	Chronic myeloid leukemia	慢性骨髄性白血病
CMV	Cytomegalovirus	サイトメガロウイルス
CNS	Central nervous system	中枢神経系
COPD	Chronic obstructive pulmonary disease	慢性閉塞性肺疾患
CPA	Chronic pulmonary aspergillosis	慢性肺アスペルギルス症
CPK	Creatine phosphokinase	クレアチンホスホキナーゼ
CRP	C-reactive protein	C-反応性蛋白
CSF	Cerebrospinal fluid	脳脊髄液
CT	Computed tomography	コンピュータ断層撮影法
CTC	Common toxicity criteria	共通毒性基準
CTCAE	Common terminology criteria for adverse events (the NCI Common terminology criteria for adverse events)	有害事象共通用語基準
C_{trough}	Trough concentration	トラフ濃度
CV	Coefficient of variation	変動係数
CYP	Cytochrome P450	チトクロム P450
DIC	Disseminated intravascular coagulation	播種性血管内凝固
DLST	Drug-induced lymphocyte stimulation test	薬剤誘発性リンパ球刺激試験
DRC	Data review committee	データレビュー委員会
DVT	Deep vein thrombosis	深部静脈血栓症
ECG	Electrocardiogram	心電図
ECOG	Eastern cooperative oncology group	ー
EFV	Efavirenz	エファビレンツ
EEG	Electroencephalogram	脳波
ELF	Epithelial-lining fluid	肺上皮被覆液
ELISA	Enzyme-linked immuno sorbent assay	酵素免疫測定法
EORTC-MSG	European organization for research and treatment of cancer-mycosis study group	ー
EOT	End of treatment	治療終了時
F	Bioavailability	バイオアベイラビリティ
FAS	Full analysis set	最大の解析対象集団
FLCZ	Fluconazole (FLU)	フルコナゾール
γ-GT	Gamma glutamyl transferase (GGT)	γ-グルタミルトランスフェラーゼ
γ-GTP	Gamma-gultamyl trans peptidase	γ-グルタミルトランスペプチダーゼ
gCV	Geometric coefficient of variation	幾何変動係数
GGT	Gamma glutamyl transferase	γ-グルタミルトランスフェラーゼ
GI	Gastrointestinal	消化管
Gluc	Glucose	グルコース
GM	Geometric mean	幾何平均
GMI	Galactomannan index	ガラクトマンナン指数
GMR	Geometric mean ratio	幾何平均比
GOT	Glutamic oxaloacetic transaminase	グルタミン酸オキサロ酢酸トランスアミナーゼ
GPT	Glutamic pyruvic transaminase	グルタミン酸ピルビン酸トランスアミナーゼ
GPV	Global pharmacovigilance	申請者の安全性評価データベース
GVHD	Graft-versus-host disease	移植片対宿主病
Hgb	Hemoglobin	ヘモグロビン
HHV-6	Human herpesvirus 6	ヒトヘルペスウイルス6
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
HLA	Human leukocyte antigen	ヒト白血球抗原
HPA	Hypothalamic-pituitary-adrenal axis	視床下部－下垂体－副腎皮質系

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略号	定義	
HSCT	Hematopoietic stem cell transplantation	造血幹細胞移植 なお、1999年2月～2002年3月に実施された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（HSCT）であった。
HUS	Haemolytic uraemic syndrome	溶血性尿毒症症候群
Hyper-CVAD	－	抗がん剤治療
IA	Invasive aspergillosis	侵襲性アスペルギルス症
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use	医薬品規制調和国際会議
IFI	Invasive fungal infection	侵襲性真菌症
INR	International normalized ratio	国際標準比
ITCZ	Itraconazole (ITZ)	イトラコナゾール
ITT	Intent-to-treat	－
IV	Intravenous	静脈内
KCZ	Ketoconazole	ケトコナゾール
k_{el}	Elimination rate constant	消失速度定数
LD	Loading dose	負荷用量
LDH	Lactose dehydrogenase	乳酸脱水素酵素
LE	Lupus erythematosus	エリテマトーデス
LT	Life-threatening	生命を脅かす
MD	Maintenance dose	維持用量
MDACC	The University of Texas MD Anderson Cancer Center	－
MDR	Multi-drug resistance	多剤耐性
MDS	Myelodysplastic syndrome	骨髄異形成症候群
MedDRA	Medical dictionary for regulatory activities	ICH 国際医薬用語集
Mg	Magnesium	マグネシウム
MIC_{90}	Minimum inhibitory concentration 90	90% 以上の株の発育を阻止する濃度
MICA	Micafungin	ミカファンギン
MID	Midazolam	ミダゾラム
MITT	Modified Intent-to-Treat	－
MK-5592	Posaconazole	ポサコナゾール
mRNA	Messenger ribonucleic acid	メッセンジャーリボ核酸
MRI	Magnetic resonance imaging	核磁気共鳴画像法
MRSA	Methicillin-resistant *Staphylococcus aureus*	メチシリン耐性黄色ブドウ球菌
NA、N/A	Not applicable	該当なし
NAUC	Dose normalized area under the curve	投与量あたりの AUC
NCI	National cancer institute	アメリカ国立がん研究所
Neut、NEUT	Neutrophil	好中球
NIAID	National institute of allergy and infectious diseases	アメリカ国立アレルギー感染症研究所
NOS	Not otherwise specified	特定不能
NPH-insulin	Neutral protamine hagedorn insulin	中間型インスリン
NPN	Non-protein nitrogen	非蛋白窒素
PAS	Periodic acid schiff	過ヨウ素酸シッフ
pC_{avg}	Predicted C_{avg} based on C_{min}	C_{min} から予測した C_{avg}
PCR	Polymerase chain reaction	ポリメラーゼ連鎖反応
PDLC	Pre-defined limit of change	事前に規定した変動の範囲
PK	Pharmacokinetics	薬物動態
Plt、PLT	Platelet	血小板
POS	Posaconazole	ポサコナゾール
PP	Per protocol set	治験実施計画書に適合した対象集団

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略号	定義	
PT	Preferred term	基本語
PTP	Primary time period	－
PUVA	Psoralen ultra-violet A	－
QD	quaque die (once daily)	1日1回
QID	quarter in die (four times daily)	1日4回
QTc	Corrected QT interval	補正した QT 間隔
QTcB	QT interval corrected for heart rate using Bazett's formula	Bazett 補正法により心拍数で補正した QT 間隔
QTcF	QT interval corrected for heart rate using Fridericia's formula	Fridericia 補正法により心拍数で補正した QT 間隔
R	Accumulation ratio	累積係数
rMSE	Root mean squared error	平均二乗誤差の平方根
RTV	Ritonavir	リトナビル
SBECD	Betadex sulfobutyl ether sodium	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
SD	Standard deviation	標準偏差
SGOT	Serum glutamic oxaloacetic transaminase	血清グルタミン酸オキサロ酢酸トランスアミナーゼ
SGPT	Serum glutamic pyruvic transaminase	血清グルタミン酸ピルビン酸トランスアミナーゼ
SIRS	Systemic inflammatory response syndrome	全身性炎症反応症候群
SMV	Simvastatin	シンバスタチン
SPCT	Short peripheral catheter thrombophlebitis	－
SpO_2	Arterial oxygen saturation	動脈血酸素飽和度
τ	Dosing interval	投与間隔
$t_{1/2}$	Elimination half-life	消失半減期
$t_{1/2abs}$	Absorption half-life	吸収相の半減期
$t_{1/2\alpha}$	Half-life at alpha phase	α 相の消失半減期
$t_{1/2\beta}$	Half-life at beta phase	β 相の消失半減期
T-Bil、T.bili、TBIL、TBILI	Total bilirubin	総ビリルビン
TID	ter in die (three times daily)	1日3回
T_{lag}	Lagtime of absorption phase	吸収のラグタイム
T_{last}	Time of last quantifiable concentration	最終測定可能時点
T_{max}	Time to reach maximum concentration	最高濃度到達時間
TNF-α	Tumor necrosis factor-α	腫瘍壊死因子-α
TSH	Thyroid-stimulating hormone	甲状腺刺激ホルモン
TTP	Thrombotic thrombocytopenic purpura	血栓性血小板減少性紫斑病
UGT	Uridine 5'-diphospho-glucuronosyltransferase	ウリジン5'-二リン酸グルクロン酸転移酵素
ULN	Upper limit of normal	基準値上限
V_d	Volume of distribution	分布容積
V_d/F	Apparent volume of distribution	見かけの分布容積
WBC	White blood cell	白血球
WHO	World health organization	世界保健機関
WHO-ART	World health organization adverse reaction terminology	WHO の副作用用語集
WOT	While on treatment	－

ポサコナゾールの薬物動態パラメータは血漿中のパラメータを表す。

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2.7.6　　個々の試験のまとめ

2.7.6.1　　臨床試験一覧表

2.7.6 項の臨床試験を一覧表で[表 2.7.6.1-1]に示す。

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表 2.7.6.1-1　　臨床試験一覧

試験の種類 （資料の分類）	試験番号 （国内／ 海外）	報告書を 添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数 （例）	対象 （健康被験者又 は診断名）	投与期間	試験の進行 状況・報告書 の種類
第Ⅰ相 （参考資料）	P07783 （海外）	[資料5.3.1.1.1: P07783]	薬物動態［新錠剤 D（黄色）の絶対的 BA、反復経口投与］、安全性及び忍容性	パート1：非盲検、無作為化、2期クロスオーバー パート2：非盲検、1期	パート1:ポサコナゾール[新錠剤 D(黄色)]300 mg を空腹時に経口投与 ポサコナゾール（静注用溶液）300 mg を空腹時に30分かけて末梢静脈内投与 パート2:ポサコナゾール[新錠剤 D(黄色)]300 mg を空腹時に1日1回［1日目1日2回（初回は空腹時、2回目は食後）］経口投与	パート1：13 パート2：12	非日本人健康被験者	パート1：単回 パート2：反復（8日間）	完了 完全な報告書
第Ⅰ相 （参考資料）	[redacted]-099 （海外）	[資料5.3.1.2.1: [redacted]_099]	薬物動態（旧錠剤及び旧カプセルの相対的 BA、食事の影響）、安全性及び忍容性	非盲検、無作為化、4期クロスオーバー	ポサコナゾール（旧錠剤及び旧カプセル）200 mg を空腹時及び高脂肪食摂取後に経口投与	24	非日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相 （参考資料）	[redacted]-099 (海外)	[資料5.3.1.2.2: [redacted]_099]	薬物動態（経口懸濁液及び旧錠剤の相対的 BA、食事の影響）、安全性及び忍容性	非盲検、無作為化、4期クロスオーバー	ポサコナゾール（経口懸濁液）200 mg を空腹時並びに高脂肪食及び無脂肪食摂取後に経口投与 ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に経口投与	20	非日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相 （参考資料）	P04975 （海外）	[資料5.3.1.2.3: P04975]	薬物動態（2種類の新錠剤、新カプセル及び経口懸濁液の相対的 BA、食事の影響）、安全性及び忍容性	非盲検、部分無作為化、2パート、4期クロスオーバー	ポサコナゾール（経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセル）100 mg を空腹時及び高脂肪食摂取後に経口投与	16	非日本人健康被験者	単回	完了 概要報告書
第Ⅰ相 （参考資料）	P07691 （海外）	[資料5.3.1.2.4: P07691]	薬物動態(2種類の新錠剤及び経口懸濁液の相対的 BA)、安全性及び忍容性	非盲検、無作為化、3期クロスオーバー、6投与順序	ポサコナゾール[新錠剤 C 及び新錠剤 D(黄色)]100 mg を空腹時、ポサコナゾール（経口懸濁液）100 mg を高脂肪食摂取後に経口投与	24	非日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相 （参考資料）	P02812 （海外）	[資料5.3.1.1.2: P02812]	薬物動態（栄養補助剤の影響）、薬力学（QTc 間隔）、安全性及び忍容性	非盲検、無作為化、2期クロスオーバー（単回投与時）	ポサコナゾール（経口懸濁液）400 mg を空腹時又は栄養補助剤摂取後、1日目及び15日目に経口投与 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後、1日2回（18～25日目、ただし25日目は朝投与のみ）経口投与	24	非日本人健康被験者	単回及び反復（8日間）	完了 完全な報告書
第Ⅰ相 （参考資料）	P112 （海外）	[資料5.3.1.1.3: P112]	薬物動態［新錠剤 D（黄色）の食事の影響］、安全性及び忍容性	非盲検、無作為化、2期クロスオーバー	ポサコナゾール［新錠剤 D（黄色）］300 mg を空腹時及び高脂肪食摂取後に経口投与	18	非日本人健康被験者	単回	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	JPC-[redacted]-361-12（国内）	[資料5.3.3.1.1: JPC_[redacted]_361_12]	薬物動態（単回経口投与及び食事の影響）、安全性及び忍容性	単盲検、プラセボ対照、並行群間、2期クロスオーバー（ステップ3のみ）	ステップ1、2、4及び5：ポサコナゾール（経口懸濁液）50、100、400及び600 mg 又はプラセボを食後に経口投与 ステップ3：ポサコナゾール（経口懸濁液）200 mg 又はプラセボを食後及び空腹時に経口投与	40	日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	I-P05011（国内）	[資料5.3.3.1.2: I_P05011]	薬物動態（反復経口投与）、安全性及び忍容性	単盲検、プラセボ対照、用量漸増、並行群間	ポサコナゾール（経口懸濁液）200、400 mg 又はプラセボを食後に1日2回経口投与（14日目は朝投与のみ）	24	日本人健康被験者	反復（14日間）	完了 完全な報告書
第Ⅰ相（参考資料）	I-P05014（国内）	[資料5.3.3.1.3: I_P05014]	薬物動態（単回経口投与）、安全性及び忍容性	非盲検、並行群間	ポサコナゾール（経口懸濁液）100、200及び400 mg を空腹時に経口投与	24	日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相（評価資料）	P067（国内）	[資料5.3.3.1.4: P067]	薬物動態（単回及び反復経口投与、単回末梢静脈内投与）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照、交互パネル（パート1）及び逐次パネル（パート2）、用量漸増	パート1:ポサコナゾール[新錠剤 D(黄色)] 200、300、400及び600 mg 又はプラセボを空腹時に経口投与 ポサコナゾール（静注用溶液）300 mg 及び静注用溶媒又はプラセボを空腹時に30分かけて末梢静脈内投与 パート2:ポサコナゾール[新錠剤 D(黄色)] 200 、400 mg 又はプラセボを空腹時に1日1回（1日目1日2回、2回目の投与のみ食後投与）経口投与	パート1：16 パート2：16	日本人健康被験者	パート1：単回 パート2：反復（10日間）	完了 完全な報告書
第Ⅰ相（参考資料）	[redacted]-098（海外）	[資料5.3.3.1.5: [redacted]_098]	薬物動態（単回経口投与）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照、並行群間、用量漸増	ポサコナゾール（旧錠剤）の50、100、200、400、800及び1200 mg 又はプラセボを高脂肪食摂取後に経口投与	54	非日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	[redacted]-089（海外）	[資料5.3.3.1.6: [redacted]_089]	薬物動態（反復経口投与）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照、並行群間、用量漸増	ポサコナゾール（旧錠剤）の50、100、200及び400 mg 又はプラセボを高脂肪朝食又は標準的夕食摂取後に1日2回経口投与	49	非日本人健康被験者	反復（14日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P05637（海外）	[資料5.3.3.1.7: P05637]	薬物動態（単回及び反復経口投与）、薬力学（副腎機能）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照、用量漸増	ポサコナゾール（新錠剤 C）200 mg（コホート1）、400 mg（コホート2）又はプラセボを空腹時に単回（1日目）並びに1日2回（6日目、コホート1のみ15～22日目も）及び1日1回（7～14日目）経口投与	25	非日本人健康被験者	単回及び反復（コホート1：17日間、コホート2：9日間）	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	P04985（海外）	[資料5.3.3.1.8: P04985]	薬物動態（静注用溶液、新錠剤C及び経口懸濁液の相対的 BA、単回及び反復末梢静脈内投与）、薬力学（副腎機能）、安全性及び忍容性	二重盲検（処置 A及び B）及び非盲検（処置C及びD）、無作為化、プラセボ対照（処置 A及び B）、用量漸増	コホート1：ポサコナゾール（静注用溶液）200 mg 又はプラセボを空腹時に90分かけて1日1回（1日目及び7～14日目）及び1日2回（6日目）末梢静脈内投与（処置 A） コホート2：ポサコナゾール（静注用溶液）400 mg 又はプラセボを空腹時に2時間かけて1日1回（1日目及び7～14日目）及び1日2回（6日目）末梢静脈内投与（処置 B） ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に経口投与（処置 C） ポサコナゾール（新錠剤 C）400 mg を空腹時に経口投与（処置 D） （コホート1で認められた投与部位の不耐容により、コホート1の単回末梢静脈内投与のみ実施）	12	非日本人健康被験者	単回（コホート1の単回のみ実施）	中止 完全な報告書
第Ⅰ相（参考資料）	P06356（海外）	[資料5.3.3.1.9: P06356]	薬物動態（単回及び反復末梢静脈内投与）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照、2パート、用量漸増	パート1：ポサコナゾール（静注用溶媒及び静注用溶液）0、50、100、200、250及び300 mg 又はプラセボを空腹時に30分かけて末梢静脈内投与 パート2：ポサコナゾール（静注用溶媒及び静注用溶液）0、100、200及び300 mg 又はプラセボを空腹時に30分かけて1日1回（1日目1日2回）末梢静脈内投与 （反復投与後の注入部位の有害事象により、パート2は100 mg 投与後に中止）	パート1：72 パート2：18	非日本人健康被験者	パート1：単回 パート2：反復（10日間）（パート2は100 mg及びプラセボ投与のみ実施）	中止 完全な報告書
第Ⅰ相（参考資料）	P04547（海外）	[資料5.3.3.1.10: P04547]	薬物動態（ELF 及び AC中濃度）、安全性及び忍容性	非盲検	ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後（8日目は空腹時）に1日2回経口投与（1日目は夜投与及び8日目は朝投与のみ）	25	非日本人健康被験者	反復（8日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P05270（海外）	[資料5.3.3.1.11: P05270]	薬物動態（皮膚中濃度）、安全性及び忍容性	非盲検、無作為化	ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回経口投与（8日目は朝投与のみ）	30	非日本人健康被験者	反復（8日間）	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	C[redacted]-104（海外）	[資料5.3.3.1.12: C[redacted]_104]	薬物動態（マスバランス）、安全性及び忍容性	非盲検	^{14}C-ポサコナゾール（経口懸濁液）の409 mg（79.3 μCi）を高脂肪食摂取後に経口投与	8	非日本人健康被験者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	P02418（海外）	[資料5.3.3.1.13: P02418]	薬物動態（マスバランス）、安全性及び忍容性	非盲検	^{14}C-ポサコナゾール（経口懸濁液）399 mg（81.7 μCi）を高脂肪食摂取後に経口投与	8	非日本人健康被験者	単回	完了 完全な報告書
後期第Ⅰ相（参考資料）	C/[redacted]-421（海外）	[資料5.3.3.2.1: C[redacted]_421]	薬物動態（反復経口投与）、安全性、忍容性及び有効性	非盲検、多施設共同、用量漸増	ポサコナゾール（経口懸濁液）200 mg を食後に1日1回経口投与 ポサコナゾール（経口懸濁液）400 mg を食後に1日1回経口投与 ポサコナゾール（経口懸濁液）200 mg を食後に1日4回経口投与	31	好中球が減少している高用量化学療法又は骨髄移植を受けた非日本人患者	反復（7～14日間）	完了 完全な報告書
後期第Ⅰ／Ⅲ相（評価資料）	P05615（海外）	[資料5.3.3.2.2: P05615]	薬物動態、安全性、忍容性及び有効性の評価	非盲検、非対照、2パート、多施設共同	ポサコナゾール［新錠剤 C 及び D（緑色）］ ・200 mg コホート（パート1A） 新錠剤 C200 mg を1日1回（治験薬投与1日目は1日2回）、食事条件を規定せず経口投与 ・300 mg コホート（パート1B 及びパート2） 新錠剤 C（パート1B）又は D（緑色）（パート2）300 mg を1日1回（治験薬投与1日目は1日2回）、食事条件を規定せず経口投与	200 mg コホート：20 300 mg コホート：215	侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症、同種造血幹細胞移植後の移植片対宿主病）	8日間以上 最長28日間	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
後期第Ⅰ／Ⅲ相（評価資料）	P05520（海外）	[資料5.3.3.2.3: P05520]	薬物動態、安全性、忍容性及び有効性の評価	非盲検、多施設共同	ポサコナゾール（静注用溶液）、ポサコナゾール（経口懸濁液）、プラセボ（5%ブドウ糖溶液） ・コホート0 静注用溶液200 mg 又はプラセボ（5%ブドウ糖溶液）を治験薬投与1日目に90分かけて単回中心静脈内投与、その約12時間後に経口懸濁液400 mg を単回経口投与、2日目以降は経口懸濁液400 mg を1日2回合計11回経口投与 ・コホート1 静注用溶液200 mg を治験薬投与1日目は1日2回、2～14日目は1日1回90分かけて中心静脈内投与、15日目以降は経口懸濁液400 mg を1日2回経口投与 ・コホート2 静注用溶液300 mg を治験薬投与1日目は1日2回、2～14日目は1日1回90分かけて中心静脈内投与、15日目以降は経口懸濁液400 mg を1日2回経口投与 ・コホート3 静注用溶液300 mg を治験薬投与1日目は1日2回、2～5日目（薬物動態評価期間の延長例では10日目まで）は1日1回90分かけて中心静脈内投与、6日目（又は11日目）以降は経口懸濁液200 mg を1日3回又は400 mg を1日2回経口投与。ただし6日以降も経口投与できない場合は可能になるまで中心静脈内投与を継続又は間欠投与。 なお、いずれのコホートとも経口懸濁液は、食後又は経口液体栄養補助剤摂取後10分以内に投与、食事又は経口液体栄養補助剤が摂れない場合は低 pH の炭酸飲料とともに投与	コホート0：ポサコナゾール静注用溶液200 mg 群：11 プラセボ群：11 コホート1：21 コホート2及び3：244	侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症、同種造血幹細胞移植後の移植片対宿主病）	・コホート0 約7日間 ・コホート1 約28日間 ・コホート2 約28日間 ・コホート3 約28日間	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
後期第Ⅰ相（参考資料）	P117（海外）	[資料5.3.3.2.4: P117]	薬物動態（反復経口投与）、安全性及び忍容性	非盲検、多施設共同、単一投与群、2サブグループ	ポサコナゾール［新錠剤 D（黄色）］300 mg を食事の有無にかかわらず1日1回（1日目1日2回）経口投与（サブグループ1：1日目及び8日目は空腹時投与）	サブグループ1：20 サブグループ2：45	中国人侵襲性真菌感染症ハイリスク患者	反復（8～28日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P02810（海外）	[資料5.3.3.3.1: P02810]	薬物動態（性別及び年齢の影響）、薬力学（QTc 間隔）、安全性及び忍容性	二重盲検、無作為化、プラセボ対照	ポサコナゾール（経口懸濁液）400 mg 又はプラセボを高脂肪食摂取後に1日2回経口投与（8日目は朝投与のみ）	若年男性：18 若年女性：18 高齢男性：17 高齢女性：16	非日本人健康被験者	反復（8日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P02811（海外）	[資料5.3.3.3.2: P02811]	薬物動態（人種の影響）、薬力学（QTc 間隔）、薬理遺伝学、安全性及び忍容性	非盲検、並行群間	ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回経口投与（8日目は朝投与のみ）	56	白人及びアフリカ系アメリカ人健康被験者	反復（8日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P111（海外）	[資料5.3.3.3.3: P111]	薬物動態（単回末梢静脈内及び経口投与、食事の影響）、安全性及び忍容性	非盲検、無作為化、3期クロスオーバー	ポサコナゾール［新錠剤 D（黄色）］300 mg を空腹時に経口投与 ポサコナゾール（静注用溶液）300 mg を空腹時に30分かけて末梢静脈内投与 ポサコナゾール［新錠剤 D（黄色）］300 mg を高脂肪食摂取後に経口投与	18	中国人健康被験者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	P01940（海外）	[資料5.3.3.3.4: P01940]	薬物動態（腎機能障害の影響）、安全性及び忍容性	非盲検、多施設共同	ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に経口投与（血液透析を必要とする重度腎機能障害者は血液透析非施行日） 血液透析を必要とする重度腎機能障害者には初回投与約2～3週間後の血液透析の約6時間前にポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に経口投与	正常腎機能者：6 軽度：6 中等度：6 血液透析を必要とする重度：6	非日本人腎機能障害者及び正常腎機能者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	[redacted]-195（海外）	[資料5.3.3.3.5: [redacted]_195]	薬物動態（肝機能障害の影響）、安全性及び忍容性	非盲検	ポサコナゾール（経口懸濁液）200 mg を高脂肪食摂取後に経口投与	正常肝機能者：4 軽度：4 中等度：4 重度：4	非日本人肝機能障害者及び正常肝機能者	単回	完了 完全な報告書
第Ⅰ相（参考資料）	P03742（海外）	[資料5.3.3.3.6: P03742]	薬物動態（肝機能障害の影響）、安全性及び忍容性	非盲検	ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に経口投与	正常肝機能者：18 軽度：6 中等度：7 重度：6	非日本人肝機能障害者及び正常肝機能者	単回	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	[redacted]-016（海外）	[資料5.3.3.4.1: [redacted]_016]	薬物動態（CYP 薬物代謝酵素に対する影響）、安全性及び忍容性	非盲検、無作為化、2期クロスオーバー	ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回経口投与（1～10日目）、9日目のポサコナゾール投与後2時間に、CYP プローブ基質（デキストロメトルファン30 mg、カフェイン200 mg、トルブタミド500 mg、クロルゾキサゾン250 mg）の混合カクテルを単回経口投与、10日目のポサコナゾール投与後2時間に、ミダゾラム0.05 mg/kg を単回静脈内投与 1～8日目は無処置、9日目に各種 CYP プローブ基質の混合カクテルを単回経口投与、10日目にミダゾラム0.05 mg/kg を単回静脈内投与	13	非日本人健康被験者	反復（10日間）	完了 完全な報告書
第Ⅰ相（参考資料）	C[redacted]-173（海外）	[資料5.3.3.4.2: C[redacted]_173]	薬物動態（シメチジンとの薬物相互作用）、安全性及び忍容性	非盲検、無作為化、2期クロスオーバー	ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回経口投与 ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回とシメチジン400 mg の1日2回経口投与を併用	12	非日本人健康被験者	反復（10日間）	完了 完全な報告書
第Ⅰ相（参考資料）	[redacted]-207（海外）	[資料5.3.3.4.3: [redacted]_207]	薬物動態（リファブチンとの薬物相互作用）、安全性及び忍容性	非盲検、非無作為化、並行群間	ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回経口投与 リファブチン300 mg を食後（-1日目のみ高脂肪食摂取後）に1日1回経口投与し（-7～-1日目）、ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回とリファブチン300 mg の1日1回経口投与を併用（1～10日目）	24	非日本人健康被験者	反復（10日間）	完了 完全な報告書
第Ⅰ相（参考資料）	C[redacted]-201（海外）	[資料5.3.3.4.4: C[redacted]_201]	薬物動態（フェニトインとの薬物相互作用）、安全性及び忍容性	非盲検、無作為化、並行群間	ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回経口投与 フェニトイン200 mg を高脂肪食摂取後に1日1回10日間経口投与 ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回とフェニトイン200 mg の1日1回経口投与を併用	36	非日本人健康被験者	反復（10日間）	完了 完全な報告書

表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	C[redacted]-247（海外）	[資料5.3.3.4.5: C[redacted]_247]	薬物動態（シクロスポリンとの薬物相互作用）、安全性及び忍容性	非盲検	ポサコナゾール（旧錠剤）200 mg を高脂肪食摂取後に1日1回とシクロスポリンの1日2回経口投与を併用（1日目はポサコナゾールの朝投与はなく、シクロスポリン投与後12時間の採血終了後に投与）	4	非日本人心臓移植患者	反復（10日間）	完了 完全な報告書
第Ⅰ相（参考資料）	P02862（海外）	[資料5.3.3.4.6: P02862]	薬物動態（タクロリムスとの薬物相互作用）、薬力学（QTc 間隔）、安全性及び忍容性	非盲検	タクロリムス0.05 mg/kg を単回経口投与（1日目） ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回（7～14日目）（14日目は空腹時に朝投与のみ）とタクロリムス0.05 mg/kg の単回経口投与を併用（14日目）	54（18例はタクロリムスのみ投与）	非日本人健康被験者	反復（8日間）	完了 完全な報告書
第Ⅰ相（参考資料）	C[redacted]-190（海外）	[資料5.3.3.4.7: C[redacted]_190]	薬物動態（核酸系逆転写酵素阻害剤及びプロテアーゼ阻害剤との薬物相互作用）、安全性及び忍容性	非盲検、非無作為化、並行群間	ポサコナゾール（旧錠剤）200 mg を食後に（-1、1及び14日目は無脂肪食）1日1回経口投与（1～14日目）、並びに核酸系逆転写酵素阻害薬（ジドブジン200 mg 1日3回又は300 mg 1日2回、ラミブジン150 mg 1日2回又は他の核酸系逆転写酵素阻害薬）及びプロテアーゼ阻害剤（リトナビル600 mg 1日2回又はインジナビル800 mg 1日3回）の経口投与（-2～14日目）と併用 ただし、1例はジドブジンの代わりにジダノシン100 mg を1日2回投与	17	非日本人 HIV 感染患者	反復（14日間）	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類 （資料の分類）	試験番号 （国内／ 海外）	報告書を 添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数 （例）	対象 （健康被験者又 は診断名）	投与期間	試験の進行 状況・報告書 の種類
第Ⅰ相 （参考資料）	P04490 （海外）	[資料5.3.3.4.8: P04490]	薬物動態（ミダゾラム、シロリムス、リトナビル・ブースト・アタザナビル又はエファビレンツとの薬物相互作用）、安全性及び忍容性	非盲検、4パート（パート1：3期、2投与順序、クロスオーバー、パート2：2期、投与順序固定、パート3：4期、2投与順序、クロスオーバー、パート4：3期、2投与順序、クロスオーバー）	パート1：ミダゾラム2 mg を高脂肪食摂取後に単回経口投与（ポサコナゾール投与開始前2日） ミダゾラム0.4 mg を空腹時に単回静脈内投与（ポサコナゾール投与開始前1日） ポサコナゾール（経口懸濁液）200 mg を高脂肪食摂取後に1日2回（ポサコナゾール投与開始後1～7日目）とミダゾラム2 mg の単回経口投与（ポサコナゾール投与開始後6日目）及び0.4 mg（ポサコナゾール投与開始後7日目）の単回静脈内投与を併用 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回（ポサコナゾール投与開始後8～14日目）とミダゾラム2 mg の単回経口投与（ポサコナゾール投与開始後13日目）及び0.4 mg（ポサコナゾール投与開始後14日目）の単回静脈内投与を併用 ミダゾラム2 mg を高脂肪食摂取後に単回経口投与（ケトコナゾール投与開始前2日） ミダゾラム0.4 mg を空腹時に単回静脈内投与（ケトコナゾール投与開始前1日） ケトコナゾール400 mg を高脂肪食摂取後に1日1回（ケトコナゾール投与開始後1～7日目）とミダゾラム2 mg の単回経口投与（ケトコナゾール投与開始後6日目）及び0.4 mg（ケトコナゾール投与開始後7日目）の単回静脈内投与を併用 パート2：シロリムス2 mg を空腹時に単回経口投与（1日目） ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回（30～45日目）とシロリムス2 mg の単回経口投与（36日目）を併用	パート1：12 パート2：12 パート3：12 パート4：17	非日本人健康被験者	パート1：反復（14日間） パート2：反復（16日間） パート3：反復（7日間） パート4：反復（10日間）	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相 （参考資料）	P04490 （海外） （続き）				パート3：食後にアタザナビル300 mg 及び空腹時にリトナビル100 mg を1日1回7日間経口投与 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回とアタザナビル300 mg 及びリトナビル100 mg の1日1回経口投与を併用 アタザナビル300 mg を食後に1日1回7日間経口投与 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回とアタザナビル300 mg の1日1回経口投与を併用 パート4：エファビレンツ400 mg を空腹時に1日1回10日間経口投与 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回とエファビレンツ400 mg の1日1回経口投与を併用 ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回経口投与				
第Ⅰ相 （参考資料）	P05359 （海外）	[資料5.3.3.4.9: P05359]	薬物動態（ミダゾラム及びシンバスタチンとの薬物相互作用）、安全性及び忍容性	非盲検、無作為化、投与順序固定、並行群間	ミダゾラム2 mg を空腹時に単回経口投与（-9日目） シンバスタチン40 mg を空腹時に単回経口投与（-6日目） ポサコナゾール（経口懸濁液）50、100又は200 mg を1日1回（1～13日目）とミダゾラム2 mg（8日目）及びシンバスタチン40 mg（11日目）の単回経口投与を併用（1～7、9～10及び12～13日目は高脂肪食摂取後、8日目及び11日目は空腹時投与）	35	非日本人健康被験者	反復（13日間）	完了 完全な報告書
第Ⅰ相 （参考資料）	P02489 （海外）	[資料5.3.3.4.10: P02489]	薬物動態（glipizide との薬物相互作用）、薬力学（血中グルコース濃度及び QTc 間隔）、安全性及び忍容性	非盲検	glipizide 10 mg を高脂肪食摂取後に単回経口投与（1日目） ポサコナゾール（経口懸濁液）400 mg を高脂肪食摂取後に1日2回（2～11日目）と glipizide 10 mg の単回経口投与（11日目）を併用	12	非日本人健康被験者	反復（10日間）	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	P04931（海外）	[資料5.3.3.4.11: P04931]	薬物動態（カスポファンギン及びミカファンギンとの薬物相互作用）、安全性及び忍容性	非盲検、無作為化、並行群間	コホート1：カスポファンギン50 mg（1日目70 mg）を高脂肪食摂取後に1日1回14日間静脈内投与 ポサコナゾール（経口懸濁液）400 mgを高脂肪食摂取後に1日2回経口投与とカスポファンギン50 mg（1日目70 mg）の1日1回静脈内投与を併用 コホート2：ミカファンギン150 mg を高脂肪食摂取後に1日1回7日間静脈内投与 ポサコナゾール（経口懸濁液）400 mgを高脂肪食摂取後に1日2回経口投与とミカファンギン150 mgの1日1回静脈内投与を併用	コホート1：35 コホート2：32	非日本人健康被験者	コホート1：反復（14日間） コホート2：反復（7日間）	完了 完全な報告書
第Ⅰ相（参考資料）	C[redacted]-120（海外）	[資料5.3.3.4.12: C[redacted]_120]	薬物動態（制酸剤との薬物相互作用）、安全性及び忍容性	非盲検、無作為化、4期クロスオーバー	ポサコナゾール（旧錠剤）200 mgを空腹時に経口投与 ポサコナゾール（旧錠剤）200 mgを空腹時に経口投与とMylanta 登録商標20 mLの単回経口投与を併用 ポサコナゾール（旧錠剤）200 mgを高脂肪食摂取後に経口投与とMylanta 登録商標20 mLの単回経口投与を併用 ポサコナゾール（旧錠剤）200 mgを高脂肪食摂取後に経口投与	12	非日本人健康被験者	単回	完了 完全な報告書

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表 2.7.6.1-1　　臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅰ相（参考資料）	P07764（海外）	[資料5.3.3.4.13: P07764]	薬物動態（Mylanta 登録商標、ラニチジン、エソメプラゾール又はメトクロプラミドとの薬物相互作用）、安全性及び忍容性	非盲検、無作為化、5期クロスオーバー	ポサコナゾール［新錠剤 D（緑色）］400 mg を空腹時に経口投与 Mylanta 登録商標20 mL の単回経口投与直後にポサコナゾール［新錠剤 D（緑色）］400 mg を空腹時に経口投与と併用 ラニチジン150 mg を空腹時に単回経口投与後1時間にポサコナゾール［新錠剤 D（緑色）］400 mg を空腹時に経口投与し、ラニチジン投与後12時間にラニチジン150 mg を空腹時に単回経口投与 エソメプラゾール40 mg を空腹時に1日1回経口投与（-4～1日目）とポサコナゾール［新錠剤 D（緑色）］400 mg の経口投与を併用（1日目） メトクロプラミド15 mg を食前30分又は就寝前に1日4回経口投与（-1日目及び1日目）とポサコナゾール［新錠剤 D（緑色）］400 mg を経口投与と併用（1日目の朝）	21	非日本人健康被験者	単回	完了 完全な報告書

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表 2.7.6.1-1臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅲ相（評価資料）	P01899（海外）	[資料5.3.5.1.1: P01899]	安全性及び有効性の比較・評価	多施設共同、無作為化、評価者盲検、実薬対照、並行群間試験	ポサコナゾール経口懸濁液、フルコナゾール経口懸濁液、イトラコナゾール内用液 ・ポサコナゾール群 経口懸濁液を200 mg 1日3回食事又は脂肪分を含む経口栄養補助剤とともに経口投与（経口投与に不耐容の場合は、アムホテリシン B デオキシコール酸製剤0.3～0.5 mg/kg/日を4～6時間かけて静脈内投与） ・フルコナゾール／イトラコナゾール群 フルコナゾール経口懸濁液を400 mg 1日1回食事条件を規定せず経口投与、又はイトラコナゾール内用液を200 mg 1日2回空腹時又はグレープフルーツ／グレープフルーツジュース非摂取時に経口投与（経口投与に不耐容の場合は、フルコナゾール静注用溶液400 mg を1日1回2時間かけて静脈内投与、又はイトラコナゾール静注用溶液200 mg を1日2回1時間かけて静脈内投与）	ポサコナゾール群：304 フルコナゾール／イトラコナゾール群：298	侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症）	最長84日間	完了 完全な報告書
第Ⅲ相（評価資料）	C/I98-316（海外）	[資料5.3.5.1.2: CI98_316]	安全性及び有効性の比較・評価	多施設共同、無作為化、二重盲検、実薬対照、並行群間、比較試験	ポサコナゾール経口懸濁液、フルコナゾールカプセル剤 ・ポサコナゾール群 経口懸濁液200 mg を1日3回食事とともに経口投与 ・フルコナゾール群 フルコナゾールカプセル剤を400 mg 1日1回食事条件を規定せず経口投与	ポサコナゾール群：301 フルコナゾール群：299	侵襲性真菌症のハイリスク患者（同種造血幹細胞移植後の移植片対宿主病）	16週間又は侵襲性真菌症の発症まで	完了 完全な報告書
第Ⅲ相（評価資料）	P02952（海外）	[資料5.3.5.1.3: P02952]	有効性の比較・評価	P00041 試験及び P02387試験の比較試験	P00041試験及び P02387試験参照	P00041試験及び P02387試験参照	標準抗真菌治療が無効又は不耐容の侵襲性真菌症	P00041試験及び P02387試験参照	完了 完全な報告書

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表 2.7.6.1-1臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅱ相（参考資料）	P01893（海外）	[資料5.3.5.1.4: P01893]	安全性、忍容性、有効性及び薬物動態の評価	多施設共同、非盲検、無作為化、用量比較試験	ポサコナゾール経口懸濁液 ・400 mg BID 群 経口懸濁液400 mg を1日2回（投与開始から2日間は200 mg を1日4回）、食事とともに又は食後直ちに経口投与 ・600 mg BID 群 経口懸濁液600 mg を1日2回（投与開始から2日間は400 mg を1日4回）、食事とともに又は食後直ちに経口投与 ・800 mg QD 群 経口懸濁液800 mg を1日1回（投与開始から2日間は800 mg を1日2回）、食事とともに又は食後直ちに経口投与	400 mg BID 群：35 600 mg BID 群：31 800 mg QD 群：32	難治性侵襲性真菌症又は発熱性好中球減少症	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	完了 完全な報告書
第Ⅲ相（評価資料）	P101（国内）	[資料5.3.5.1.5: P101]	安全性及び有効性の比較・評価	多施設共同、実薬対照、非盲検比較試験	ポサコナゾール［静注用溶液又は新錠剤 D（黄色）のいずれかを選択する］、ボリコナゾール（注射用ボリコナゾール又はボリコナゾール錠のいずれかを選択する） ・ポサコナゾール群 静注用溶液300 mg を1日1回（治験薬投与1日目は1日2回）中心静脈内投与又は新錠剤300 mg を1日1回（治験薬投与1日目は1日2回）経口投与 ・ボリコナゾール群 注射用ボリコナゾール4 mg/kg（治験薬投与1日目は6 mg/kg）を1日2回静脈内投与又はボリコナゾール錠200 mg（治験薬投与1日目は300 mg）を1日2回経口投与	・コホート1 ポサコナゾール群：15 ボリコナゾール群：7 ・コホート2 ポサコナゾール群：63 ボリコナゾール群：31	深在性真菌症	84日間	完了 完全な報告書

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表 2.7.6.1-1臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
第Ⅲ相（評価資料）	P00041（海外）	[資料5.3.5.2.1: P00041]	安全性、忍容性及び有効性の評価	多施設共同、非対照、非盲検試験	ポサコナゾール経口懸濁液 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 を1日4回、退院後は400 mgを1日2回、外来被験者には、ポサコナゾール経口懸濁液400 mgを1日2回、いずれも食事又は栄養補助剤とともに経口投与	336	標準抗真菌治療が無効又は不耐容の侵襲性真菌症	28日間以上かつ侵襲性真菌症の症状の回復後7日間以上（最長365日） なお、以下の疾患では別途投与期間を設定した。 ・カンジダ血症、播種性／転移性（深部器官）、肝脾カンジダ症、カンジダ心内膜炎： 14日間以上かつ症状の回復後7日間以上 ・好中球減少症（完全奏効例）： 好中球減少症の回復後14日間以上	完了 完全な報告書
第Ⅲ相（評価資料）	P02387（海外）	[資料5.3.5.2.2: P02387]	有効性のデータベースをレトロスペクティブに構築	多施設共同、レトロスペクティブ、カルテレビュー試験	ポサコナゾール以外の標準的抗真菌治療（アムホテリシン B 製剤、アゾール系抗真菌薬等）。 なお、治験薬（ポサコナゾール）の投与はしていない	2073（スクリーニング例）	標準的抗真菌治療が無効又は不耐容の侵襲性真菌症	- （治験薬は投与せず）	完了 完全な報告書
第Ⅱ相（参考資料）	C/I97-280（海外）	[資料5.3.5.2.3: CI97_280]	安全性、忍容性及び有効性の評価	多施設共同、非盲検、非対照試験	ポサコナゾール旧カプセル ポサコナゾール旧カプセルを400 mg 1日1回食事とともに経口投与	20	慢性活動性肺コクシジオイデス症又は非髄膜性播種性コクシジオイデス症	6ヵ月間	完了 完全な報告書

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表 2.7.6.1-1臨床試験一覧（続き）

試験の種類（資料の分類）	試験番号（国内／海外）	報告書を添付した場所	試験の目的	試験デザイン	治験薬 投与方法 投与経路	被験者数（例）	対象（健康被験者又は診断名）	投与期間	試験の進行状況・報告書の種類
後期第Ⅲ相（参考資料）	P02095（海外）	[資料5.3.5.2.4: P02095]	安全性の評価	多施設共同、非対照、非盲検、治療使用（treatment-use）試験	ポサコナゾール経口懸濁液 ・重篤な疾患を有する被験者 ポサコナゾール経口懸濁液200 mg を1日4回（状態安定後は400 mg を1日2回）食事又は栄養補助剤とともに経口又は経腸投与 ・状態が安定している外来の被験者 ポサコナゾール経口懸濁液400 mg を1日2回食事又は栄養補助剤とともに経口投与 ・体重34 kg 未満の被験者 ポサコナゾール経口懸濁液を書面で指示した投与レジメンで投与 ・小児被験者 ポサコナゾール経口懸濁液を体重に応じ以下の用量で1日2回食事とともに経口投与 ≥34 kg：400 mg 20-33.9 kg：200 mg 15-19.9 kg：100 mg ＜15 kg：6 mg/kg	治験データベース：985 Global Pharmacovigilance（GPV）データベース：989	臨床的に適切な治療がすべて無効又はポサコナゾールを用いた維持療法の継続若しくは二次予防が必要な侵襲性真菌症	28日間以上又は一部奏効以上の臨床症状効果が認められるまで投与 なお、以下の疾患では別途投与期間を設定した。 ・カンジダ血症、播種性／転移性（深部器官）、肝脾カンジダ症、カンジダ心内膜炎：14日間以上又は症状の回復後7日間以上 ・好中球減少症（完全奏効例）：好中球減少症の回復後14日間以上	完了 完全な報告書
本申請製造販売承認申請資料では、治験総括報告書の記載にかかわらず、試験自体の相を記載した。 AC：肺胞上皮細胞、BA：バイオアベイラビリティ、CYP：チトクロム P450、ELF：肺上皮被膜液、HIV：ヒト免疫不全ウイルス、QD：1日1回、BID：1日2回									

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2.7.6.2　個々の臨床薬理試験のまとめ

2.7.6.2.1　非日本人健康被験者を対象とした新錠剤 D（黄色）の絶対的バイオアベイラビリティ及び反復経口投与試験（P07783試験）［参考資料］

治験総括報告書[資料5.3.1.1.1: P07783]の概要を以下に示す。

2.7.6.2.1.1　試験方法

治験実施計画書標題／番号

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 D（黄色）の絶対的バイオアベイラビリティの評価及び反復投与時の薬物動態を評価する並行群間、薬物動態試験／P07783試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第 I 相

目的

【パート1：主要目的】

健康被験者を対象として、ポサコナゾール新錠剤 D（黄色、市販予定製剤）300 mg を単回経口投与した際の、ポサコナゾール静注用溶液300 mg 単回末梢静脈内投与に対する絶対的バイオアベイラビリティを評価する。

【パート1：副次目的】

健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）を単回経口投与及び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際の安全性及び忍容性を評価する。

【パート2：主要目的】

健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）300 mg を1日1回（1日目は1日2回）8日間反復経口投与した際の定常状態の薬物動態を評価する。

【パート2：副次目的】

健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）300 mg を1日1回（1日目は1日2回）8日間反復経口投与した際の安全性及び忍容性を評価する。

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試験デザイン

【パート1】

健康被験者を対象とした、ポサコナゾール静注用溶液に対する新錠剤 D（黄色）の絶対的バイオアベイラビリティを評価する非盲検、無作為化、2期クロスオーバー、単回投与試験であった。第1期又は第2期にポサコナゾール新錠剤 D（黄色）300 mg（処置 A）又はポサコナゾール静注用溶液300 mg（処置 B）のいずれかを投与した。投与期の間は10日以上間隔を空けた。

【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 D（黄色）の薬物動態を評価する非盲検、1期、反復投与試験であった。ポサコナゾール新錠剤 D（黄色）300 mg を1日1回8日間（1日目は1日2回）反復経口投与した（処置 C）。

投与期間

処置 A 及び B：単回

処置 C：反復（8日間）

用法・用量

処置 A 及び B はいずれも10時間絶食後、ポサコナゾール新錠剤 D（黄色）又は静注用溶液をそれぞれ単回投与した。

処置 C は、ポサコナゾール新錠剤 D（黄色）を1日目は1日2回（初回は10時間以上絶食後、2回目は食後）、以降2～8日目はいずれも10時間以上絶食後に1日1回反復経口投与した。

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg（100 mg×3錠）を空腹時に単回経口投与

処置 B：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

処置 C：ポサコナゾール新錠剤 D（黄色）300 mg（100 mg×3錠）を1日1回8日間
［1日目は1日2回（初回は空腹時、2回目は食後）］空腹時に反復経口投与

治験薬の内容を、[表 2.7.6.2.1-1]に示す。

表 2.7.6.2.1-1　治験薬の内容（P07783 試験）

薬剤	力価	剤形
ポサコナゾール新錠剤 D（黄色）	ポサコナゾール100 mg	錠剤
ポサコナゾール静注用溶液	ポサコナゾール18 mg/mL	注射剤

診断／選択基準

スクリーニング時に体格指数（BMI）が18 kg/m^{2}以上30 kg/m^{2}以下で、18歳以上65歳以下の健康な男性及び女性

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評価基準

【パート1：薬物動態】

血漿中薬物濃度測定用検体は、投与前及び投与開始後168時間までの規定した時点で採取した。

ポサコナゾールの薬物動態パラメータ［C_{max}、T_{max}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、$t_{1/2}$、消失速度定数（k_{el}）、CL 又は CL/F、V_d 又は V_d/F、バイオアベイラビリティ（F）等］を算出した。

【パート2：薬物動態】

血漿中薬物濃度測定用検体は、1、6、7及び8日目の投与前並びに8日目の投与後168時間までの規定した時点で採取した。

定常状態におけるポサコナゾールの薬物動態パラメータ C_{max}、$C_{24\ hr}$、平均濃度（C_{avg}）、T_{max}、$AUC_{0\text{-}24\ hr}$、$t_{1/2}$、k_{el}、CL/F、V_d/F を算出した。

【安全性】

バイタルサイン、身体所見（パート1のみ注入部位の局所忍容性、血栓性静脈炎も評価）心電図、臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

血漿中濃度は、試験パート及び処置ごとに要約した。各時点の血漿中濃度は、要約統計量を示した。

薬物動態パラメータは、試験パート、被験者、投与順序、投与期及び処置ごとに一覧で示した。

処置ごとに、各時点の被験者の血漿中濃度を線形及び片対数尺度でプロットした。また、平均血漿中濃度を、各時点に対して、線形及び片対数尺度でプロットした。パート1でポサコナゾールを末梢静脈内投与及び経口投与した際の個々の被験者の血漿中濃度を同じグラフに重ねてプロットした。

【パート1：絶対的バイオアベイラビリティの評価】

ポサコナゾールの $AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$の対数変換値に対して、処置及び投与期を固定効果、無構造型の共分散行列を用いた線形混合効果モデルを用いて解析した。静注用溶液に対する新錠剤D（黄色）の幾何平均比を、絶対的バイオアベイラビリティの推定値として算出し、90%信頼区間も算出した。C_{max} についても $AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$と同様に解析した。

【パート2：定常状態の薬物動態の評価】

定常状態は、投与日を固定効果、無構造型の共分散行列を用いた線形混合効果モデルを6、7及び8日目のトラフ濃度（C_{trough}）の対数変換値を用いて評価した。各投与日と以降の投与日の平均値の比の推定値及び90%信頼区間を示した。反復投与時の定常状態を図も用いて評価した。6、7

及び8日目の投与前の C_{trough} の平均値を、時間に対して、線形尺度でプロットした。

【安全性】

ポサコナゾール新錠剤 D（黄色）及び静注用溶液を投与した際の安全性及び忍容性を、有害事象の臨床評価及び安全性に関するその他の評価に基づき検討した。臨床検査値、心電図及びバイタルサインの要約統計量を算出して示した。すべての安全性パラメータは要約統計量を算出した。

2.7.6.2.1.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.1-2]及び[表 2.7.6.2.1-3]に示す。

表 2.7.6.2.1-2　　被験者の内訳（P07783 試験）

	パート1				パート2		合計	
	投与順序 AB		投与順序 BA		処置 C			
	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	7		6		12		25	
内訳								
完了	7	(100.0)	6	(100.0)	11	(91.7)	24	(96.0)
中止	0	(0.0)	0	(0.0)	1	(8.3)	1	(4.0)
有害事象	0	(0.0)	0	(0.0)	1	(8.3)	1	(4.0)

Data source: [資料5.3.1.1.1: P07783] Table 14.1-1

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表 2.7.6.2.1-3　　被験者の背景（P07783 試験）

	パート1				パート2		合計	
	投与順序 AB		投与順序 BA		処置 C			
	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	7		6		12		25	
性別								
男性	5	(71.4)	4	(66.7)	6	(50.0)	15	(60.0)
女性	2	(28.6)	2	(33.3)	6	(50.0)	10	(40.0)
年齢（歳）								
算術平均	37.4		34.7		35.9		36.0	
標準偏差	12.39		12.64		12.36		11.95	
中央値	36.0		32.0		34.0		35.0	
範囲	24 - 61		20 - 51		19 - 55		19 - 61	
体重（kg）								
算術平均	79.91		73.53		75.21		76.12	
標準偏差	14.871		10.921		16.891		14.737	
中央値	76.40		71.70		74.60		75.00	
範囲	61.6 - 99.8		57.4 - 90.2		53.0 - 100.8		53.0 - 100.8	
身長（cm）								
算術平均	179.6		170.0		172.7		174.0	
標準偏差	8.62		8.58		10.55		9.94	
中央値	181.0		172.0		173.5		173.0	
範囲	169 - 190		156 - 181		151 - 185		151 - 190	
BMI（kg/m^2）								
算術平均	24.64		25.35		24.97		24.97	
標準偏差	3.027		2.456		3.658		3.122	
中央値	25.40		24.20		24.55		24.50	
範囲	19.7 - 27.9		23.3 - 29.3		19.8 - 29.8		19.7 - 29.8	
人種								
白人	3	(42.9)	3	(50.0)	5	(41.7)	11	(44.0)
黒人又はアフリカ系アメリカ人	4	(57.1)	3	(50.0)	7	(58.3)	14	(56.0)
民族								
ヒスパニック系又はラテン系	0	(0.0)	2	(33.3)	3	(25.0)	5	(20.0)
非ヒスパニック系又は非ラテン系	7	(100.0)	4	(66.7)	9	(75.0)	20	(80.0)

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
処置 B：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
処置 C：ポサコナゾール新錠剤 D（黄色）300 mg を1日1回8日間空腹時に反復経口投与

Data source: [資料5.3.1.1.1: P07783] Table 14.1-2.1, 14.1-2 2

2.7.6.2.1.3　　薬物動態の結果

パート1：絶対的バイオアベイラビリティ

本試験のパート1では、ポサコナゾール新錠剤 D（黄色）及び静注用溶液をいずれかの投与順序で投与した被験者13例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者に空腹時にポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与又は静注用溶液300 mg を単回末梢静脈内投与した際の血漿中薬物動態パラメータの要約及び比較を[表 2.7.6.2.1-4]及び[表 2.7.6.2.1-5]に示す。

ポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与した際の C_{max} の算術平均（614 ng/mL）は、静注用溶液300 mg を末梢静脈内投与した際の C_{max} の算術平均（4258 ng/mL）の約1/7であった。ポサコナゾール新錠剤 D（黄色）及び静注用溶液の T_{max} の中央値はそれぞれ5時間及び0.50時間（投与終了時点）であった。

ポサコナゾール新錠剤 D（黄色）の $AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$ の算術平均（それぞれ22722及び23647 ng·hr/mL）は、静注用溶液の算術平均（それぞれ42905及び44380 ng·hr/mL）の約1/2であった。ポサコナゾール静注用溶液に対する新錠剤 D（黄色）の絶対的バイオアベイラビリティ（$AUC_{0\text{-}\infty}$）は幾何平均比（90%信頼区間）で0.51（0.43, 0.61）であった。

ポサコナゾールの $t_{1/2}$ の算術平均は、新錠剤 D（黄色）で約28時間、静注用溶液で約29時間であり、製剤間で同程度であった。新錠剤の CL/F 及び V_d/F はそれぞれ15.4 L/hr 及び583 L であり、静注用溶液の CL 及び V_d はそれぞれ7.6 L/hr 及び295 L であった。

表 2.7.6.2.1-4　健康被験者に空腹時にポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与又は静注用溶液 300 mg を単回末梢静脈内投与した際の血漿中薬物動態パラメータの要約（P07783 試験、パート 1）

薬物動態パラメータ	処置 A N = 13	処置 B N = 13
C_{max} (ng/mL)	613.8 (37.9)	4257.7 (19.1)
T_{max} (hr)	5.00 (2.98 - 6.00)	0.50 (0.25 - 0.50)
$t_{1/2}$ (hr)	28.1 (25.6)	28.8 (27.8)
$AUC_{0\text{-}last}$ (ng·hr/mL)	22721.9 (46.0)	42904.7 (30.7)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	23647.3 (47.8)	44380.4 (32.2)
V_d 又は V_d/F (L)	583.3 (36.0)	294.6 (24.8)
CL 又は CL/F (L/hr)	15.4 (45.8)	7.6 (41.4)

算術平均（%CV）ただし、T_{max} は中央値（範囲）
処置 A：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
処置 B：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
CV：変動係数

Data source: [資料5.3.1.1.1: P07783] Table 14.2-1.3

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表 2.7.6.2.1-5　健康被験者に空腹時にポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与又は静注用溶液 300 mg を単回末梢静脈内投与した際の血漿中薬物動態パラメータの比較（P07783 試験、パート 1）

薬物動態パラメータ	処置 B N=13‡		処置 A N=13‡		比（A/B）		被験者内 %CV
	GM	90%CI	GM	90%CI	GMR	90%CI	
$AUC_{0-\infty}$ (ng·hr/mL) †	41942.45	(35096.46, 50123.83)	21450.06	(17042.41, 26997.66)	0.511	(0.427, 0.612)	25.53
AUC_{0-last} (ng·hr/mL) †	40648.00	(34174.18, 48348.18)	20665.59	(16402.51, 26036.66)	0.508	(0.423, 0.611)	25.98
C_{max} (ng/mL) †	4175.99	(3735.51, 4668.40)	571.51	(467.11, 699.24)	0.137	(0.112, 0.168)	28.94

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
処置 B：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
CI：信頼区間、CV：変動係数、GM：幾何平均、GMR：幾何平均比
† 混合効果モデルからの最小二乗平均及び信頼区間の自然対数変換値を逆変換した。
‡ 混合効果モデルの解析に含まれる被験者数

Data source: [資料5.3.1.1.1: P07783] Table 14 2-2.1

<u>パート2：定常状態の薬物動態の評価</u>

本試験のパート2では、ポサコナゾール新錠剤 D（黄色）を投与した被験者11例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を1日1回8日間（1日目は1日2回）反復経口投与した際の定常状態（8日目）の血漿中薬物動態パラメータの要約を[表 2.7.6.2.1-6]に示す。

ポサコナゾール新錠剤 D（黄色）300 mg を反復経口投与した際、6、7及び8日目の血漿中 C_{trough} の最小二乗平均（90%信頼区間）はそれぞれ1646（1414, 1917）、1749（1504, 2033）及び1717（1462, 2018）ng/mL で、6日目までに定常状態に到達した。

表 2.7.6.2.1-6　健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を 1 日 1 回 8 日間（1 日目は 1 日 2 回）反復経口投与した際の定常状態（8 日目）における血漿中薬物動態パラメータの要約（P07783 試験、パート 2）

薬物動態パラメータ	処置 C N=11
C_{max} (ng/mL)	2763.6 (20.6)
T_{max} (hr)	3.98 (3.00 - 6.03)
$t_{1/2}$ (hr)	34.9 (39.6)
$AUC_{0-24\ hr}$ (ng·hr/mL)	51618.0 (25.4)
$C_{24\ hr}$ (ng/mL)	1784.7 (28.5)
C_{avg} (ng/mL)	2150.8 (25.4)
V_d/F (L)	294.3 (29.5)
CL/F (L/hr)	6.2 (25.6)

算術平均（%CV）ただし、T_{max} は中央値（範囲）
処置 C：ポサコナゾール新錠剤 D（黄色）300 mg を1日1回8日間空腹時に反復経口投与
CV：変動係数

Data source: [資料5.3.1.1.1: P07783] Table 14.2-1.4

2.7.6.2.1.4　　安全性の結果

パート1：安全性

本試験のパート1では、治験薬を投与した全被験者13例を安全性解析対象集団に含めた。健康被験者にポサコナゾール新錠剤 D（黄色）300 mg 及び静注用溶液300 mg を単回経口投与又は単回末梢静脈内投与した際、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、有害事象で中止した被験者もいなかった。ポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与した被験者13例中3例に合計5件の有害事象が認められた。軽度の有害事象が2例に2件認められ、中等度の有害事象が1例に3件認められ、いずれも副作用ではないと判定された。ポサコナゾール静注用溶液300 mg を末梢静脈内投与した被験者13例中3例に合計6件の有害事象が認められ、軽度及び中等度の有害事象がそれぞれ4件及び2件であった。このうち4件（緊張性頭痛2件、悪心1件、静脈炎1件）は副作用と判定され、被験者3例に認められた。

その他すべての臨床検査値、バイタルサイン及び心電図の経時的な値及びベースラインからの変化に意味のある一貫した変化は認められなかった。

パート2：安全性

本試験のパート2では、治験薬を投与した全被験者12例を安全性解析対象集団に含めた。健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を1日1回8日間（1日目は1日2回）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、妊娠及び死亡はなかった。ポサコナゾール新錠剤 D（黄色）300 mg を反復経口投与した被験者12例中9例に合計39件の有害事象が認められた。軽度の有害事象は8例に33件、中等度の有害事象は5例に6件認められ、このうち8例に認められた有害事象26件は、副作用と判定された。

最もよくみられた有害事象は器官別大分類の「胃腸障害」であり、悪心（3例）、下痢（3例）、腹痛（2例）、便秘（2例）、腹部膨満（1例）及び歯痛（1例）が含まれた。便秘の1件及び歯痛を除き、これらの胃腸障害はいずれも副作用と判定された。器官別大分類の「一般・全身障害および投与部位の状態」では胸痛2例、疲労2例が認められた。疲労はいずれも副作用と判定された。1例の被験者で中等度の胸痛がみられ、副作用と判定され、試験中止に至った。1例に有害事象の軽度の肝酵素上昇［最も高かった異常値は、アラニンアミノトランスフェラーゼ（ALT）では基準値上限の4.1倍、アスパラギン酸アミノトランスフェラーゼ（AST）では基準値上限の2.1倍］が認められ、本事象は副作用と判定されたが試験終了までに回復した。

その他すべての臨床検査値（肝酵素上昇の有害事象を除く）、バイタルサイン及び心電図の経時的な値及びベースラインからの変化に意味のある一貫した変化は認められなかった。

2.7.6.2.1.5　　結論

パート1：薬物動態、絶対的バイオアベイラビリティ

1)　ポサコナゾール新錠剤 D（黄色）300 mg 及び静注用溶液300 mg を単回投与した際の絶対的バイオアベイラビリティの幾何平均比は0.51であった。

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パート2：薬物動態、定常状態の薬物動態

2)　ポサコナゾール新錠剤 D（黄色）300 mg を1日1回（1日目は1日2回）8日間反復経口投与した結果、定常状態には6日目までに到達した。

安全性

3)　ポサコナゾール新錠剤 D（黄色）300 mg の単回経口投与、静注用溶液300 mg の単回末梢静脈内投与及び新錠剤 D（黄色）300 mg の1日1回（1日目は1日2回）8日間反復経口投与は、安全で忍容性は良好であった。

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2.7.6.2.2　非日本人健康被験者を対象とした旧錠剤及び旧カプセルの相対的バイオアベイラビリティに対する食事の影響試験（[redacted]-099試験）［参考資料］

治験総括報告書[資料5.3.1.2.1: [redacted]_099]の概要を以下に示す。

2.7.6.2.2.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象とした2つの経口製剤（旧錠剤及び旧カプセル）の相対的バイオアベイラビリティに対する食事の影響試験／[redacted]-099試験

治験責任医師／実施医療機関

[redacted]（オランダ）

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

健康被験者を対象として、ポサコナゾール旧錠剤及び旧カプセルを空腹時又は高脂肪食摂取後に投与した際の相対的バイオアベイラビリティを評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾールの2種類の剤形（旧錠剤及び旧カプセル）を投与した際の相対的バイオアベイラビリティに対する食事の影響を評価する、非盲検、無作為化、4期クロスオーバー、単回投与試験であった。ポサコナゾール旧錠剤（処置 B）又は旧カプセル（処置 D）を高脂肪食摂取後に単回経口投与した。さらに、ポサコナゾール旧錠剤（処置 A）又は旧カプセル（処置 C）を空腹時に単回経口投与した。投与期の間は7日以上間隔を空けた。

投与期間

単回

用法・用量

処置 B 及び D はポサコナゾール旧錠剤又は旧カプセルをいずれも高脂肪食摂取後にそれぞれ単回経口投与した。処置 A 及び C はポサコナゾール旧錠剤又は旧カプセルをいずれも10時間絶食後、それぞれ単回経口投与した。

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処置 A：ポサコナゾール旧錠剤200 mg（100 mg×2錠）を空腹時に単回経口投与
処置 B：ポサコナゾール旧錠剤200 mg（100 mg×2錠）を高脂肪食摂取後に単回経口投与
処置 C：ポサコナゾール旧カプセル200 mg（100 mg×2カプセル）を空腹時に単回経口投与
処置 D：ポサコナゾール旧カプセル200 mg（100 mg×2カプセル）を高脂肪食摂取後に単回経口投与
治験薬の内容を、[表 2.7.6.2.2-1]に示す。

表 2.7.6.2.2-1　　治験薬の内容（[redacted]-099 試験）

薬剤	力価	剤形
ポサコナゾール旧錠剤	ポサコナゾール100 mg	錠剤
ポサコナゾール旧カプセル	ポサコナゾール100 mg	カプセル剤

診断／選択基準
スクリーニング時に保険数理表に基づく体重の±15%以内の体重で、18歳以上60歳以下の健康な男性又は女性

評価基準
【薬物動態】
血漿中薬物濃度測定用検体は、投与前及び投与後72時間までの規定した時点で採取した。ポサコナゾールの薬物動態パラメータ（AUC、C_{max}、T_{max} 及び $t_{1/2}$等）を算出した。

【安全性】
バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析
【薬物動態】
クロスオーバーデザイン型の分散分析モデルを用いて薬物動態パラメータの解析を実施した。空腹時に投与した旧錠剤と旧カプセル間、高脂肪食摂取後に投与した旧錠剤と旧カプセル間、旧錠剤の高脂肪食摂取後投与と空腹時投与間、旧カプセルの高脂肪食摂取後投与と空腹時投与間の薬物動態を比較した。

【安全性】
ポサコナゾール旧錠剤及び旧カプセルを空腹時又は高脂肪食摂取後に投与した際の安全性及び忍容性を、有害事象の臨床評価及び安全性に関するその他の評価に基づき検討した。安全性に関

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する臨床検査値、心電図及びバイタルサインの要約統計量を算出して示した。すべての安全性パラメータに対して要約統計量を算出した。

2.7.6.2.2.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.2-2]及び[表 2.7.6.2.2-3]に示す。

表 2.7.6.2.2-2　　被験者の内訳（[redacted]-099 試験）

	合計 n	(%)
総被験者数	24	
内訳		
完了	21	(87.5)
中止	3	(12.5)
有害事象	3†	(12.5)

† 被験者1例は肝機能検査値上昇により処置 B の投与後に試験を中止した。別の被験者1例は、心電図異常により処置 A の投与後に試験を中止した。もう1例の被験者は、足関節部骨折により、処置 A の投与後に試験を中止した。

Data source: [資料5 3 1 2 1: [redacted]_099] Appendix B-4 Subject Listing

表 2.7.6.2.2-3　　被験者の背景（[redacted]-099 試験）

	男性 n	女性 n
総被験者数	12	12
年齢（歳）		
算術平均	32.6	53.2
中央値	24	56
範囲	18 - 60	44 - 60
人種		
アジア系	0	1
黒人	1	0
白人	11	11
身長（cm）		
算術平均	182.5	164.6
中央値	182.5	165.0
範囲	176.0 - 187.0	153.0 - 173.0
体重（kg）		
算術平均	80.2	67.9
中央値	81.0	66.5
範囲	67.0 - 91.0	53.0 - 88.0

Data source: [資料5.3.1.2.1: [redacted]_099] Appendix B-4 Demographic Profile

2.7.6.2.2.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者21例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール旧錠剤及び旧カプセル200 mg を空腹時又は高脂

肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.2-4]、空腹時投与に対する高脂肪食摂取後投与及び旧錠剤に対する旧カプセルの比較を[表 2.7.6.2.2-5]に示す。

高脂肪食摂取後に投与した際の C_{max} 及び $AUC_{0-\infty}$は、空腹時投与と比べていずれも高く、旧錠剤ではそれぞれ空腹時投与の5.1倍及び3.5倍、旧カプセルではそれぞれ5.2倍及び4倍に相当した。

空腹時及び高脂肪食摂取後投与において、旧錠剤及び旧カプセルの製剤間でポサコナゾールの血漿中濃度推移は概して類似していた。旧錠剤に対する旧カプセルの曝露量の比は同程度又は旧カプセルでやや高かった（点推定値の範囲：C_{max} で1.18 - 1.22、$AUC_{0-\infty}$で1.00 - 1.15）。

表 2.7.6.2.2-4　健康被験者にポサコナゾール旧錠剤及び旧カプセル 200 mg を空腹時又は高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約（[redacted]-099 試験）

薬物動態パラメータ	処置 A (n=21)	処置 B (n=21)	処置 C (n=21)	処置 D (n=21)
C_{max} (ng/mL)	85.4 (38)	431.7 (28)	102.3 (39)	531.4 (32)
T_{max} (hr)	3.98 (39)	6.24 (37)	3.95 (40)	5.05 (16)
$AUC_{0-\infty}$ (ng·hr/mL)	3585 (35)	12505 (38)	3588 (37)	14293 (38)
$t_{1/2}$ (hr)	29.0 (29)	25.5 (30)	28.7 (26)	26.1 (29)

算術平均（%CV）
処置 A：ポサコナゾール旧錠剤200 mg を空腹時に単回経口投与
処置 B：ポサコナゾール旧錠剤200 mg を高脂肪食摂取後に単回経口投与
処置 C：ポサコナゾール旧カプセル200 mg を空腹時に単回経口投与
処置 D：ポサコナゾール旧カプセル200 mg を高脂肪食摂取後に単回経口投与
CV：変動係数

Data source: [資料5.3.1.2.1: [redacted]_099] Appendix B-1 Display 2

表 2.7.6.2.2-5　健康被験者にポサコナゾール旧錠剤及び旧カプセル 200 mg を空腹時又は高脂肪食摂取後に単回経口投与した際の空腹時投与に対する高脂肪食摂取後投与及び旧錠剤に対する旧カプセルの比較（[redacted]-099 試験）

薬物動態パラメータ	比	点推定値	90%CI
C_{max}	処置 B／処置 A	5.136	4.25, 6.21
	処置 D／処置 C	5.307	4.39, 6.42
	処置 C／処置 A	1.178	0.97, 1.42
	処置 D／処置 B	1.217	1.01, 1.47
$AUC_{0-\infty}$	処置 B／処置 A	3.434	2.99, 3.95
	処置 D／処置 C	3.955	3.44, 4.55
	処置 C／処置 A	0.997	0.87, 1.15
	処置 D／処置 B	1.148	1.00, 1.32

処置 A：ポサコナゾール旧錠剤200 mg を空腹時に単回経口投与
処置 B：ポサコナゾール旧錠剤200 mg を高脂肪食摂取後に単回経口投与
処置 C：ポサコナゾール旧カプセル200 mg を空腹時に単回経口投与
処置 D：ポサコナゾール旧カプセル200 mg を高脂肪食摂取後に単回経口投与
CI：信頼区間

Data source: [資料5.3.1.2.1: [redacted]_099] Appendix B-1 Display 7

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2.7.6.2.2.4　　安全性の結果

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。健康被験者にポサコナゾール旧錠剤200 mg 又は旧カプセル200 mg をそれぞれ空腹時又は高脂肪食摂取後に単回経口投与した際の忍容性は概して良好であった。重篤な有害事象が2例の被験者に認められた。妊娠及び死亡は認められなかった。被験者3例が有害事象により試験を中止した。24例中20例で有害事象が認められ、このうち12例で副作用が認められた。ほとんどの有害事象は軽度と判定され、処置又は血漿中ポサコナゾール濃度との明確な関連はなかった。1例は、副作用と判定された肝機能検査値上昇により、旧錠剤200 mg を高脂肪食摂取後に投与した後に試験を中止した。当該被験者は、旧錠剤200 mg を高脂肪食摂取後に投与した後に軽度の ALT 上昇（グレード1）を発現したが、AST、乳酸脱水素酵素（LDH）及びアルカリホスファターゼ（ALP）値は正常であり、予定通り投与した。旧カプセル200 mg の投与前（空腹時）に ALT 値がグレード2に上昇し重篤な有害事象として判定された。軽度の AST 上昇（グレード1）もみられたが、LDH 及び ALP 値は正常であった。γ-グルタミルトランスペプチダーゼ（γ-GTP）値は旧錠剤200 mg の投与前（空腹時）から事後検査まで、軽度の上昇を示した。投与中止後約2週間の事後検査時の ALT 及び AST は基準値内であった。その後、治験参加1年前に原因不明の肝機能検査異常が認められていたことが当該被験者により明らかになった。別の1例では、旧錠剤200 mg を空腹時に投与した後の心電図に T 波平低化及び QTc 延長が認められ（最大で投与後約6.5時間後に475 msec）、副作用と判定された。また、旧錠剤200 mg を空腹時に投与したのみで試験を中止した。心臓専門医により、「この変化は非特異的なものである」と評価された。投与後72時間の事後検査時の心電図はベースライン値に復した。当該被験者の旧錠剤200 mg を空腹時に投与した際の血漿中ポサコナゾール C_{max} 及び AUC は、旧錠剤200 mg を空腹時に投与した他の被験者と類似しており、臨床的に意味のある心電図の異常が認められなかった旧錠剤200 mg 及び旧カプセル200 mg を高脂肪食摂取後に投与した他の被験者の濃度よりも低かった。別の1例が、足関節部骨折の重篤な有害事象により旧錠剤200 mg を空腹時に投与した後に試験を中止した。本事象は副作用ではないと判定された。その他の臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.2.5　　結論

1) ポサコナゾール旧錠剤及び旧カプセルを空腹時及び高脂肪食摂取後に単回経口投与した際の血漿中ポサコナゾール濃度推移は概して類似していた。
2) ポサコナゾール旧錠剤及び旧カプセルを高脂肪食摂取後に単回経口投与した際の AUC に基づくバイオアベイラビリティは、空腹時に単回経口投与した際と比べ有意に高かった（空腹時投与の約3～4倍に相当）。
3) ポサコナゾールの曝露量と関連のある有害事象はみられなかった。

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2.7.6.2.3　非日本人健康被験者を対象とした経口懸濁液の相対的バイオアベイラビリティ試験（[redacted]-099試験）［参考資料］

治験総括報告書[資料5.3.1.2.2: [redacted]_099]の概要を以下に示す。

2.7.6.2.3.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としたポサコナゾール旧錠剤に対する経口懸濁液の相対的バイオアベイラビリティ試験／[redacted]-099試験

治験責任医師／実施医療機関

[redacted]（ドイツ）

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

健康被験者を対象として、ポサコナゾール経口懸濁液を高脂肪朝食摂取後に単回経口投与した際の、旧錠剤の単回経口投与に対する相対的バイオアベイラビリティを評価する。ポサコナゾール経口懸濁液を投与した際の相対的バイオアベイラビリティに対する高脂肪食及び無脂肪食の影響を空腹時と比較する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾールの2種類の剤形（経口懸濁液及び旧錠剤）を投与した際の相対的バイオアベイラビリティ及び相対的バイオアベイラビリティに対する食事の影響を評価する、非盲検、無作為化、4期クロスオーバー、単回投与試験であった。ポサコナゾール経口懸濁液200 mg を空腹時（処置 A）、高脂肪食（処置 B）又は無脂肪食（処置 C）摂取後、並びにポサコナゾール旧錠剤200 mg を高脂肪食摂取後（処置 D）に経口投与した。投与期の間は7日以上間隔を空けた。

投与期間

単回

用法・用量

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処置 A は10時間絶食後、ポサコナゾール経口懸濁液を単回経口投与した。処置 B、D はいずれも高脂肪食摂取後に経口懸濁液又は旧錠剤をそれぞれ単回経口投与した。処置 C は無脂肪食摂取後に経口懸濁液を単回経口投与した。

処置 A：ポサコナゾール経口懸濁液200 mg を空腹時に単回経口投与

処置 B：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

処置 C：ポサコナゾール経口懸濁液200 mg を無脂肪食摂取後に単回経口投与

処置 D：ポサコナゾール旧錠剤200 mg（100 mg×2錠）を高脂肪食摂取後に単回経口投与

治験薬の内容を、[表 2.7.6.2.3-1]に示す。

表 2.7.6.2.3-1　　治験薬の内容（[redacted]-099 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
ポサコナゾール旧錠剤	ポサコナゾール100 mg	錠剤

診断／選択基準

スクリーニング時に保険数理表に基づく体重の±15%以内の体重で、18歳以上45歳以下の健康な男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体は、投与前及び投与後72時間までの規定した時点で採取した。ポサコナゾールの薬物動態パラメータ（AUC、C_{max}、T_{max} 及び $t_{1/2}$等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

クロスオーバーデザイン型の分散分析モデルを用いて薬物動態パラメータの解析を実施した。高脂肪食摂取後に投与した経口懸濁液と旧錠剤を比較した。高脂肪食及び無脂肪食摂取後に投与した経口懸濁液を、空腹時に投与した経口懸濁液と比較した。

【安全性】

ポサコナゾール旧錠剤及び経口懸濁液を投与した際の安全性及び忍容性を、有害事象の臨床評

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価及び安全性に関するその他の評価に基づき検討した。安全性に関する臨床検査値、心電図及びバイタルサインの要約統計量を算出して示した。すべての安全性パラメータに対して要約統計量を算出した。

2.7.6.2.3.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.3-2]及び[表 2.7.6.2.3-3]に示す。

表 2.7.6.2.3-2　　被験者の内訳（[redacted]-099 試験）

	合計	
	n	(%)
総被験者数	20	
内訳		
完了	20	(100)
中止	0	(0.0)

Data source: [資料5.3.1.2.2: [redacted]_099] Appendix B-4 Subject Listing

表 2.7.6.2.3-3　　被験者の背景（[redacted]-099 試験）

	合計
	n
総被験者数	20
年齢（歳）	
算術平均	34.7
中央値	38
範囲	22 - 45
性別	
男性	20
人種	
白人	20
身長（cm）	
算術平均	180.6
中央値	181.5
範囲	170.0 - 197.0
体重（kg）	
算術平均	76.3
中央値	76.5
範囲	61.0 - 91.0

Data source: [資料5.3.1.2.2: [redacted]_099] Appendix B-4 Demographic Profile

2.7.6.2.3.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者20例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール経口懸濁液200 mg を空腹時、高脂肪食又は無脂肪食摂取後、並びにポサコナゾール旧錠剤200 mg を高脂肪食摂取後に単回経口投与した際の血漿

中薬物動態パラメータの要約を[表 2.7.6.2.3-4]、高脂肪食摂取後に投与した旧錠剤に対する経口懸濁液の相対的バイオアベイラビリティ、並びに経口懸濁液の相対的バイオアベイラビリティに対する高脂肪食及び無脂肪食の影響の解析結果を、それぞれ[表 2.7.6.2.3-5]並びに[表 2.7.6.2.3-6]に示す。

ポサコナゾールは緩やかに吸収され、T_{max} の算術平均は概して4.1～5.5時間の範囲であったが、空腹時にポサコナゾール経口懸濁液を単回経口投与した際に1例の被験者で T_{max} が投与後36時間となり、C_{max} にあたるその時点での濃度は45.7 ng/mL であった。そのため、T_{max} に大きなばらつきが示された。当該被験者の投与後4時間（他の被験者の T_{max} に相当する時点）の血漿中ポサコナゾール濃度は44 ng/mL で、36時間にわたり概して一定であった。投与後4時間及び36時間の血漿中濃度の差に大きな違いはなく、投与後4時間時点のデータを算出に用いた場合、T_{max} の算術平均は3.4時間となった。この経口懸濁液を空腹時に単回経口投与した際に認められた T_{max} の算術平均の3.4時間と比べ、無脂肪食摂取後にポサコナゾール経口懸濁液を単回経口投与した際の T_{max} は延長し、高脂肪食摂取後では更に延長した。

ポサコナゾールは投与後緩やかに消失し、いずれの処置でも $t_{1/2}$の算術平均は同程度で、約21～24時間であった。ポサコナゾール経口懸濁液を高脂肪食摂取後に単回経口投与した際の C_{max} 及び AUC の算術平均は、空腹時に投与した際より高く、約4倍に相当した。また、無脂肪食摂取後でも空腹時投与と比較して高い曝露量が認められたが、増加の程度は高脂肪食摂取後よりも小さく、空腹時投与に対し、C_{max} は約3倍、AUC は約2.5倍に相当した。

ポサコナゾール経口懸濁液を高脂肪食摂取後に単回経口投与した際の C_{max} 及び $AUC_{0\text{-}last}$ は、旧錠剤を投与した際と比べそれぞれ23%及び36%高かった。

表 2.7.6.2.3-4　健康被験者にポサコナゾール経口懸濁液 200 mg を空腹時、高脂肪食又は無脂肪食摂取後、並びにポサコナゾール旧錠剤 200 mg を高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約（[redacted]-099 試験）

薬物動態パラメータ	処置 A (n=20)	処置 B (n=20)	処置 C (n=20)	処置 D (n=20)
C_{max} (ng/mL)	132 (50)	512 (34)	378 (43)	413 (33)
T_{max} (hr)	5.0‡ (149)	4.8 (9)	4.1 (21)	5.5 (32)
$AUC_{0\text{-}last}$ (ng·hr/mL)	3553 (36)	13885 (41)	9511 (38)	10304 (41)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)†	4179 (31)	15059 (26)	10753 (35)	10304 (39)
$t_{1/2}$ (hr)†	23.5 (25)	23.0 (19)	22.2 (18)	21.1 (15)

算術平均（%CV）
処置 A：ポサコナゾール経口懸濁液200 mg を空腹時に単回経口投与
処置 B：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
処置 C：ポサコナゾール経口懸濁液200 mg を無脂肪食摂取後に単回経口投与
処置 D：ポサコナゾール旧錠剤200 mg を高脂肪食摂取後に単回経口投与
CV：変動係数
† n=15
‡ T_{max} が36時間となった被験者について、投与後4時間を T_{max} とした場合、T_{max} の算術平均（%CV）は3.4 (42)時間となる。

Data source: [資料5.3.1.2.2: [redacted]_099] Appendix B-1 Display 2

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表 2.7.6.2.3-5　健康被験者にポサコナゾール経口懸濁液又は旧錠剤 200 mg を高脂肪食摂取後に単回経口投与した際の経口懸濁液の旧錠剤に対する相対的バイオアベイラビリティ（[redacted]-099 試験）

薬物動態パラメータ	比	相対的バイオアベイラビリティ（%）	90%CI
C_{max}	処置 B／処置 D	123.3	104, 146
$AUC_{0\text{-}last}$ †	処置 B／処置 D	136.5	119, 156

処置 B：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
処置 D：ポサコナゾール旧錠剤200 mg を高脂肪食摂取後に単回経口投与
CI：信頼区間
† 全被験者のすべての投与について算出可能であったため $AUC_{0\text{-}last}$ を本比較に用いた。

Data source: [資料5.3.1.2.2: [redacted]_099] Appendix B-2 Section 3 Results and Discussion

表 2.7.6.2.3-6　健康被験者にポサコナゾール経口懸濁液 200 mg を高脂肪食摂取後又は無脂肪食摂取後に単回経口投与した際の相対的バイオアベイラビリティに対する高脂肪食及び無脂肪食の影響（[redacted]-099 試験）

薬物動態パラメータ	比	相対的バイオアベイラビリティ（%）	90%CI
C_{max}	処置 B／処置 A	417	352, 493
	処置 C／処置 A	296	250, 350
$AUC_{0\text{-}last}$	処置 B／処置 A	392	343, 448
	処置 C／処置 A	264	231, 302

処置 A：ポサコナゾール経口懸濁液200 mg を空腹時に単回経口投与
処置 B：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
処置 C：ポサコナゾール経口懸濁液200 mg を無脂肪食摂取後に単回経口投与
CI：信頼区間

Data source: [資料5.3.1.2.2: [redacted]_099] Appendix B-2 Section 3 Results and Discussion

2.7.6.2.3.4　安全性の結果

本試験では、治験薬を投与した全被験者20例を安全性解析対象集団に含めた。健康被験者にポサコナゾール経口懸濁液200 mg を空腹時、高脂肪食摂取後又は無脂肪食摂取後及びポサコナゾール旧錠剤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。20例中9例で有害事象が認められ、そのうち8例に副作用が認められた。最もよくみられた有害事象は頭痛（4例）及び疲労（4例）であった。1例で認められた中等度の歯肉炎を除き、いずれの有害事象も軽度であった。その他、臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.3.5　結論

1) 高脂肪食摂取後において、ポサコナゾール経口懸濁液投与時のバイオアベイラビリティは、旧錠剤投与時と比べ37%高かった。
2) 高脂肪食の摂取により、ポサコナゾール経口懸濁液のバイオアベイラビリティは空腹時投与の約4倍に上昇した。

3)　無脂肪食の摂取により、ポサコナゾール経口懸濁液のバイオアベイラビリティは空腹時投与の約2.5～3倍に上昇した。

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2.7.6.2.4　非日本人健康被験者を対象とした経口懸濁液、新カプセル及び新錠剤の相対的バイオアベイラビリティ試験（P04975試験）［参考資料］

治験総括報告書[資料5.3.1.2.3: P04975]の概要を以下に示す。

2.7.6.2.4.1　試験方法

治験実施計画書標題／番号

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と新カプセル及び新錠剤（A 及び B）のポサコナゾールの薬物動態を比較する試験／P04975試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第 I 相

目的

【主要目的】

健康被験者を対象として、ポサコナゾール新カプセル及び新錠剤（A 及び B）を空腹時及び高脂肪食摂取後に単回経口投与した際のポサコナゾールの薬物動態を、ポサコナゾール経口懸濁液を空腹時及び高脂肪食摂取後に投与した際の薬物動態とそれぞれ比較する。

【副次目的】

健康被験者を対象として、ポサコナゾール新カプセル及び新錠剤（A 及び B）を単回経口投与した際の安全性及び忍容性を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール新カプセル及び新錠剤（A 及び B）を空腹時及び高脂肪食摂取後に単回経口投与した際のポサコナゾールの薬物動態を、ポサコナゾール経口懸濁液を空腹時及び高脂肪食摂取後に投与した際の薬物動態とそれぞれ比較する、非盲検、部分無作為化、4期クロスオーバー、2パート、単回投与試験であった。2つの投与順序（各8例）に組み入れた。いずれの被験者にも、第1期にポサコナゾール経口懸濁液（処置 A）、第4期に新カプセル（処置 D）を投与し、第2期及び第3期で新錠剤 A（処置 B）又は新錠剤 B（処置 C）を投与する群のいずれかに無作為に割り付けた。投与期の間は7～10日以上間隔を空けた。パート1及

びパート2のいずれでも同じ投与順序で投与したが、パート1では空腹時、パート2では高脂肪食摂取後に投与した。

投与期間

単回

用法・用量

パート1の第1期にポサコナゾール経口懸濁液100 mg（処置 A）、第2期及び第3期に新錠剤 A（処置 B）又は新錠剤 B（処置 C）、第4期に新カプセル（処置 D）をいずれも10時間絶食後に単回経口投与した。パート2の第1期にポサコナゾール経口懸濁液100 mg（処置 A）、第2期及び第3期に新錠剤 A（処置 B）又は新錠剤 B（処置 C）、第4期に新カプセル（処置 D）をいずれも高脂肪朝食摂取後に単回経口投与した。

処置 A：ポサコナゾール経口懸濁液100 mg を単回経口投与

処置 B：ポサコナゾール新錠剤 A 100 mg（100 mg×1錠）を単回経口投与

処置 C：ポサコナゾール新錠剤 B 100 mg（100 mg×1錠）を単回経口投与

処置 D：ポサコナゾール新カプセル100 mg（100 mg×1カプセル）を単回経口投与

治験薬の内容を[表 2.7.6.2.4-1]に示す。

表 2.7.6.2.4-1　治験薬の内容（P04975 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
ポサコナゾール新錠剤 A	ポサコナゾール100 mg	錠剤
ポサコナゾール新錠剤 B	ポサコナゾール100 mg	錠剤
ポサコナゾール新カプセル	ポサコナゾール100 mg	カプセル剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^{2}以上32 kg/m^{2}以下で、18歳以上55歳以下の健康な男性又は女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、両パートの各期で1日目の投与前及び投与後168時間までの規定した時点で採取した。ポサコナゾールの血漿中薬物動態パラメータ（AUC_{0-t}、$AUC_{0-\infty}$、C_{max}、T_{max}、CL/F、V_d/F 及び $t_{1/2}$等）を算出した。

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【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

血漿中薬物濃度及び薬物動態パラメータの一覧表を作成し、要約統計量及びグラフを用いて各パートで処置ごとに要約した。

【安全性】

有害事象について、器官別大分類及び重症度ごとに表に示し、各パートで処置ごとに要約した。血液学的検査及び血液生化学検査の結果を被験者ごとに一覧にし、基準値から外れた値にマーカーを付けた。バイタルサイン測定及び心電図の結果を各パートで投与期及び評価時点ごとに一覧表にした。

2.7.6.2.4.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.4-2]及び[表 2.7.6.2.4-3]に示す。

表 2.7.6.2.4-2　被験者の内訳（P04975 試験）

	投与順序 ABCD		投与順序 ACBD	
	n	(%)	n	(%)
総被験者数	8		8	
内訳				
完了	7	(88)	8	(100)
中止	1	(13)	0	(0.0)
有害事象	1†	(13)	0	(0.0)

処置 A：ポサコナゾール経口懸濁液100 mg を単回経口投与
処置 B：ポサコナゾール新錠剤 A 100 mg を単回経口投与
処置 C：ポサコナゾール新錠剤 B 100 mg を単回経口投与
処置 D：ポサコナゾール新カプセル100 mg を単回経口投与
† 被験者1例がパート1の第4期（空腹時投与）の11日目に発現した軽度の歯痛の有害事象のため試験を中止した。

Data source: [資料5.3.1.2.3: P04975]Table 14.1.1

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表 2.7.6.2.4-3　　被験者の背景（P04975 試験）

	投与順序 ABCD		投与順序 ACBD		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	8		8		16	
性別（例）						
女性	3	(38)	5	(63)	8	(50)
男性	5	(63)	3	(38)	8	(50)
人種（例）						
白人	5	(63)	5	(63)	10	(63)
黒人又はアフリカ系アメリカ人	2	(25)	2	(25)	4	(25)
アジア系	1	(13)	0	(0)	1	(6)
ハワイ原住民又はその他の太平洋諸島の住民	0	(0)	0	(0)	0	(0)
アメリカンインディアン又はアラスカ原住民	0	(0)	0	(0)	0	(0)
混血	0	(0)	1	(13)	1	(6)
民族（例）						
ヒスパニック系又はラテン系	4	(50)	0	(0)	4	(25)
非ヒスパニック系又は非ラテン系	4	(50)	8	(100)	12	(75)
年齢（歳）						
算術平均（標準偏差）	31.4	(7.48)	31.4	(7.27)	31.4	(7.13)
中央値	33.0		30.0		31.0	
範囲	19 - 42		20 - 45		19 - 45	
18～65歳未満	8	(100)	8	(100)	16	(100)

処置 A：ポサコナゾール経口懸濁液100 mg を単回経口投与
処置 B：ポサコナゾール新錠剤 A 100 mg を単回経口投与
処置 C：ポサコナゾール新錠剤 B 100 mg を単回経口投与
処置 D：ポサコナゾール新カプセル100 mg を単回経口投与

Data source: [資料5.3.1.2.3: P04975]Table 14.1.2

2.7.6.2.4.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者16例から得られた血漿中薬物濃度データを薬物動態解析に含めた。パート1で健康被験者にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセル100 mg を空腹時に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.4-4]に示す。経口懸濁液投与時において被験者1例で $AUC_{0-\infty}$の外挿部分が25%を超えたため、$t_{1/2}$の推定値を用いて算出した当該被験者の薬物動態パラメータはすべて要約統計量の算出から除外した。空腹時に投与したポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの C_{max} 及び AUC は経口懸濁液と比べ極めて高く、それら3製剤のポサコナゾールの薬物動態パラメータは AUC 及び C_{max} を含め、類似していた。ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの T_{max} の中央値は5時間、経口懸濁液の T_{max} の中央値は4時間であり、$t_{1/2}$の算術平均は25.0～29.2時間で、いずれの製剤でも同程度であった。ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの C_{max} 及び AUC の被験者間変動は、経口懸濁液と比べ小さかった。ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの C_{max} 及び AUC の変動係数は22%～28%だったが、経口懸濁液の変動係数は44%～

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62%であった。

パート2で、健康被験者に高脂肪食摂取後にポサコナゾール100 mg を単回経口投与した際の薬物動態パラメータの要約を[表 2.7.6.2.4-5]に示す。高脂肪食摂取後投与において、ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの C_{max} 及び AUC は経口懸濁液と比べ高く、それら3製剤のポサコナゾールの薬物動態パラメータは AUC 及び C_{max} を含め、類似していた。検討したこれら4製剤間で $t_{1/2}$は類似しており、算術平均の範囲は23.1～25.3時間であった。また、T_{max} の中央値は6～8時間であった。

ポサコナゾール経口懸濁液を高脂肪食摂取後に投与した際の C_{max} 及び AUC は、空腹時投与と比べ約2.5～3倍となった。しかし、新錠剤 A、新錠剤 B 及び新カプセルでは、食事による著しい曝露量の変化は認められなかった。

表 2.7.6.2.4-4　健康被験者にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B、及び新カプセル 100 mg を空腹時に単回経口投与した際の血漿中薬物動態パラメータの要約

（パート 1、P04975 試験）

薬物動態パラメータ	経口懸濁液 (n=16)	新錠剤 A (n=16)	新錠剤 B (n=16)	新カプセル (n=16)
AUC_{0-t} (ng·hr/mL)	2970.4 (50)	11359 (26)	11030.8 (22)	10659.5 (26)
$AUC_{0-\infty}$ (ng·hr/mL)	3416.9 (44)‡	11729.3 (26)	11294.8 (22)	10952.7 (25)
C_{max} (ng/mL)	84.0 (62)	385.4 (28)	358.2 (23)	334.6 (27)
T_{max}† (hr)	4.00 (2.00 - 8.00)	5.00 (3.00 - 6.00)	5.00 (2.00 - 8.00)	5.00 (4.00 - 8.00)
$t_{1/2}$ (hr)	29.2 (31)‡	26.1 (28)	25.0 (25)	25.1 (27)
CL/F (L/hr)	33.95 (38)‡	9.16 (29)	9.25 (22)	9.67 (26)
V_d/F (L)	1449.4 (54)‡	345.4 (45)	331.3 (34)	348.6 (36)

算術平均（%CV）
CV：変動係数
†　中央値（範囲）
‡　n=15

Data source: [資料5.3.1.2.3: P04975] Table 14 2 2 1

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表 2.7.6.2.4-5　健康被験者にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセル 100 mg を高脂肪食摂取後に単回経口投与した際の薬物動態パラメータの要約（パート 2、P04975 試験）

薬物動態パラメータ	経口懸濁液 (n=15)	新錠剤 A (n=15)	新錠剤 B (n=15)	新カプセル (n=15)
$AUC_{0\text{-}t}$ (ng·hr/mL)	8473.8 (25)	11673.5 (24)	12113.4 (25)	12008.4 (28)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	8753.3 (24)	11914.0 (23)	12438.8 (25)	12291.0 (28)
C_{max} (ng/mL)	242.9 (18)	327.3 (23)	348.0 (32)	330.2 (34)
T_{max}† (hr)	6.00 (5.00 - 12.0)	8.00 (3.00 - 24.0)	6.00 (3.00 - 24.0)	8.00 (5.00 - 24.0)
$t_{1/2}$ (hr)	25.1 (35)	23.7 (21)	25.3 (24)	23.1 (21)
CL/F (L/hr)	12.09 (26)	8.97 (32)	8.64 (32)	8.85 (34)
V_d/F (L)	426.5 (39)	304.7 (34)	305.2 (27)	289.9 (33)

算術平均（%CV）
CV：変動係数
†　　中央値（範囲）

Data source: [資料5.3.1.2.3: P04975] Table 14 2 2 2

2.7.6.2.4.4　　安全性の結果

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。健康被験者にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセル100 mg を空腹時又は高脂肪食摂取後に単回経口投与した際、安全で忍容性は概して良好であった。重篤な有害事象、妊娠及び死亡はなかった。被験者1例は、パート1の第4期（空腹時にポサコナゾール新カプセルを投与）の11日目に発現した副作用ではない軽度の歯痛の有害事象のため、治験担当医師の判断により試験を中止した。空腹時又は高脂肪食摂取後にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセルを単回経口投与した際の有害事象発現率は同程度で、明らかな投与に関連する傾向はなかった。ポサコナゾール新カプセルを空腹時に単回経口投与した際の有害事象発現率が最も高かった（16例中4例）が、2例以上で認められた有害事象はなかった。空腹時にポサコナゾール新錠剤 B、高脂肪食摂取後にポサコナゾール新錠剤 A を単回経口投与した際、有害事象は認められなかった。空腹時及び高脂肪食摂取後投与のいずれも、2件の中等度の有害事象を除くすべての有害事象が軽度であった。重度の有害事象はなく、いずれも試験の終了までに回復した。被験者1例に発現した頭痛は、治験担当医師により副作用と判定されたが、その他の有害事象はいずれも副作用ではないと判定された。その他、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。

2.7.6.2.4.5　　結論

1) 空腹時及び高脂肪食摂取後単回経口投与のいずれでも、ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの AUC は、経口懸濁液と比べ高かった。
2) 空腹時及び高脂肪食摂取後単回経口投与のいずれでも、ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの C_{max} 及び AUC は類似していた。

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3) ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルを空腹時に単回経口投与した際の C_{max} 及び AUC の被験者間変動は、ポサコナゾール経口懸濁液と比べ小さかった。
4) これまでの試験の結果と同様、ポサコナゾールの経口懸濁液を投与した際、高脂肪食摂取によりポサコナゾールの C_{max} 及び AUC の算術平均は約2.5～3倍高くなった。しかし、ポサコナゾール新錠剤 A、新錠剤 B 及び新カプセルの AUC は、食事による著しい変化は認められず、食事に関係なく投与可能であることが示唆された。
5) 健康被験者にポサコナゾール経口懸濁液、新錠剤 A、新錠剤 B 及び新カプセル100 mg を空腹時及び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。

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2.7.6.2.5　非日本人健康被験者を対象とした経口懸濁液及び2種類の新錠剤の相対的バイオアベイラビリティ試験（P07691試験）［参考資料］

治験総括報告書[資料5.3.1.2.4: P07691]の概要を以下に示す。

2.7.6.2.5.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としてポサコナゾール新錠剤2種類［新錠剤 C 及び新錠剤 D（黄色）］並びに経口懸濁液の薬物動態を比較する相対的バイオアベイラビリティ試験／P07691試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第 I 相

目的

【主要目的】

1) 健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）100 mg を単回経口投与した際の、ポサコナゾール新錠剤 C 100 mg の単回経口投与に対する相対的バイオアベイラビリティを推定する。
2) 健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）100 mg を単回経口投与した際の、ポサコナゾール経口懸濁液100 mg の単回経口投与に対する相対的バイオアベイラビリティを推定する。

【副次目的】

健康被験者を対象として、ポサコナゾール新錠剤 C 100 mg、新錠剤 D（黄色）100 mg 及び経口懸濁液100 mg を単回経口投与した際の安全性及び忍容性を評価する。

試験デザイン

本試験は、健康被験者を対象とした、3種類のポサコナゾールの製剤間［新錠剤 C、新錠剤 D（黄色）及び経口懸濁液］の相対的バイオアベイラビリティを評価する、非盲検、無作為化、3期クロスオーバー、6投与順序、単回経口投与試験であった。各投与期の1日目にポサコナゾール新錠剤 C（処置 A）、ポサコナゾール新錠剤 D（黄色）（処置 B）又はポサコナゾール経口懸濁液（処置 C）

のいずれかを投与した。投与期の間は10日以上間隔を空けた。

投与期間

単回

用法・用量

処置 A 及び B はいずれも10時間以上絶食後にポサコナゾール新錠剤 C 又は新錠剤 D（黄色）を単回経口投与した。処置 C は、高脂肪食摂取後にポサコナゾール経口懸濁液を単回経口投与した。

処置 A：ポサコナゾール新錠剤 C 100 mg（100 mg×1錠）を空腹時に単回経口投与

処置 B：ポサコナゾール新錠剤 D（黄色）100 mg（100 mg×1錠）を空腹時に単回経口投与

処置 C：ポサコナゾール経口懸濁液100 mg を高脂肪食摂取後に単回経口投与

治験薬の内容を、[表 2.7.6.2.5-1]に示す。

表 2.7.6.2.5-1　治験薬の内容（P07691 試験）

薬剤	力価	剤形
ポサコナゾール新錠剤 C	ポサコナゾール100 mg	錠剤
ポサコナゾール新錠剤 D（黄色）	ポサコナゾール100 mg	錠剤
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤

診断／選択基準

スクリーニング時に BMI が18 kg/m^{2}以上30 kg/m^{2}以下で、18歳以上65歳以下の健康な男性又は女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体は投与前及び投与後168時間までの規定した時点で採取した。ポサコナゾールの薬物動態パラメータ（C_{max}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、T_{max} 及び $t_{1/2}$等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

薬物動態パラメータを被験者、投与順序、投与期及び処置ごとに一覧表で示した。

ポサコナゾールの $AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$及び C_{max} の対数変換値を処置及び投与期を固定効果とする

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線形混合効果モデルを用いて解析した。共分散構造は heterogeneous-compound-symmetry covariance matrix を用いた。剤形の影響を明らかにするために、本モデルに基づき、新錠剤 D（黄色）対新錠剤 C、新錠剤 D（黄色）対経口懸濁液の幾何平均比及び90%信頼区間を算出した。各処置間の幾何平均比の90%信頼区間は、対数尺度上の平均値の差の90%信頼区間の逆変換により算出した。個々の被験者における $AUC_{0-\infty}$及び C_{max} の製剤間の比［新錠剤 D（黄色）／新錠剤 C、新錠剤 D（黄色）／経口懸濁液］、並びにその幾何平均比及び90%信頼区間をプロットした。

【安全性】

ポサコナゾール新錠剤 C、新錠剤 D（黄色）及び経口懸濁液を投与した際の安全性及び忍容性を、有害事象の臨床評価及び安全性に関するその他の評価に基づき検討した。臨床検査値、心電図及びバイタルサインの要約統計量を算出して示した。すべての安全性パラメータは要約統計量を算出した。

2.7.6.2.5.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.5-2]及び[表 2.7.6.2.5-3]に示す。

表 2.7.6.2.5-2　　被験者の内訳（P07691 試験）

	合計	
	n	(%)
総被験者数	24	
内訳		
完了	22	(91.7)
中止	2	(8.3)
有害事象	1	(4.2)
治験責任医師の判断	1	(4.2)

Data source: [資料5.3.1.2.4: P07691] Table 14 1-1, Listing 16.2.1-1.1

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表 2.7.6.2.5-3　　被験者の背景（P07691 試験）

	合計	
	n	(%)
総被験者数	24	
性別		
男性	11	(45.8)
女性	13	(54.2)
年齢（歳）		
算術平均	37.7	
標準偏差	9.57	
中央値	36.0	
範囲	23 - 59	
体重（kg）		
算術平均	77.69	
標準偏差	12.617	
中央値	75.00	
範囲	55.4 - 100.0	
身長（cm）		
算術平均	173.4	
標準偏差	9.78	
中央値	175.0	
範囲	156 - 189	
BMI（kg/m^2）		
算術平均	25.73	
標準偏差	2.781	
中央値	25.75	
範囲	22.0 - 30.0	
人種		
白人	6	(25.0)
黒人又はアフリカ系アメリカ人	18	(75.0)
民族		
ヒスパニック系又はラテン系	2	(8.3)
非ヒスパニック系又は非ラテン系	22	(91.7)

Data source: [資料5.3.1.2.4: P07691] Table 14.1-2.1, Table 14.1-2.2

2.7.6.2.5.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者23例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾールの3種類の製剤［新錠剤 C、新錠剤 D（黄色）及び経口懸濁液］を投与した際の血漿中薬物動態パラメータの比較を[表 2.7.6.2.5-4]及び[表 2.7.6.2.5-5]に示す。

被験者2例が治験を中止し、うち1例は、2処置（新錠剤 C 投与後に経口懸濁液を投与）を受けた後に中止した。他の1例には経口懸濁液のみが投与され、その後、中止した（本被験者は薬物動態の要約統計量から除外した）。

ポサコナゾール新錠剤 C と新錠剤 D（黄色）の比較

[表 2.7.6.2.5-4]に示すように、ポサコナゾール新錠剤 D（黄色）の AUC 及び C_{max} の幾何平均は、

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ポサコナゾール新錠剤 C と比較してわずかに低く、主要な評価項目である新錠剤 D（黄色）／新錠剤 C の $AUC_{0-\infty}$、AUC_{0-last} 及び C_{max} の幾何平均比はそれぞれ0.894、0.880及び0.856で、それらの90%信頼区間は0.748～0.980の範囲であった。この製剤間のポサコナゾールの曝露量の差は臨床的に重要ではないと考えられた。

また、T_{max} の中央値はこれら2製剤で同程度（4時間及び5時間）であり、$t_{1/2}$の算術平均（変動係数）はいずれも約27時間［新錠剤 C では24.0%、新錠剤 D（黄色）では26.6%］であった。

表 2.7.6.2.5-4　健康被験者にポサコナゾール新錠剤 C 及び新錠剤 D（黄色）100 mg を空腹時に単回経口投与した際の血漿中曝露量の比較（P07691 試験）

		$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-last} (ng·hr/mL)	C_{max} (ng/mL)
新錠剤 C	GM	9207.80	8774.86	309.82
n=23	90%CI	(8214.15, 10321.65)	(7803.55, 9867.06)	(271.19, 353.95)
新錠剤 D（黄色）	GM	8236.26	7723.30	265.28
n=22	90%CI	(7253.45, 9352.23)	(6732.63, 8859.75)	(229.47, 306.68)
新錠剤 D（黄色）	GMR	0.894	0.880	0.856
／新錠剤 C	90%CI	(0.821, 0.975)	(0.799, 0.970)	(0.748, 0.980)
CI：信頼区間、GM：幾何平均、GMR：幾何平均比				

Data source: [資料5.3.1.2.4: P07691] Table 14.2-2.1

ポサコナゾール経口懸濁液と新錠剤 D（黄色）の比較

ポサコナゾール新錠剤 D（黄色）を空腹時に単回経口投与した際の薬物動態プロファイルは、ポサコナゾール経口懸濁液を高脂肪食摂取後に単回経口投与した際のプロファイルと類似していた[表 2.7.6.2.5-5]。

新錠剤 D（黄色）の AUC 及び C_{max} の幾何平均は経口懸濁液と同程度であり、主要な評価項目である新錠剤 D（黄色）／経口懸濁液の $AUC_{0-\infty}$、AUC_{0-last} 及び C_{max} の幾何平均比はそれぞれ1.015、1.013及び1.098で、それらの90%信頼区間は0.920～1.243の範囲であった。

また、T_{max} の中央値はこれら2製剤でいずれも5時間であった。$t_{1/2}$の算術平均（変動係数）も同程度であり、新錠剤 D（黄色）では約27時間（26.6%）、経口懸濁液では約26時間（26.1%）であった。

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表 2.7.6.2.5-5　　健康被験者にポサコナゾール新錠剤 D（黄色）100 mg を空腹時及び経口懸濁液 100 mg を高脂肪食摂取後に単回経口投与した際の血漿中曝露量の比較（P07691 試験）

		$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-last} (ng·hr/mL)	C_{max} (ng/mL)
経口懸濁液 n=23	GM	8111.25	7625.72	241.59
	90%CI	(7295.69, 9017.98)	(6802.12, 8549.05)	(220.97, 264.14)
新錠剤 D（黄色） n=22	GM	8236.26	7723.30	265.28
	90%CI	(7253.45, 9352.23)	(6732.63, 8859.75)	(229.47, 306.68)
新錠剤 D（黄色）／経口懸濁液	GMR	1.015	1.013	1.098
	90%CI	(0.933, 1.105)	(0.920, 1.115)	(0.970, 1.243)

CI：信頼区間、GM：幾何平均、GMR：幾何平均比

Data source: [資料5.3.1.2.4: P07691] Table 14.2-2.2

2.7.6.2.5.4　　安全性の結果

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。健康被験者にポサコナゾール新錠剤 C 及び新錠剤 D（黄色）100 mg を空腹時、経口懸濁液100 mg を高脂肪食摂取後に単回経口投与した際、安全で忍容性は概して良好であった。重篤な有害事象、妊娠及び死亡はなかった。1例が有害事象（肝酵素上昇）により試験を中止した。24例中9例の被験者で20件の有害事象が認められ、それぞれ新錠剤 C で4例に5件、新錠剤 D（黄色）で3例に7件、経口懸濁液で8例に8件であった。このうち、4例で認められた8件の有害事象は、治験担当医師により副作用と判定された。有害事象の重症度は、軽度が17件、中等度が3件であった。最もよくみられた有害事象は便秘（3例）であった。治験担当医師により副作用と判定された有害事象を発現した被験者数はそれぞれの処置で同程度であり、各2例［それぞれ新錠剤 C で2件、新錠剤 D（黄色）で4件、経口懸濁液で2件］であった。その他、肝酵素上昇を除いた臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.5.5　　結論

1) 健康被験者にポサコナゾール新錠剤 D（黄色）100 mg を空腹時に単回経口投与した際の AUC 及び C_{max} は新錠剤 C よりわずかに低かったが、臨床的に意味のある差ではないと考えられた。
2) 健康被験者にポサコナゾール新錠剤 D（黄色）100 mg を空腹時に単回経口投与した際の AUC 及び C_{max} は、経口懸濁液を高脂肪食摂取後に単回経口投与した際と同程度であった。
3) ポサコナゾール新錠剤 C 及び新錠剤 D（黄色）100 mg を空腹時、経口懸濁液100 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。

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2.7.6.2.6　非日本人健康被験者を対象とした栄養補助剤の影響を評価した単回及び反復経口投与試験（P02812試験）［参考資料］

治験総括報告書[資料5.3.1.1.2: P02812]の概要を以下に示す。

2.7.6.2.6.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象にポサコナゾールの薬物動態に対する栄養補助剤の影響を評価した非盲検、無作為化試験／P02812試験

治験責任医師／実施医療機関

[redacted]（米国）

公表文献

Courtney R, Sansone A, Calzetta A, et al. The effect of a nutritional supplement (Boost Plus^{TM}) on the oral bioavailability of posaconazole. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sept. 14-17, Chicago, IL, Abstract A-1604.

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

健康被験者を対象として、ポサコナゾール経口懸濁液を栄養補助剤摂取後に投与した際のポサコナゾールの薬物動態の評価及びポサコナゾール経口懸濁液を反復経口投与した際の心電図パラメータを評価する。

【副次目的】

健康被験者を対象として、ポサコナゾール経口懸濁液を投与した際の安全性及び忍容性を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール経口懸濁液を栄養補助剤摂取後に単回経口投与した際の薬物動態、反復経口投与した際の心電図パラメータを評価する、非盲検、無作為

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化、2期クロスオーバー、単回及び反復投与試験であった。クロスオーバーで1日目及び15日目にポサコナゾール経口懸濁液400 mg を空腹時投与（処置 A）又は高脂肪製剤である栄養補助剤（Boost Plus 登録商標）と併用投与（処置 B）した。さらに、18～24日目にポサコナゾール経口懸濁液400 mg を1日2回、高脂肪食（朝食及び夕食）摂取後投与した。25日目には朝のみ投与した。

投与期間

単回及び反復（8日間）

用法・用量

ポサコナゾール経口懸濁液400 mg を1日目及び15日目に空腹時（処置 A）又は栄養補助剤（Boost Plus 登録商標、処置 B）摂取後に単回経口投与した。本試験の反復投与部分（18～25日目）では、ポサコナゾール経口懸濁液の400 mg を1日2回、高脂肪食摂取後に8日間反復経口投与した。なお、25日目には朝のみ投与した。

処置 A：ポサコナゾール経口懸濁液400 mg を空腹時に単回経口投与

処置 B：ポサコナゾール経口懸濁液400 mg を栄養補助剤（Boost Plus 登録商標）摂取後に単回経口投与

反復投与期（18～25日目）：ポサコナゾール経口懸濁液400 mg を高脂肪食（朝食及び夕食）摂取後に反復経口投与（25日目は朝のみ）

治験薬の内容を、[表 2.7.6.2.6-1]に示す。

表 2.7.6.2.6-1　治験薬の内容（P02812 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
栄養補助剤（Boost Plus 登録商標）	360 kcal/237 mL	液剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^{2}以上27 kg/m^{2}以下で、18歳以上55歳以下の健康な男性又は女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1、15及び25日目の投与前、並びに投与後72時間までの規定した時点で採取した。また、トラフ検体を、23日目の夜投与前、並びに24日目の朝投与前及び夜投与前に採取した。血漿中ポサコナゾールの薬物動態パラメータ（AUC、C_{max} 及び T_{max} 等）を算出し、評価した。

【薬力学】

時間を一致させた心電図を-1日目（ベースライン）及び25日目（最終投与日）にそれぞれ24時間で7回測定し、反復経口投与時の心電図パラメータに与える影響を評価した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

各時点の薬物動態パラメータ及び濃度データの要約統計量を算出した。単回経口投与した際のデータについて、クロスオーバー型の分散分析モデルを適用し、薬物動態パラメータを解析した。投与順序、投与順序内被験者、投与期、処置及び性別の影響を評価した。AUC 及び C_{max} の処置間の差は、処置間の対数変換したデータに基づく幾何平均比として示した。幾何平均比とその両側90%信頼区間を算出するとともに、20%の処置間の差の検出力を両側有意水準0.05の場合で算出した。反復経口投与した際のデータについて、23日目（朝）、24日目（朝及び夜）及び25日目（朝及び夜）の C_{min} 間の比の90%信頼区間が80%～120%の範囲内のとき定常状態に到達していると判定した。

【薬力学】

QT、QTcF、QTcB、PR、QRS 間隔、及び心拍数の要約統計量を算出した。また、心電図のパラメータ（QTc の最大値、平均 QTc、25日目のベースライン（-1日目）からの QTc の変化量の最大値、25日目のベースライン（-1日目）からの QTc の変化量の平均値及び時間を一致させた QTc の平均変化量）を算出した。

【安全性】

ポサコナゾール経口懸濁液を単回又は反復経口投与した際の安全性及び忍容性を、有害事象の臨床評価及び安全性に関するその他の評価に基づき検討した。安全性に関する臨床検査値及び心電図の要約統計量を算出して示した。

2.7.6.2.6.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.6-2]及び[表 2.7.6.2.6-3]に示す。

表 2.7.6.2.6-2　　被験者の内訳（P02812 試験）

	合計	
	n	(%)
総被験者数	24	
内訳		
完了	23	(96)
中止	1	(4)
試験と無関係な理由による中止	1	(4)

Data source: [資料5.3.1.1.2: P02812] 16.2.4.1

表 2.7.6.2.6-3　　被験者の背景（P02812 試験）

	男性		女性		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	12		12		24	
年齢（歳）						
算術平均	40.3		38.5		39.4	
標準偏差	7.9		7.4		7.6	
中央値	43.0		40.5		41.5	
範囲	24.0 - 47.0		27.0 - 53.0		24.0 - 53.0	
体重（kg）						
算術平均	79.5		64.2		71.8	
標準偏差	6.9		5.2		9.8	
中央値	78.4		63.1		71.4	
範囲	68.4 - 88.8		56.2 - 74.7		56.2 - 88.8	
身長（cm）						
算術平均	172.3		158.8		165.5	
標準偏差	7.0		7.5		9.9	
中央値	170.0		158.0		165.8	
範囲	162.0 - 183.0		142.0 - 169.0		142.0 - 183.0	
BMI（kg/m^2）						
算術平均	26.8		25.5		26.2	
標準偏差	2.3		2.5		2.4	
中央値	27.4		25.0		26.3	
範囲	21.8 - 30.4		20.5 - 30.0		20.5 - 30.4	
人種						
白人	5	(42)	0	(0)	5	(21)
黒人	1	(8)	1	(8)	2	(8)
ヒスパニック系又はラテン系	5	(42)	11	(92)	16	(67)
その他	1	(8)	0	(0)	1	(4)

Data source: [資料5.3.1.1.2: P02812] 14.1.2.1, 14.1.2.2, 14.1.2.3

2.7.6.2.6.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者23例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール経口懸濁液400 mg を空腹時に単独又は栄養補助剤（Boost Plus 登録商標）摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.6-4]に示す。

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表 2.7.6.2.6-4　　健康被験者にポサコナゾール経口懸濁液 400 mg を空腹時に単独又は栄養補助剤（Boost Plus 登録商標）摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約（n=23）（P02812 試験）

薬物動態パラメータ	ポサコナゾール単独		ポサコナゾールと栄養補助剤（Boost Plus 登録商標）を併用	
	算術平均	%CV	算術平均	%CV
C_{max} (ng/mL)	121	75	355	43
T_{max} (hr)†	4.00 (2.00 - 12.00)	-	5.00 (4.00 - 8.00)	-
$t_{1/2}$ (hr)	27.3‡	26	26.0‡	19
$AUC_{0\text{-}last}$ (ng·hr/mL)	3552	53	9076	42
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	5258‡	48	11295‡	40

CV：変動係数
†　　中央値（範囲）
‡　　n=10、$AUC_{0\text{-}\infty}$の外挿部分が全体の25%を超える被験者では、$t_{1/2}$、CL/F、V_d/F 及び $AUC_{0\text{-}\infty}$を報告しなかった。

Data source: [資料5.3.1.1.2: P02812] 16.2.5.3.1

栄養補助剤（Boost Plus 登録商標）との併用投与は、ポサコナゾールの経口バイオアベイラビリティに重要な影響を及ぼした。空腹下でのポサコナゾール単独投与時に対するポサコナゾールと栄養補助剤（Boost Plus 登録商標）併用投与時の対数変換した $AUC_{0\text{-}last}$ 及び C_{max} の相対的バイオアベイラビリティの推定値の幾何平均比（90%信頼区間）は、それぞれ2.63（2.26, 3.07）及び3.35（2.74, 4.10）であった。栄養補助剤（Boost Plus 登録商標）の併用により、ポサコナゾールの吸収量は増加したが、T_{max} には影響しなかった。

また、ポサコナゾール経口懸濁液400 mg を1日2回8日間高脂肪食摂取後に反復経口投与した際、次投与以後の C_{min} に対する6日目午前の C_{min} の幾何平均比の90%信頼区間が80%～120%の範囲に含まれたことより、ポサコナゾールは8日間の反復経口投与により定常状態に到達したことが示された［8日目投与前の C_{min} の算術平均（変動係数）は2525 ng/mL（32%）］。

2.7.6.2.6.4　　薬力学の結果

本試験では、ポサコナゾールを反復経口投与し評価が可能であった22例の被験者の結果を用いた。QTcF の測定時点別のベースラインからの平均変化量は、-5.27（投与後2時間）～-1.45 msec（投与後6時間）であった。個々の被験者で QTcF のベースラインから最も延長していた時点は、投与後2、5及び6時間でそれぞれ26 msec の延長が認められ、反対に最も短縮していた時点は、投与後6及び12時間でそれぞれ36 msec の短縮が認められた。QTcF のベースラインからの変化量と T_{max} の中央値との間に明確な関連性は認められなかった。投与後5時間の QTcF のベースラインからの平均変化量は-3.91 msec であり、24時間を通じた投与後の QTcF の平均変化量（-3.81 msec）と同程度であった。QTcF の変化量の分布から、大部分の被験者（約58%）で投与後に QTcF の短縮が認められた。すべての被験者で、時間を一致させた QTcF の平均変化量は30 msec 以下であり、24時間を通じて時間を一致させた QTcF の平均変化量の最大値（QTcF の延長）は10.86 msec であった。

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2.7.6.2.6.5　　安全性の結果

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。健康被験者にポサコナゾール経口懸濁液400 mg を空腹時に単独又は栄養補助剤（Boost Plus 登録商標）摂取後に単回経口投与、若しくはポサコナゾール経口懸濁液400 mg を高脂肪食（朝食及び夕食）摂取後に1日2回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、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。ポサコナゾール経口懸濁液400 mg を栄養補助剤（Boost Plus 登録商標）と併用又は単独で単回経口投与した際いずれも有害事象は認められなかった。ポサコナゾール経口懸濁液400 mg を高脂肪食摂取後に反復経口投与した際に2例の被験者で有害事象が認められた。いずれの有害事象も軽度で、副作用ではないと判定され、処置なく回復した。臨床検査値のいずれにも臨床的に意味のある変化は認められなかった。なお、9例の被験者で軽度の肝酵素上昇が認められ、多くは反復経口投与時に認められた。さらに、1例の被験者で反復経口投与時に中等度の肝酵素上昇が認められた。いずれも投与終了後にはベースライン値付近に低下していた。その他の臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.6.6　　結論

1) Boost Plus 登録商標の併用投与は、ポサコナゾール経口懸濁液の相対的経口バイオアベイラビリティに臨床的に重要な影響を及ぼすと考えられ、$AUC_{0\text{-last}}$ 及び C_{max} をそれぞれ約2.6倍及び3.4倍に増加させポサコナゾールの吸収量を増加させたが、T_{max} には影響を及ぼさなかった。
2) ポサコナゾール経口懸濁液400 mg の1日2回反復経口投与は QTc を延長させなかった。
3) 栄養補助剤（Boost Plus 登録商標）併用又は単独投与時のポサコナゾール経口懸濁液400 mg 単回経口投与、並びにポサコナゾール経口懸濁液400 mg 1日2回反復経口投与は安全で、忍容性は良好であった。
4) 固形食が摂取不能な患者では、可能な限り、ポサコナゾールの吸収を改善させるため栄養補助剤（高脂肪製剤が望ましい）と併用することが推奨される。

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2.7.6.2.7　非日本人健康被験者を対象とした市販予定製剤の食事の影響試験（P112試験）［参考資料］

治験総括報告書[資料5.3.1.1.3: P112]の概要を以下に示す。

2.7.6.2.7.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としてポサコナゾール新錠剤 D（黄色）を投与した際のポサコナゾールの薬物動態に対する食事の影響を評価する相対的バイオアベイラビリティ試験／P112試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第 I 相

目的

健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）300 mg を単回経口投与した際のポサコナゾールの薬物動態に対する食事の影響を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール新錠剤 D（黄色）の薬物動態に対する食事の影響を評価する非盲検、無作為化、2期クロスオーバー、単回投与試験であった。第1期又は第2期にポサコナゾール新錠剤 D（黄色）300 mg を空腹時又は高脂肪食摂取後のいずれかで投与し、相対的バイオアベイラビリティを比較した。投与期の間は7日以上間隔を空けた。

投与期間

単回

用法・用量

処置 A は10時間以上の絶食後、処置 B は高脂肪食摂取後にポサコナゾール新錠剤 D（黄色）を単回経口投与した。

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg（100 mg×3錠）を空腹時に単回経口投与

処置 B：ポサコナゾール新錠剤 D（黄色）300 mg（100 mg×3錠）を高脂肪食摂取後に

単回経口投与

治験薬の内容を、[表 2.7.6.2.7-1]に示す。

表 2.7.6.2.7-1　　治験薬の内容（P112 試験）

薬剤	力価	剤形
ポサコナゾール新錠剤 D（黄色）	ポサコナゾール100 mg	錠剤

診断／選択基準

スクリーニング時に BMI が18.0 kg/m^{2}以上30.0 kg/m^{2}以下で、18歳以上65歳以下の健康な男性又は女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を投与前及び投与後72時間までの規定した時点に採取した。薬物動態の主要な評価項目として、C_{max}、T_{max}、$AUC_{0\text{-}last}$を評価した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

ポサコナゾール新錠剤 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の$AUC_{0\text{-}last}$及び C_{max} の幾何平均比（高脂肪食摂取後投与／空腹時投与）を算出した。$AUC_{0\text{-}last}$及びC_{max} の自然対数変換値を処置及び投与期を固定効果、共分散行列を unstructured symmetry covariance matrix とする線形混合効果モデルを用い、幾何平均比（高脂肪食摂取後投与／空腹時投与）及び90%信頼区間を算出した。幾何平均比及びその90%信頼区間は、対数尺度上の平均値の差とその90%信頼区間を逆変換することにより算出した。

【安全性】

ポサコナゾール新錠剤 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の安全性及び忍容性を、有害事象の臨床評価及び安全性に関するその他の評価に基づき検討した。安全性に関する臨床検査値及びバイタルサインの要約統計量を算出して示した。

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2.7.6.2.7.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.7-2]及び[表 2.7.6.2.7-3]に示す。

表 2.7.6.2.7-2　　被験者の内訳（P112 試験）

	合計	
	n	(%)
総被験者数	18	
内訳		
完了	16	(88.9)
中止	2	(11.1)
同意撤回	1	(5.6)
治験実施計画書からの逸脱	1	(5.6)

Data source: [資料5.3.1.1.3: P112] 14.1.1

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表 2.7.6.2.7-3　　被験者の背景（P112 試験）

	処置 A		処置 B		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	17		17		18	
性別						
男性	6	(35.3)	6	(35.3)	6	(33.3)
女性	11	(64.7)	11	(64.7)	12	(66.7)
年齢（歳）						
算術平均	46.1		44.4		45.1	
標準偏差	16.40		16.70		16.40	
中央値	54.0		51.0		52.5	
範囲	19 - 65		19 - 65		19 - 65	
体重（kg）						
算術平均	73.2		73.5		72.9	
標準偏差	10.90		10.60		10.60	
中央値	75.0		75.0		72.0	
範囲	54 - 92		54 - 92		54 - 92	
身長（cm）						
算術平均	167.00		168.00		167.00	
標準偏差	8.810		8.570		8.710	
中央値	167.00		168.00		168.00	
範囲	155 - 187		155 - 187		155 - 187	
BMI（kg/m^2）						
算術平均	26.20		26.00		26.00	
標準偏差	2.250		2.420		2.350	
中央値	26.30		26.30		26.20	
範囲	20.7 - 29.4		20.7 - 29.4		20.7 - 29.4	
人種						
白人	15	(88.2)	14	(82.4)	15	(83.3)
アジア人	1	(5.88)	1	(5.88)	1	(5.56)
黒人又はアフリカ系アメリカ人	1	(5.88)	2	(11.8)	2	(11.1)
民族						
非ヒスパニック系又は非ラテン系	17	(100.0)	17	(100.0)	18	(100.0)

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
処置 B：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

Data source: [資料5.3.1.1.3: P112] 16.2.4.1, 16.2.7.2

2.7.6.2.7.3　　薬物動態の結果

本試験では、ポサコナゾールを投与した被験者から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を空腹時及び高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの比較を[表 2.7.6.2.7-4]に示す。

本試験には男女の健康被験者18例を組み入れ、うち16例は治験実施計画書に従って試験を完了した。2例が第1期終了後に試験を中止したため、空腹時投与及び高脂肪食摂取後投与を受けた被験者はそれぞれ17例となった。

4例（空腹時投与3例、高脂肪食摂取後投与1例）の被験者で2処置目（第2期）のポサコナゾール投与前値が C_{max} の5%超であった。これらの被験者のデータを除外し、空腹時投与の14例及び高脂肪食摂取後投与の16例で比較した。その結果、ポサコナゾールの C_{max} 及び $AUC_{0\text{-}last}$ の空腹時投与

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に対する高脂肪食摂取後投与の幾何平均比（90%信頼区間）は、それぞれ1.16（0.96, 1.41）及び1.51（1.33, 1.72）であった。また、T_{max}の中央値は空腹時投与での5時間から高脂肪食摂取後投与での6時間に延長した。

表 2.7.6.2.7-4　健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を空腹時及び高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの比較（P112 試験）

薬物動態パラメータ	処置 A 空腹時（N=14†）		処置 B 高脂肪食摂取後（N=16‡）		高脂肪食摂取後／空腹時		被験者内 %CV§
	GM	95%CI	GM	95%CI	GMR	90%CI	
C_{max}‖ (ng/mL)	893	(731, 1090)	1040	(915, 1180)	1.16	(0.96, 1.41)	29.4
$AUC_{0\text{-}last}$‖ (ng·hr/mL)	25600	(21500, 30400)	38700	(35000, 42700)	1.51	(1.33, 1.72)	17.2
T_{max}¶ (hr)	5.00	(3.00 - 8.00)	6.00	(5.00 - 24.00)	-	-	-

処置 A：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
処置 B：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
CI：信頼区間、CV：変動係数、GM：最小二乗平均を用いて算出した幾何平均、GMR：最小二乗平均を用いて算出した幾何平均比
† 1例の被験者は同意撤回で試験を中止したため、処置 A の薬物動態データは得られなかった。また、他の3例の被験者は、第2期の投与前値（処置 A）が C_{max} の5%超であったため除外した。
‡ 1例の被験者は、治験実施計画書からの逸脱で試験を中止したため、処置 B の薬物動態データは得られなかった。別の1例の被験者では、第2期の投与前値（処置 B）が C_{max} の5%超であったため除外した。
§ 被験者内%CV = $100\times(\sqrt{(\hat{\sigma}_A^2+\hat{\sigma}_B^2-2\hat{\sigma}_{AB})/2})$。$\hat{\sigma}_A^2$及び$\hat{\sigma}_B^2$は両処置の対数尺度上の分散の推定値、$\hat{\sigma}_{AB}$はその共分散の推定値であり、いずれも線形混合効果モデルから求めた。
‖ 自然対数変換値を用いて線形混合効果モデルで求めた最小二乗平均及び信頼区間を逆変換した値
¶ 中央値（範囲）

Data source: [資料5.3.1.1.3: P112] 14.2.2, 16.2.6.5

2.7.6.2.7.4　安全性の結果

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。健康被験者にポサコナゾール新錠剤 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例中6例に1件以上の有害事象が認められ、その内訳は悪寒、疲労、食欲減退及び頭痛であった。悪寒は、高脂肪食摂取後投与の1例に認められた。疲労は、空腹時投与の1例、高脂肪食摂取後投与の5例に認められた。食欲減退及び頭痛は高脂肪食摂取後の1例にそれぞれ認められた。すべての有害事象は軽度で、副作用と判定された。すべての有害事象は試験中に処置なく回復した。一部の臨床検査値は基準値範囲外であったが、これらの値は治験担当医師により臨床的に重要ではないと判断された。バイタルサインの異常は認められなかった。第2期の投与前に被験者1例で心電図異常（洞調律の異常）1件がみられたが、臨床的に重要ではないと判断された。その他、臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.7.5　結論

1)　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すると、空腹時

投与と比較して $AUC_{0\text{-}last}$ 及び C_{max} がそれぞれ約51%及び16%増加した。

2) 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すると、T_{max} の中央値は空腹時に投与した際の5時間から6時間に延長した。

3) 健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を空腹時及び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。

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2.7.6.2.8　　日本人健康被験者を対象とした単回経口投与及び食事の影響試験（JPC-[redacted]-361-12試験）［参考資料］

治験総括報告書[資料5.3.3.1.1: JPC_[redacted]_361_12]の概要を以下に示す。

2.7.6.2.8.1　　試験方法

治験実施計画書標題／番号

日本人健康被験者を対象としたポサコナゾールの第Ｉ相単回投与試験／JPC-[redacted]-361-12試験

治験責任医師／実施医療機関

[redacted]（日本）

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ｉ相

目的

日本人健康被験者を対象としてポサコナゾール経口懸濁液を単回経口投与した際の薬物動態、安全性及び忍容性、並びにそれらに対する食事の影響について検討する。

試験デザイン

本試験は、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を単回経口投与した際の薬物動態、安全性及び忍容性、並びにそれらに対する食事の影響を評価する、単盲検、プラセボ対照、並行群間、単回投与試験であった。5つの投与ステップで各8例の被験者にポサコナゾール経口懸濁液50、100、200、400及び600 mg（6例／ステップ）又はプラセボ（2例／ステップ）を単回経口投与した。また、食事の影響を検討するため、ステップ3（200 mg 又はプラセボ）のみ2期クロスオーバーデザインとし、同一被験者に2回（食後及び空腹時）の投与を行った。

投与期間

単回

用法・用量

ステップ1～5でポサコナゾール経口懸濁液50、100、200、400及び600 mg 又はプラセボを単回経口投与した。食後投与については、規定の朝食（ロールパン2個、ゆで卵1個、オレンジジュース100 mL、牛乳150 mL、オレンジマーマレード20 g、バター8 g 及びチーズ20 g）を摂取後5分に

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治験薬を投与した。ステップ3については、空腹時にも治験薬を投与した。

治験薬の内容を、[表 2.7.6.2.8-1]に示す。

表 2.7.6.2.8-1　　治験薬の内容（JPC-[redacted]-361-12 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
ポサコナゾール経口懸濁液のプラセボ	-	液剤

診断／選択基準

スクリーニング時に体重が80 kg 以下でかつ（身長－100）×0.9±20%の範囲にある、20歳以上40歳以下の日本人の健康な男性

評価基準

【薬物動態】

空腹時又は規定の朝食摂取後にポサコナゾール経口懸濁液又はプラセボを単回経口投与し、血漿中薬物濃度測定用検体を投与前及び投与後216時間までの規定した時点で採取した。また尿中薬物濃度測定用検体を投与前及び投与後48時間まで採取した。ポサコナゾールの血漿中薬物動態パラメータ［C_{max}、最終測定可能時点での濃度（C_{last}）、T_{max}、最終測定可能時点（T_{last}）、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、k_{el}、$t_{1/2}$、CL/F、V_d/F 等］並びに尿中薬物動態パラメータ（尿中排泄量及び尿中排泄率）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

ステップ1～5の各用量群における実薬群から得られた血漿中ポサコナゾール濃度データに基づき、ノンコンパートメントモデル解析で C_{max}、C_{last}、T_{max}、T_{last}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、$t_{1/2}$、CL/F 及び V_d/F 等の薬物動態パラメータを算出した。また、血漿中ポサコナゾール濃度推移の視覚的評価において二相性の消失パターンが観察されたことから、非線形最小二乗法に基づく2-コンパートメントモデル解析により、吸収のラグタイム（T_{lag}）、吸収相の半減期（$t_{1/2abs}$）、α 相の消失半減期（$t_{1/2\alpha}$）、β 相の消失半減期（$t_{1/2\beta}$）等を算出した。

薬物動態パラメータの比較：

1)　比較項目：食後投与と空腹時投与の間で比較した。

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2) 解析：ノンコンパートメントモデル解析により算出した T_{max}、C_{max}、$t_{1/2}$、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、CL/F 及び V_d/F についてそれぞれ2投与条件2期の線形混合効果モデルによる解析を実施した。

3) 信頼区間の推定：C_{max}、$AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$について線形混合効果モデルで得られた誤差分散を用い、空腹時投与における平均値から食後投与における平均値の差の90%信頼区間（非対称）を算出した。

尿中排泄量（率）の計算：

ステップ1～5の各用量群における実薬群より得られた各蓄尿区間ごとの尿量及び尿中ポサコナゾール濃度データに基づき、尿中排泄量（μg）及び尿中排泄率（% of dose）を算出した。

【安全性】

有害事象の発現率及び各種検査の投与開始日以降の変動を検討した。

2.7.6.2.8.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.8-2]及び[表 2.7.6.2.8-3]に示す。

表 2.7.6.2.8-2　被験者の内訳（JPC-[redacted]-361-12 試験）

	ポサコナゾール 50 mg 又はプラセボ	ポサコナゾール 100 mg 又はプラセボ	ポサコナゾール 200 mg 又はプラセボ	ポサコナゾール 400 mg 又はプラセボ	ポサコナゾール 600 mg 又はプラセボ
総被験者数	8	8	8	8	8
内訳					
完了	7	8	8	8	8
中止	1	0	0	0	0
同意撤回	1†	0	0	0	0

† 治験薬投与直後に同意撤回したため、血漿及び尿中薬物濃度測定用検体は採取しなかった。

Data source: [資料5 3 3 1 1: JPC_[redacted]_361_12] 14.1.2

表 2.7.6.2.8-3　被験者の背景（JPC-[redacted]-361-12 試験）

		年齢（歳）	身長（cm）	体重（kg）	肥満度†（%）
全体	算術平均±標準偏差	24.8 ± 5.1	171.1 ± 4.4	64.4 ± 6.5	0.9 ± 9.4
	中央値	23.0	170.9	63.3	0.6
	範囲	(20 - 39)	(162.0 - 180.1)	(52.0 - 77.3)	(-16.6 - 19.9)
実薬	算術平均±標準偏差	24.5 ± 5.2	171.3 ± 4.7	64.4 ± 6.5	0.3 ± 8.9
	中央値	22.0	173.0	63.4	0.6
	範囲	(20 - 39)	(162.0 - 180.1)	(52.0 - 77.3)	(-16.6 - 19.9)
プラセボ	算術平均±標準偏差	25.9 ± 4.9	170.0 ± 3.6	64.5 ± 7.0	2.5 ± 11.1
	中央値	24.0	169.4	62.7	1.3
	範囲	(20 - 34)	(165.1 - 178.2)	(55.0 - 76.0)	(-11.9 - 18.1)

† 体重／［(身長－100) ×0.9］×100－100

Data source: [資料5.3.3.1.1: JPC_[redacted]_361_12] 14.1.1

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2.7.6.2.8.3　　薬物動態の結果

本試験では、ポサコナゾール経口懸濁液を投与した被験者30例のうち薬物濃度測定用検体が得られた29例の血漿中薬物濃度データを薬物動態解析に含めた。日本人健康被験者にポサコナゾール経口懸濁液50～600 mg を食後に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.8-4]に示す。

血漿中薬物動態パラメータを用量間で比較した結果、T_{max} の範囲は用量間でほぼ同様であり、T_{lag}、$t_{1/2abs}$、$t_{1/2\alpha}$ 及び $t_{1/2\beta}$ はいずれも用量間で明らかな差はなかった。一方、C_{max} 及び AUC は50～200 mg の用量範囲では概して用量比に応じて増加したが、200 mg 及び400 mg の用量間では C_{max} 及び $AUC_{0-\infty}$の上昇率はそれぞれ1.17及び1.46と用量比（2倍）を下回っていた。さらに400 mg 及び600 mg の用量間では C_{max} 及び AUC のいずれも明らかな増加が認められず、吸収の頭打ちが示唆された。

尿中ポサコナゾール濃度は大部分の被験者及び蓄尿区間において定量下限未満（<20 ng/mL）であり、ポサコナゾールの尿中排泄率は全被験者で投与量の<0.1%未満であった。

表 2.7.6.2.8-4　　日本人健康被験者にポサコナゾール経口懸濁液 50～600 mg を食後に単回経口投与した際の血漿中薬物動態パラメータの要約（JPC-[redacted]-361-12 試験）

用量（mg）	50	100	200	400	600
例数	5	6	6	6	6
ノンコンパートメントモデル解析					
C_{max} (ng/mL)	128 (43)	276 (12)	429 (45)	501 (39)	547 (35)
$AUC_{0\text{-}last}$ (ng·hr/mL)	2900 (46)	6536 (13)	10790 (42)	15546 (44)	14143 (44)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	3152 (42)	6706 (13)	11019 (41)	16109 (43)	14411 (44)
T_{max} (hr)	5 (3 - 6)	4.5 (3 - 6)	5 (4 - 8)	4.5 (3 - 6)	5.5 (5 - 6)
$t_{1/2}$ (hr)	20.0 (15)	17.9 (18)	18.2 (15)	24.5 (18)	17.9 (15)
CL/F (L/hr)	19.7 (60)	15.2 (15)	20.3 (33)	30.3 (54)	49.8 (46)
V_d/F (L)	544 (51)	387 (16)	534 (34)	1063 (52)	1258 (41)
2-コンパートメントモデル解析					
T_{lag} (hr)	1.29 (35)†	1.68 (32)	1.11 (38)‡	1.31 (31)†	1.54 (4)‡
$t_{1/2abs}$ (hr)	1.61 (32)†	1.33 (42)	2.15 (52)‡	1.38 (45)†	1.46 (19)‡
$t_{1/2\alpha}$ (hr)	1.66 (28)†	1.52 (28)	2.18 (55)‡	1.59 (29)†	1.65 (22)‡
$t_{1/2\beta}$ (hr)	21.4 (19)†	20.3 (17)	23.3 (13)‡	24.4 (7)†	20.3 (10)‡

算術平均（%CV）、T_{max}は中央値（範囲）
CV：変動係数
† n=4
‡ n=3

Data source: [資料5.3.3.1.1: JPC_[redacted]_361_12] 16.1.9.1

ポサコナゾール経口懸濁液200 mg を空腹時又は食後に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.8-5]に示す。ポサコナゾール経口懸濁液を空腹時に単回経口投与した際、平均血漿中濃度推移は食後投与と比較して明らかに低く、C_{max}、$AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$の各薬物動態パラメータはいずれも食後投与時の約1/4に低下した。また、T_{max} 及び $t_{1/2}$に食事条件間で有意な差は認められなかったが、食後投与で T_{max} が若干遅延する傾向が認められた。C_{max}、$AUC_{0\text{-}last}$

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及び $AUC_{0-\infty}$の幾何平均比（90%信頼区間）（空腹時／食後）はそれぞれ0.254（0.181, 0.358）、0.246（0.176, 0.343）及び0.267（0.196, 0.365）であった。

表 2.7.6.2.8-5　　日本人健康被験者にポサコナゾール経口懸濁液 200 mg を空腹時又は食後に単回経口投与した際の血漿中薬物動態パラメータの要約（JPC-[redacted]-361-12 試験）

食事条件	食後	空腹時	幾何平均比（90%信頼区間）
例数	6	6	［空腹時／食後］
C_{max} (ng/mL)	429 (45)	109 (43)	0.254 (0.181, 0.358)
$AUC_{0\text{-}last}$ (ng·hr/mL)	10790 (42)	2640 (40)	0.246 (0.176, 0.343)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	11019 (41)	2905 (35)	0.267 (0.196, 0.365)
T_{max} (hr)	5 (4 - 8)	4 (3 - 5)	-
$t_{1/2}$ (hr)	18.2 (15)	23.0 (33)	-
CL/F (L/hr)	20.3 (33)	75.2 (29)	-
V_d/F (L)	534 (34)	2625 (54)	-
算術平均（%CV）、T_{max}は中央値（範囲）、薬物動態パラメータはノンコンパートメントモデル解析により算出した。 CV：変動係数			

Data source: [資料5.3.3.1.1: JPC_[redacted]_361_12] 16.1.9.1

2.7.6.2.8.4　　安全性の結果

本試験では、治験薬を投与した全被験者40例を安全性解析対象集団に含めた。日本人健康被験者にポサコナゾール経口懸濁液50～600 mgを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。治験薬を投与された被験者40例中5例に有害事象が発現した。被験者1例でみられた歯痛は中等度であり、鎮痛薬（メフェナム酸250 mg）の2日間内服により消失した。それ以外はすべて軽度であり、いずれも処置なく、血中コルチゾール減少（プラセボ）を除き、24時間未満で消失した。副作用と判断されたのは頭痛1例（100 mg）のみであった。その他、臨床検査、バイタルサイン、心電図において特記すべき事項は認められなかった。

2.7.6.2.8.5　　結論

1) 日本人健康被験者にポサコナゾール経口懸濁液を食後に単回経口投与した際、50～200 mgの用量範囲ではポサコナゾールの体内動態は概して線形性を示した。400 mgまで用量を増加して投与した際、全身曝露量は上昇したが、400 mgを超える用量では明らかな吸収の頭打ちが確認された。
2) 日本人健康被験者にポサコナゾール経口懸濁液200 mgを空腹時に単回経口投与した際のバイオアベイラビリティは、食後投与と比較して約1/4であった。
3) 日本人健康被験者にポサコナゾール経口懸濁液を単回経口投与した際の未変化体の尿中排泄量は痕跡量であることが確認された。
4) 日本人健康被験者にポサコナゾール経口懸濁液50～600 mgを食後又は空腹時に単回経口投与した際、安全性に関して問題となる所見は認められなかった。

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2.7.6.2.9　　日本人健康被験者を対象とした反復経口投与試験（I-P05011試験）［参考資料］

治験総括報告書[資料5.3.3.1.2: I_P05011]の概要を以下に示す。

2.7.6.2.9.1　　試験方法

治験実施計画書標題／番号

日本人健康被験者を対象としたポサコナゾールの第Ⅰ相反復投与試験／I-P05011試験

治験責任医師／実施医療機関

[redacted]（日本）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

日本人健康被験者を対象として、ポサコナゾール経口懸濁液200 mg 又は400 mg を1日2回14日間、食後に反復経口投与した際の薬物動態、安全性及び忍容性について検討する。

試験デザイン

本試験は、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200 mg 又は400 mg を食後に反復経口投与した際の薬物動態、安全性及び忍容性を評価する、単盲検、プラセボ対照、用量漸増、並行群間、反復経口投与試験であった。グループ1にはポサコナゾール経口懸濁液200 mg 又はプラセボ、グループ2には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14日間（14日目は朝のみ）食後に反復経口投与した。

投与期間

反復（14日間）

用法・用量

グループ1にはポサコナゾール経口懸濁液200 mg 又はプラセボ、グループ2にはポサコナゾール経口懸濁液400 mg 又はプラセボを、朝夕の摂食開始後30分以内に1日2回14日間経口投与した。14日目は朝食後のみ投与した。

治験薬の内容を、[表 2.7.6.2.9-1]に示す。

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表 2.7.6.2.9-1　　治験薬の内容（I-P05011 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
ポサコナゾール経口懸濁液のプラセボ	-	液剤

診断／選択基準

スクリーニング時に BMI が17.6 kg/m^{2}以上27.5 kg/m^{2}以下で、20歳以上45歳以下の日本人の健康な男性

評価基準

【薬物動態】

ポサコナゾール経口懸濁液を1日2回食後に反復経口投与し、血漿中薬物濃度測定用検体を投与前及び最終投与後144時間までの規定した時点で採取した。血漿中ポサコナゾール濃度推移及び薬物動態パラメータを指標として、定常状態到達時間、累積係数、定常状態における薬物動態を評価した。また、ポサコナゾールの全身曝露量を用量間で比較した。

【安全性】

バイタルサイン、身体所見、心電図、臨床検査（血液学的検査、血液生化学検査及び尿検査）及び副腎皮質刺激ホルモン（ACTH）負荷試験により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

初回又は最終投与（14日目朝投与）後の血漿中ポサコナゾール濃度に基づき、ノンコンパートメントモデル解析により、C_{max}、C_{avg}、$C_{12\,hr}$、T_{max}、$AUC_{0\text{-}12\,hr}$、$t_{1/2}$、CL/F 及び V_d/F 等の薬物動態パラメータを算出した。各薬物動態パラメータについて、投与量（200 mg 及び400 mg 1日2回）及び投与時期（初回及び最終）ごとに要約統計量を算出した。各薬物動態パラメータは用量別に要約した。

また、定常状態到達時間は、$C_{12\,hr}$の推移に基づき視覚的に評価した。C_{max}、$C_{12\,hr}$及び $AUC_{0\text{-}12\,hr}$の累積係数を最終投与／初回投与の比より算出した。薬物動態パラメータを用量間で比較した。

【安全性】

有害事象は用量別（200 mg 1日2回、400 mg 1日2回及びプラセボ）に集計した。臨床検査値、体重及びバイタルサイン並びに心電図パラメータについては、用量別、測定時期ごとに要約統計量を算出した。

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2.7.6.2.9.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.9-2]及び[表 2.7.6.2.9-3]に示す。

表 2.7.6.2.9-2　　被験者の内訳（I-P05011 試験）

	グループ1		グループ2	
	ポサコナゾール 200 mg 1日2回	プラセボ 1日2回	ポサコナゾール 400 mg 1日2回	プラセボ 1日2回
総被験者数	8	4	8	4
内訳				
完了	7	4	8	4
中止	1	0	0	0
被験者の都合	1†	0	0	0

† 最終投与日（14日目）の早朝（投与前）に被験者の都合（治験薬投与又はその他の処置との関連なし）により中止した。

Data source: [資料5.3.3.1.2: I_P05011] 10.1

表 2.7.6.2.9-3　　被験者の背景（I-P05011 試験）

	治験薬	被験者数	算術平均	標準偏差	範囲
年齢（歳）	ポサコナゾール200 mg 1日2回	8	27.63	3.25	21.00 - 31.00
	ポサコナゾール400 mg 1日2回	8	26.75	4.03	21.00 - 33.00
	プラセボ 1日2回	8	28.63	3.58	23.00 - 34.00
身長（cm）	ポサコナゾール200 mg 1日2回	8	173.01	5.53	163.50 - 179.50
	ポサコナゾール400 mg 1日2回	8	174.05	3.39	170.30 - 180.40
	プラセボ 1日2回	8	173.43	4.81	165.80 - 180.60
体重（kg）	ポサコナゾール200 mg 1日2回	8	64.26	6.74	52.90 - 72.00
	ポサコナゾール400 mg 1日2回	8	64.30	3.59	59.60 - 69.30
	プラセボ 1日2回	8	63.83	4.62	58.10 - 70.00
BMI（kg/m^2）	ポサコナゾール200 mg 1日2回	8	21.43	1.63	19.10 - 23.60
	ポサコナゾール400 mg 1日2回	8	21.26	1.55	19.60 - 23.50
	プラセボ 1日2回	8	21.21	1.16	19.30 - 22.90

Data source: [資料5.3.3.1.2: I_P05011] 表5

2.7.6.2.9.3　　薬物動態の結果

本試験では、ポサコナゾール経口懸濁液を投与した全被験者16例から得られた血漿中薬物濃度データを薬物動態解析に含めた。日本人健康被験者にポサコナゾール経口懸濁液200 mg 又は400 mg を1日2回14日間食後に反復経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.9-4]に示す。

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表 2.7.6.2.9-4　　日本人健康被験者にポサコナゾール経口懸濁液 200 mg 又は 400 mg を 1 日 2 回 14 日間食後に反復経口投与した際の血漿中薬物動態パラメータの要約（I-P05011 試験）

薬物動態パラメータ		ポサコナゾール 200 mg 1日2回	ポサコナゾール 400 mg 1日2回	
		N=8†	N=8	N=7‡
1日目	T_{max} (hr)	5.00 (4 - 8)	5.00 (4 - 8)	5.00 (4 - 8)
	C_{max} (ng/mL)	563 (42)	569 (29)	526 (23)
	$C_{12\ hr}$ (ng/mL)	313 (31)	388 (22)	370 (20)
	$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	3609 (29)	4420 (24)	4145 (19)
14日目	T_{max} (hr)	5.00 (2 - 12)	4.00 (3 - 6)	4.00 (3 - 6)
	C_{max} (ng/mL)	3353 (26)	3704 (40)	3229 (20)
	$C_{12\ hr}$ (ng/mL)	2901 (29)	3026 (40)	2636 (21)
	C_{avg} (ng/mL)	2675 (24)	3206 (39)	2806 (22)
	$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	32098 (24)	38475 (39)	33669 (22)
	$t_{1/2}$ (hr)	19.2 (25)	25.4 (40)	21.8 (8)
	V_d/F (L)	181 (34)	391 (20)	389 (22)
	CL/F (L/hr)	6.58 (26)	11.5 (30)	12.4 (21)
累積係数	C_{max}	6.10 (27)	6.51 (20)	6.29 (20)
	$C_{12\ hr}$	9.07 (22)	7.80 (27)	7.32 (23)
	$AUC_{0\text{-}12\ hr}$	8.73 (14)	8.60 (20)	8.20 (18)

算術平均（%CV）、T_{max}は中央値（範囲）
CV：変動係数
† 14日目は N=7
‡ 棄却検定（Smirnov-Grubbs test）の結果、外れ値と判定された1例を除いた結果。当該被験者の最終投与後の $t_{1/2}$は群内平均値の約2倍となる50.3時間であった。

Data source: [資料5.3.3.1.2: I_P05011] 16.1.9.2

日本人健康被験者にポサコナゾール経口懸濁液を1日2回14日間食後に反復経口投与した際、200 mg 及び400 mg のいずれでも、血漿中ポサコナゾール濃度は、投与開始後8日目（6～10日目）に、概して定常状態に到達した。$AUC_{0\text{-}12\ hr}$の累積係数［14日目（最終投与）／1日目（初回投与）］の算術平均は、それぞれ8.73及び8.60であった。

各薬物動態パラメータを用量間で比較した結果、1日目の T_{max} には用量間で差は認められなかった（いずれも4～8時間）が、14日目では400 mg 1日2回投与（3～6時間）より200 mg 1日2回投与（2～12時間）で大きなばらつきが認められた。最終投与後の $t_{1/2}$の算術平均（変動係数）は、200 mg 及び400 mg 1日2回投与後でそれぞれ19.2時間（25%）及び25.4時間（40%）であった。400 mg 1日2回投与した8例中1例が外れ値（50.3時間）を示し、この1例を除くと、残り7例の算術平均（変動係数）は21.8時間（8%）であり、両投与群でほぼ同じであった。

C_{max} は、1日目及び14日目ともに用量間で明確な相違はなかった。$AUC_{0\text{-}12\ hr}$ には用量に依存した増加傾向が認められたものの、その増加の程度は200 mg 及び400 mg 1日2回投与時の比較において、1日目で1.22倍、14日目で1.20倍であり、いずれも用量比（2倍）を下回った。

2.7.6.2.9.4　　安全性の結果

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。日本人健康被験者にポサコナゾール経口懸濁液200 mg 及び400 mg 又はプラセボを1日2回14日間食後に反復経口

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。治験薬を投与された被験者24例中15例に有害事象が発現し、そのうち副作用は12例（200 mg：4例、400 mg：7例、プラセボ：1例）であった。最もよくみられた副作用は、ACTH 刺激試験異常6例（200 mg：1例、400 mg：4例、プラセボ：1例、すべて軽度）、血中コルチゾール減少5例（200 mg：1例、400 mg：3例、プラセボ：1例、すべて軽度）、発疹4例（200 mg：1例、400 mg：3例、すべて中等度）であった。副作用はいずれも治験薬投与期間中又は投与後に軽快あるいは消失した（血中コルチゾール低値が継続していた1例については、追跡調査により安全性上問題となる臨床的意義はないと判断された）。9例で報告された臨床検査の副作用を除いたその他の臨床検査値、バイタルサイン及び心電図で、治験薬との関連が疑われた特記すべき異常所見は認められなかった。

2.7.6.2.9.5　　結論

1) 日本人健康被験者にポサコナゾール経口懸濁液200 mg 及び400 mg を1日2回14日間食後に反復経口投与した際の薬物動態は、投与開始8日目に概して定常状態に到達することが確認され、$AUC_{0\text{-}12\ hr}$ に基づく累積係数は約9であった。
2) 日本人健康被験者にポサコナゾール経口懸濁液200 mg 及び400 mg を1日2回14日間食後に反復経口投与した際の1日目及び14日目の C_{max} 及び $AUC_{0\text{-}12\ hr}$ を200 mg 及び400 mg の用量間で比較した結果、C_{max} には用量間で明確な相違が認められず、$AUC_{0\text{-}12\ hr}$ の増加（平均1.2倍に増加）は用量比（2倍）を下回ったことから、ポサコナゾール経口懸濁液の1日2回14日間食後反復経口投与では、1回用量200～400 mg の範囲において吸収の飽和が生じている可能性が示唆された。
3) 日本人健康被験者にポサコナゾール経口懸濁液200 mg 及び400 mg 又はプラセボを1日2回14日間食後に反復経口投与した際の忍容性は、許容範囲内であると考えられた。

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2.7.6.2.10　　日本人健康被験者を対象とした単回経口投与試験（I-P05014試験）［参考資料］

治験総括報告書[資料5.3.3.1.3: I_P05014]の概要を以下に示す。

2.7.6.2.10.1　　試験方法

治験実施計画書標題／番号

日本人健康被験者を対象としたポサコナゾールの空腹時投与におけるバイオアベイラビリティ比較試験／I-P05014試験

治験責任医師／実施医療機関

[redacted]（日本）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

日本人健康被験者を対象として、ポサコナゾール経口懸濁液100、200又は400 mg を空腹時に単回経口投与した際の薬物動態プロファイル及び安全性について検討する。

試験デザイン

本試験は、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100、200又は400 mg を空腹時に単回経口投与した際の薬物動態プロファイル及び安全性を評価する、非盲検、並行群間、単回投与試験であった。各群8例の3群に割り付けられた被験者に、ポサコナゾール経口懸濁液100、200又は400 mg をそれぞれ空腹時に単回経口投与した。

投与期間

単回

用法・用量

第1～3群にポサコナゾール経口懸濁液100、200又は400 mg をいずれも空腹時に単回経口投与した。

治験薬の内容を、[表 2.7.6.2.10-1]に示す。

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表 2.7.6.2.10-1　治験薬の内容（I-P05014 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤

診断／選択基準

スクリーニング時に BMI が17.6 kg/m^{2}以上27.5 kg/m^{2}未満で、20歳以上45歳以下の日本人の健康な男性

評価基準

【薬物動態】

空腹時にポサコナゾール経口懸濁液を単回経口投与し、血漿中薬物濃度測定用検体を投与前及び投与後144時間までの規定した時点で採取した。ポサコナゾールの血漿中薬物動態パラメータ（C_{max}、T_{max}、C_{last}、T_{last}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、$t_{1/2}$、CL/F 及び V_d/F 等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

各用量群で得られた血漿中ポサコナゾール濃度データに基づき、ノンコンパートメントモデル解析により、C_{max}、T_{max}、C_{last}、T_{last}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、$t_{1/2}$、CL/F 及び V_d/F 等の薬物動態パラメータを算出した。また、血漿中ポサコナゾール濃度推移に二相性の消失パターンが観察されたことから、非線形最小二乗法に基づく2-コンパートメントモデル解析により、T_{lag}、$t_{1/2abs}$、$t_{1/2\alpha}$ 及び $t_{1/2\beta}$ を算出した。

各種薬物動態パラメータについて用量群別に集計し、要約統計量を算出した。

【安全性】

有害事象は用量群別及び程度別に集計した。

臨床検査値、体重、バイタルサイン及び心電図パラメータについては用量群別、測定時期ごとに要約統計量を算出した。

2.7.6.2.10.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.10-2]及び[表 2.7.6.2.10-3]に示す。

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表 2.7.6.2.10-2　　被験者の内訳（I-P05014 試験）

	ポサコナゾール 100 mg	ポサコナゾール 200 mg	ポサコナゾール 400 mg
総被験者数	8	8	8
内訳			
完了	8	8	8
中止	0	0	0

Data source: [資料5.3.3.1.3: I_P05014] 14.1.1

表 2.7.6.2.10-3　　被験者の背景（I-P05014 試験）

	群	算術平均	標準偏差	範囲
年齢（歳）	第1群	24.63	4.57	20.00 - 33.00
	第2群	24.88	2.70	21.00 - 29.00
	第3群	27.38	6.91	23.00 - 44.00
身長（cm）	第1群	171.36	4.22	166.40 - 176.00
	第2群	172.00	2.65	166.60 - 175.70
	第3群	170.68	4.17	163.40 - 177.00
体重（kg）	第1群	63.63	6.62	54.00 - 72.10
	第2群	62.81	5.62	55.50 - 69.50
	第3群	63.94	4.28	58.50 - 69.50
BMI（kg/m^2）	第1群	21.66	1.93	19.50 - 24.20
	第2群	21.23	1.71	18.70 - 23.60
	第3群	21.99	1.81	19.90 - 25.50

第1群：ポサコナゾール経口懸濁液100 mg を空腹時に単回経口投与
第2群：ポサコナゾール経口懸濁液200 mg を空腹時に単回経口投与
第3群：ポサコナゾール経口懸濁液400 mg を空腹時に単回経口投与

Data source: [資料5.3.3.1.3: I_P05014] 14.1.2

2.7.6.2.10.3　　薬物動態の結果

本試験では、ポサコナゾール経口懸濁液を投与した被験者24例から得られた血漿中薬物濃度データを薬物動態解析に含めた。日本人健康被験者にポサコナゾール経口懸濁液100、200及び400 mg を空腹時に単回経口投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.10-4]に示す。

血漿中ポサコナゾールの薬物動態パラメータを用量間で比較した結果、100、200及び400 mg の用量範囲で経口懸濁液を空腹時投与した際、C_{max} 及び AUC の算術平均については100 mg 群と200 mg 群との間では増加が認められなかったが、200 mg 群と400 mg 群との間ではほぼ用量比に応じた増加が認められた。また、CL/F 及び V_d/F も用量間で異なっており、薬物動態の非線形性が示唆された。T_{max} は用量間でほぼ同様で（棄却検定で外れ値と判定された被験者1例を除く）、$t_{1/2}$も用量間に明らかな違いは認められなかった。

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表 2.7.6.2.10-4　日本人健康被験者にポサコナゾール経口懸濁液 100、200 及び 400 mg を空腹時に単回経口投与した際の血漿中薬物動態パラメータの要約（I-P05014 試験）

用量（mg）	100	200	200	400
例数	8	8	7†	8
ノンコンパートメントモデル解析				
C_{max} (ng/mL)	123 (45)	88.8 (44)	97.5 (34)	248 (70)
T_{last} † (hr)	84.0 (48 - 120)	72.0 (48 - 96)	72.0 (48 - 96)	72.0 (48 - 120)
C_{last}† (ng/mL)	10.2 (30)	8.71 (26)	9.03 (24)	9.13 (35)
$AUC_{0\text{-}last}$ (ng·hr/mL)	3288 (51)	2520 (32)	2617 (31)	5610 (77)
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	3686 (44)	2833 (30)	2945 (29)	5877 (72)
T_{max} (hr)	3.50 (2 - 6)	4.50 (2 - 48)	3.00 (2 - 6)	3.00 (2 - 4)
$t_{1/2}$ (hr)	26.1 (46)	24.4 (24)	24.5 (26)	19.8 (21)
CL/F (L/hr)	32.8 (48)	75.0 (23)	71.8 (22)	108 (67)
V_d/F (L)	1221 (63)	2595 (27)	2505 (28)	3260 (78)
2-コンパートメントモデル解析				
T_{lag} (hr)	0.443 (52) ‡	-†	0.478 (68) ‡	0.676 (46) §
$t_{1/2abs}$ (hr)	1.10 (35) ‡	-†	0.987 (76) ‡	0.784 (86) §
$t_{1/2\alpha}$ (hr)	2.01 (40) ‡	-†	2.47 (35) ‡	1.91 (56) §
$t_{1/2\beta}$ (hr)	31.4 (43) ‡	-†	25.2 (29) ‡	21.7 (34) §

算術平均（%CV）、T_{max} 及び T_{last} は中央値（範囲）
CV：変動係数
† 他の被験者とは明らかに異なる血漿中濃度推移を示した1例から得られたデータには2-コンパートメントモデル解析を適用できなかった。
‡ n=6
§ n=7

Data source: [資料5.3.3.1.3: I_P05014] 16.1.9.2

2.7.6.2.10.4　安全性の結果

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。日本人健康被験者にポサコナゾール経口懸濁液100、200及び400 mg を空腹時に単回経口投与した際、安全で忍容性は良好であった。咽頭炎（後述）以外の重篤な有害事象及び死亡はなく、有害事象により中止した被験者はいなかった。ポサコナゾール投与後、24例中2例に有害事象が発現し、咽頭炎及び白血球数増加であった。咽頭炎については、併用薬による処置が行われ、事後検査時に軽快した。本事象は、他の被験者への感染予防のため、別の病室に移されたこと（本対応を入院と判断）、及び治験での入所期間が延長されたことから、重篤な有害事象として取り扱った。いずれの有害事象も中等度であり、副作用ではないと判断された。その他、臨床検査、バイタルサイン、心電図において特記すべき事項は認められなかった。

2.7.6.2.10.5　結論

1) 日本人健康被験者にポサコナゾール経口懸濁液100、200又は400 mg を空腹時に単回経口投与した結果、血漿中曝露量に関して明らかな用量相関性は認められず、薬物動態に線形性はみられなかった。
2) 日本人健康被験者にポサコナゾール経口懸濁液100、200又は400 mg を空腹時に単回経口投与した結果、安全性で忍容性は良好であった。

2.7.6.2.11　日本人健康被験者を対象とした単回及び反復経口投与並びに単回静脈内投与試験（P067試験）［評価資料］

治験総括報告書[資料5.3.3.1.4: P067]の概要を以下に示す。

2.7.6.2.11.1　試験方法

治験実施計画書標題／番号

日本人健康被験者を対象としたポサコナゾールの安全性、忍容性及び薬物動態の評価を目的とした単回及び反復経口投与並びに単回末梢静脈内投与試験／P067試験

治験責任医師／実施医療機関

[redacted]（日本）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

パート1

日本人健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）を用量漸増単回経口投与及びポサコナゾール静注用溶液を単回末梢静脈内投与した際の安全性及び忍容性を評価する。

パート2

日本人健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）を用量漸増反復経口投与した際の安全性及び忍容性を評価する。

【副次目的】

パート1

日本人健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）を用量漸増単回経口投与及びポサコナゾール静注用溶液を単回末梢静脈内投与した際の薬物動態パラメータに関する情報を得る。

パート2

日本人健康被験者を対象として、ポサコナゾール新錠剤 D（黄色）を用量漸増反復経口投与し

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た際の薬物動態パラメータに関する情報を得る。

【探索的目的】

パート1

日本人健康被験者にポサコナゾール新錠剤 D（黄色）を用量漸増単回経口投与した際の薬物動態パラメータ、ポサコナゾール静注用溶液を単回末梢静脈内投与した際の薬物動態パラメータを非日本人健康被験者（P05637試験又はP06356試験）と比較する。さらに、日本人健康被験者にポサコナゾール新錠剤 D（黄色）を用量漸増単回経口投与した際の絶対的バイオアベイラビリティを算出する。

パート2

日本人健康被験者にポサコナゾール新錠剤 D（黄色）を用量漸増反復経口投与した際の薬物動態パラメータを非日本人健康被験者（P05637試験）と比較する。

試験デザイン

【パート1】

本試験のパート1は、日本人健康被験者を対象とした、ポサコナゾール新錠剤 D（黄色）を単回経口投与及びポサコナゾール静注用溶液を単回末梢静脈内投与した際の安全性、忍容性及び薬物動態を評価する、二重盲検、無作為化、プラセボ対照、交互パネル、用量漸増単回経口投与及び単回末梢静脈内投与試験であった。パネル A には、ポサコナゾール新錠剤 D（黄色）200 mg 又はプラセボ（第1期）、400 mg 又はプラセボ（第2期）を空腹時に単回経口投与した。第3期では、静注用溶媒［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（SBECD)］又はプラセボを空腹時に単回末梢静脈内投与した。パネル B には、ポサコナゾール新錠剤 D（黄色）300 mg 又はプラセボ（第1期）、600 mg 又はプラセボ（第2期）を空腹時に単回経口投与した。第3期では、ポサコナゾール静注用溶液300 mg 又はプラセボを空腹時に単回末梢静脈内投与した。投与期の間は8日以上間隔を空けた。

【パート2】

本試験のパート2は、日本人健康被験者を対象とした、ポサコナゾール新錠剤 D（黄色）を反復経口投与した際の安全性、忍容性及び薬物動態を評価する、二重盲検、無作為化、プラセボ対照、逐次パネル、用量漸増反復投与試験であった。パネル C にはポサコナゾール新錠剤 D（黄色）200 mg 又はプラセボ、パネル D には400 mg 又はプラセボを1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後)］空腹時に反復経口投与した。

投与期間

パート1：単回

パート2：反復（10日間）

用法・用量

パート1では、いずれも10時間以上絶食後、第1期及び第2期でポサコナゾール新錠剤 D（黄色）又はプラセボを単回経口投与し、第3期でポサコナゾール静注用溶液、SBECD（ポサコナゾール非含有）又はポサコナゾール静注用溶液のプラセボ（5%ブドウ糖注射液）を単回末梢静脈内投与した。

パート2では、ポサコナゾール新錠剤 D（黄色）又はプラセボを1日目は1日2回（初回は10時間以上絶食後、2回目は規定の夕食摂取後）、以降2～10日はいずれも10時間以上絶食後に1日1回反復経口投与した。

【パート1】

パネル A 第1期：ポサコナゾール新錠剤 D（黄色）200 mg（100 mg×2錠）又はプラセボを空腹時に単回経口投与

パネル A 第2期：ポサコナゾール新錠剤 D（黄色）400 mg（100 mg×4錠）又はプラセボを空腹時に単回経口投与

パネル A 第3期：SBECD 又はポサコナゾール静注用溶液のプラセボを空腹時に30分かけて単回末梢静脈内投与

パネル B 第1期：ポサコナゾール新錠剤 D（黄色）300 mg（100 mg×3錠）又はプラセボを空腹時に単回経口投与

パネル B 第2期：ポサコナゾール新錠剤 D（黄色）600 mg（100 mg×6錠）又はプラセボを空腹時に単回経口投与

パネル B 第3期：ポサコナゾール静注用溶液300 mg 又はポサコナゾール静注用溶液のプラセボを空腹時に30分かけて単回末梢静脈内投与

【パート2】

パネル C：ポサコナゾール新錠剤 D（黄色）200 mg（100 mg×2錠）又はプラセボを1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与

パネル D：ポサコナゾール新錠剤 D（黄色）400 mg（100 mg×4錠）又はプラセボを1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与

治験薬の内容を、[表 2.7.6.2.11-1]に示す。

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表 2.7.6.2.11-1　　治験薬の内容（P067 試験）

薬剤	力価	剤形
ポサコナゾール新錠剤 D（黄色）	ポサコナゾール100 mg	錠剤
ポサコナゾール新錠剤 D（黄色）のプラセボ	-	錠剤
ポサコナゾール静注用溶液	ポサコナゾール18 mg/mL	注射剤
ポサコナゾール静注用溶液のプラセボ（5%ブドウ糖注射液）	-	注射剤
SBECD（静注用溶媒）	-	注射剤

診断／選択基準

スクリーニング時に BMI が18.5 kg/m^{2}以上28 kg/m^{2}未満で、20歳以上45歳以下の日本人の健康な男性

評価基準

【薬物動態】

パート1では、ポサコナゾール単回経口投与及び単回末梢静脈内投与した際の血漿中薬物濃度測定用検体を、各投与前及び各投与後又は各投与開始後168時間までの規定した時点で頻回採取した。

パート2では、血漿中薬物濃度測定用検体を、1日目の朝投与前及び朝投与後12時間まで、並びに10日目の朝投与前及び朝投与後168時間までの規定した時点で頻回採取した。また、トラフ検体を、2～9日目の投与前に採取した。

ポサコナゾールの血漿中薬物動態パラメータ（AUC、C_{max}、C_{trough} 等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。パート1では、short peripheral catheter thrombophlebitis（SPCT）スコアを用いて投与部位反応／局所忍容性を評価した。また、パート2では ACTH 負荷投与試験並びに血中アルドステロン濃度及び尿中アルドステロン濃度を測定し、ポサコナゾールの副腎への影響を評価した。パート1では、ポサコナゾールを単回末梢静脈内投与した際の心血管系への影響を評価するため、投与1日前と投与後の同時刻に心電図を測定した。

統計計画及び解析

【薬物動態】

パート1では、投与群を固定効果、被験者を変量効果とした線形混合効果モデルにより、ポサコナゾール300 mg を投与した際の単回末梢静脈内投与時に対する単回経口投与時の AUC の幾何平均比及び90%信頼区間を算出し、ポサコナゾールの絶対的バイオアベイラビリティを推定した。用量比例性は、AUC、C_{max} 及び C_{trough} データに基づき、パネル、用量とパネルの交互作用を固定効果の項、パネル内被験者を変量効果とした線形混合効果モデルを用いて評価した。日本人健康被験者と非日本人健康被験者のポサコナゾール単回投与時の薬物動態の類似性は P05637試験と P067試験のポサコナゾール200 mg 及び400 mg 経口投与時のデータ、及び P06356試験と P067試験

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のポサコナゾール300 mg 末梢静脈内投与時のデータを用いて、AUC、C_{max} 及び C_{trough} の幾何平均比及び90%信頼区間を算出し、評価した。

パート2では、ポサコナゾールの $AUC_{0\text{-}12\ hr}$ 及び $C_{12\ hr}$ の幾何平均比（第10日／第1日）及び90%信頼区間を算出し、蓄積性を評価した。定常状態への到達時期は、投与2日目～10日目までの反復投与中の血漿中 C_{trough} に基づいて推定した。反復投与後（第10日）の日本人健康被験者及び非日本人健康被験者（本試験の10日目、及び P05637試験の14日目）の薬物動態の類似性は、人種を固定効果、対数用量を共変量、人種と対数用量の交互作用を固定効果の項とした共分散分析モデルにより解析し、AUC、C_{max} 及び C_{trough} の幾何平均比（日本人／非日本人）の点推定値及びその90%信頼区間を算出し、評価した。

【安全性】

有害事象を集計し、一覧表に示した。身体所見、バイタルサイン、心電図及び臨床検査値の要約統計量も算出した。ACTH 負荷試験、血中アルドステロン濃度及び尿中アルドステロン濃度を投与群ごとに要約した。SPCT スコアの評価カテゴリごとの発現数及び発現率(%)を算出した。Total thrombophlebitis score の要約統計量を算出した。

2.7.6.2.11.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.11-2]及び[表 2.7.6.2.11-3]に示す。

表 2.7.6.2.11-2　被験者の内訳（P067 試験）

	パート1		パート2		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	16		16		32	
内訳						
完了	16	(100.0)	15	(93.8)	31	(96.9)
中止	0	(0.0)	1	(6.3)	1	(3.1)
臨床症状の有害事象	0	(0.0)	1	(6.3)	1	(3.1)
臨床検査値の有害事象	0	(0.0)	0	(0.0)	0	(0.0)
その他	0	(0.0)	0	(0.0)	0	(0.0)

Data source: [資料5.3.3.1.4: P067]14.1.1.1

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表 2.7.6.2.11-3　　被験者の背景（P067 試験）

	パート1		パート2		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	16		16		32	
性別						
男性	16	(100.0)	16	(100.0)	32	(100.0)
年齢（歳）						
0～19歳	0	(0.0)	0	(0.0)	0	(0.0)
20～29歳	9	(56.3)	9	(56.3)	18	(56.3)
30～39歳	6	(37.5)	7	(43.8)	13	(40.6)
39歳超	1	(6.3)	0	(0.0)	1	(3.1)
算術平均	29.6		27.7		28.7	
標準偏差	6.5		5.4		5.9	
中央値	28.5		27.5		28.0	
範囲	21 - 44		20 - 36		20 - 44	
人種						
アジア系	16	(100.0)	16	(100.0)	32	(100.0)
身長（cm）						
算術平均	171.7		173.3		172.5	
標準偏差	7.3		4.9		6.2	
中央値	170.3		171.3		170.8	
範囲	158.7 - 183.1		168.2 - 184.9		158.7 - 184.9	
体重（kg）						
算術平均	66.8		65.3		66.0	
標準偏差	10.2		7.0		8.6	
中央値	64.4		64.1		64.1	
範囲	54.7 - 86.2		57.3 - 77.9		54.7 - 86.2	
BMI（kg/m^2）						
算術平均	22.6		21.8		22.2	
標準偏差	2.5		2.3		2.4	
中央値	22.0		21.4		21.6	
範囲	19.4 - 26.7		19.1 - 26.4		19.1 - 26.7	

Data source: [資料5.3.3.1.4: P067]14.1.1.4

2.7.6.2.11.3　　薬物動態の結果

<u>パート1</u>

本試験のパート1では、ポサコナゾール新錠剤 D（黄色）200～600 mg 及びポサコナゾール静注用溶液300 mg を投与した被験者12例から得られた血漿中薬物濃度データを薬物動態解析に含めた。日本人健康被験者にポサコナゾール新錠剤 D（黄色）200～600 mg を空腹時に単回経口投与及び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血漿中薬物動態パラメータの要約を[表 2.7.6.2.11-4]に示す。ポサコナゾールは4.00～5.50時間の T_{max} 中央値で C_{max} に到達した。また、終末相の $t_{1/2}$（幾何平均）は21.80～23.23時間であった。CL/F 及び V_d/F と用量との間に明らかな傾向は認められず、ポサコナゾールの血漿中曝露量は検討した用量範囲において、概して用量に比例して増加することが示唆された。ポサコナゾール静注用溶液300 mg の末梢静脈内投与時に対するポサコナゾール新錠剤 D（黄色）300 mg の単回経口投与時の $AUC_{0-\infty}$

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の幾何平均比（90%信頼区間）は0.60（0.49, 0.74）であり、したがって経口投与時の絶対的バイオアベイラビリティは約60%と推定された。末梢静脈内投与時の終末相の $t_{1/2}$（幾何平均）は21.62時間で、経口投与時と類似していた。

ポサコナゾール新錠剤 D（黄色）200又は400 mg を空腹時に単回経口投与した際、非日本人健康被験者と比較した日本人健康被験者の $AUC_{0-\infty}$の幾何平均比（90%信頼区間）はそれぞれ0.58（0.43, 0.79）及び0.63（0.47, 0.85）で、日本人でやや $AUC_{0-\infty}$は低かったが、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際の $AUC_{0-\infty}$は類似していた［幾何平均比（90%信頼区間）: 1.07（0.86, 1.33）］。

<u>パート2</u>

本試験のパート2では、ポサコナゾール新錠剤 D（黄色）200又は400 mg を投与した被験者12例から得られ血漿中薬物濃度データを薬物動態解析に含めた。日本人健康被験者にポサコナゾール新錠剤 D（黄色）200又は400 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与した際の血漿中薬物動態パラメータの要約を[表2.7.6.2.11-5]に示す。ポサコナゾール新錠剤 D（黄色）200又は400 mg を1日1回10日間反復経口投与した際の1日目に対する10日目の $AUC_{0-12\ hr}$ の累積係数（90%信頼区間）はそれぞれ3.55（2.79, 4.51）及び4.31（3.34, 5.57）であり、$C_{12\ hr}$ でも同様の蓄積係数が認められた。1日目と10日目で T_{max}（中央値）は類似していた。また、反復経口投与10日目の終末相の $t_{1/2}$は、パート1の単回経口投与時と同程度であった。

反復経口投与5日目にはすべての被験者で $C_{24\ hr}$ が定常状態の90%に到達しており、400 mg 投与時の定常状態における $AUC_{0-24\ hr}$ の90%信頼区間は目標曝露量とした28800 ng·hr/mL を超えたが、200 mg 投与時では90%信頼区間の下限値がわずかであるが、28800 ng·hr/mL よりも低かった。

ポサコナゾール新錠剤 D（黄色）200又は400 mg を反復経口投与した際、非日本人健康被験者と比較した日本人健康被験者の定常状態の $AUC_{0-24\ hr}$ の幾何平均比（90%信頼区間）は1.05（0.80, 1.38）で、日本人健康被験者と非日本人健康被験者で $AUC_{0-24\ hr}$ は類似していた。C_{max} 及び $C_{24\ hr}$ でも同様の傾向が認められた。

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表 2.7.6.2.11-4　日本人健康被験者にポサコナゾール新錠剤 D（黄色）200～600 mg を空腹時に単回経口投与又はポサコナゾール静注用溶液 300 mg を空腹時に単回末梢静脈内投与した際のポサコナゾールの薬物動態パラメータ（P067 試験、パート 1）

薬物動態パラメータ	パネル A 第1期 (n=6)	パネル B 第1期 (n=6)	パネル A 第2期 (n=6)	パネル B 第2期 (n=6)	パネル B 第3期 (n=6)	rMSE
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)†	2991.33 (2242.77, 3989.74)	6845.75 (5132.28, 9131.28)	6192.10 (4642.56, 8258.82)	10781.23 (8083.07, 14380.06)	15401.34 (11546.43, 20543.26)	0.301
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)†	5928.16 (4584.91, 7664.95)	13221.13 (10224.56, 17095.92)	11980.83 (9266.11, 15490.87)	21645.45 (16740.27, 27987.94)	24529.79 (18970.12, 31718.87)	0.266
$AUC_{0\text{-}\infty}$ (ng·hr/mL)†	13291.53 (10215.06, 17294.54)	29426.77 (22613.27, 38293.21)	27753.41 (21329.57, 36111.91)	51615.01 (39745.94, 67028.46)	48860.12 (37547.00, 63581.93)	0.258
C_{max} (ng/mL)†	401.04 (285.75, 562.84)	890.98 (634.80, 1250.53)	830.98 (592.10, 1166.23)	1474.95 (1054.89, 2062.29)	3131.63 (2231.22, 4395.39)	0.319
$C_{12\ hr}$ (ng/mL)†	268.63 (209.55, 344.38)	597.02 (465.64, 765.46)	526.30 (410.54, 674.70)	992.20 (775.79, 1268.96)	849.35 (662.45, 1088.98)	0.239
$C_{24\ hr}$ (ng/mL)†	216.51 (170.53, 274.88)	471.41 (371.27, 598.56)	434.47 (342.21, 551.61)	815.19 (642.07, 1034.99)	681.57 (536.79, 865.41)	0.245
T_{max} (hr)‡	4.00 (3.00 - 8.00)	5.00 (4.00 - 6.00)	4.00 (4.00 - 6.00)	5.50 (4.00 - 6.00)	0.50 (0.50 - 1.00)	-
$t_{1/2}$ (hr)§	23.23 (12.78)	21.80 (12.64)	22.39 (24.12)	21.96 (15.91)	21.62 (13.70)	-
CL/F 又は CL (L/hr)§	14.69 (49.10)	10.39 (30.53)	14.27 (22.81)	11.78 (29.58)	6.26 (15.67)	-
V_d/F 又は V_d (L)§	492.40 (45.66)	326.67 (28.84)	461.15 (20.97)	373.23 (26.61)	195.12 (16.60)	-

パネル A 第1期：ポサコナゾール新錠剤 D（黄色）200 mg を空腹時に単回経口投与
パネル B 第1期：ポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与
パネル A 第2期：ポサコナゾール新錠剤 D（黄色）400 mg を空腹時に単回経口投与
パネル B 第2期：ポサコナゾール新錠剤 D（黄色）600 mg を空腹時に単回経口投与
パネル B 第3期：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
CI：信頼区間、CV：変動係数、GM：幾何平均、rMSE：線形混合効果モデルで求めた平均二乗誤差の平方根。rMSE × 100%は元の尺度での被験者内%CV の近似値となる。
† 自然対数変換値を用いて線形混合効果モデルで求めた最小二乗平均及び95%CI を逆変換した値
‡ 中央値（範囲）
§ GM 及び GM%CV
Data source: [資料5.3.3.1.4: P067] 16.2.5.3

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表 2.7.6.2.11-5　　日本人健康被験者にポサコナゾール新錠剤 D（黄色）200 mg 又は 400 mg を 1 日 1 回 10 日間空腹時に反復経口投与した際のポサコナゾールの薬物動態パラメータ（P067 試験、パート 2）

薬物動態パラメータ	パネル C (n=6)	パネル D (n=6[#])	rMSE
1日目（反復投与初日）			
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)[†]	4700.25 (3761.09, 5873.91)	6367.17 (5094.95, 7957.06)	0.228
C_{max} (ng/mL)[†]	683.98 (528.50, 885.22)	910.33 (703.38, 1178.15)	-
$C_{12\ hr}$ (ng/mL)[†]	380.59 (321.12, 451.08)	590.26 (498.03, 699.57)	0.192
T_{max} (hr)[‡]	4.00 (3.00 - 5.00)	4.50 (4.00 - 6.00)	-
10日目（反復投与最終日）			
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)[†]	16668.64 (13338.09, 20830.83)	27466.08 (21462.12, 35149.65)	-
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)[§]	31112.99 (25786.54, 37539.68)	51796.63 (42166.67, 63625.87)	-
$AUC_{0\text{-}\infty}$ (ng·hr/mL)[§]	80725.12 (59155.23, 110160.1)	135883.85 (96664.21, 191016.10)	-
C_{max} (ng/mL)[†]	1775.63 (1371.98, 2298.04)	2768.19 (2077.11, 3689.19)	-
$C_{12\ hr}$ (ng/mL)[†]	1254.32 (1058.32, 1486.61)	2044.78 (1692.17, 2470.88)	-
$C_{24\ hr}$ (ng/mL)[§]	1149.32 (921.17, 1433.97)	1953.58 (1533.05, 2489.45)	-
T_{max} (hr)[‡]	4.50 (3.00 - 6.00)	4.00 (4.00 - 6.00)	-
$t_{1/2}$ (hr)[‖]	23.95 (22.97)	24.18 (28.33)	-
CL/F (L/hr)[‖]	6.43 (20.87)	7.72 (20.13)	-
V_d/F (L)[‖]	222.13 (16.34)	269.39 (11.06)	-
累積係数（10日目／1日目）[¶]			
$AUC_{0\text{-}12\ hr}$	3.55 (2.79, 4.51)	4.31 (3.34, 5.57)	-
$C_{12\ hr}$	3.30 (2.69, 4.03)	3.46 (2.80, 4.29)	-

パネル C：ポサコナゾール新錠剤 D（黄色）200 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与
パネル D：ポサコナゾール新錠剤 D（黄色）400 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与
CI：信頼区間、CV：変動係数、GM：幾何平均、rMSE：線形混合効果モデルで求めた平均二乗誤差の平方根。rMSE × 100%は元の尺度での被験者内%CV の近似値となる。
† 自然対数変換値を用いて線形混合効果モデルで求めた最小二乗平均及び95%CI を逆変換した値
‡ 中央値 （範囲）
§ 自然対数変換値を用いて分散分析モデルで求めた最小二乗平均及び95%CI を逆変換した値
‖ GM 及び GM%CV
¶ 自然対数変換値を用いて線形混合効果モデルで求めた最小二乗平均差及び90%CI を逆変換した値
# パネル D の10日目は n=5

Data source: [資料5.3.3.1.4: P067] 16.2.5.3

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2.7.6.2.11.4　　安全性の結果

本試験では、治験薬を投与した全被験者32例を安全性解析対象集団に含めた。日本人健康被験者にポサコナゾール新錠剤 D（黄色）200～600 mg を空腹時に単回経口投与、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及びポサコナゾール新錠剤 D（黄色）200 mg 又は400 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後）］空腹時に反復経口投与した際、安全で忍容性は良好であった。32例の被験者のうち、治験期間中に5例に有害事象が認められ、いずれも副作用と判断された。本試験で認められた有害事象及び副作用を、[表 2.7.6.2.11-6]及び[表 2.7.6.2.11-7]に示す。有害事象はポサコナゾール新錠剤 D（黄色）200 mg の単回経口投与を受けた1例、ポサコナゾール静注用溶液300 mg の単回末梢静脈内投与を受けた2例、ポサコナゾール新錠剤 D（黄色）400 mg の反復経口投与を受けた1例、プラセボの反復経口投与を受けた1例に認められた。重篤な有害事象は認められなかった。ポサコナゾール新錠剤 D（黄色）400 mg の反復経口投与を受けた1例は、発熱のため2日目に試験を中止した。すべての有害事象は一過性で、発熱を除いて処置を要することなく消失した。その他、すべての臨床検査値、バイタルサイン及び心電図の経時的な値及びベースラインからの変化に重要な傾向は認められなかった。さらに、SBECD を投与したが、関連する有害事象や所見は認められなかった。また、ACTH 負荷試験、血中アルドステロン濃度及び尿中アルドステロン濃度、SPCT スコア、Total thrombophlebitis score についても評価したが、ポサコナゾールと関連した変化は認められなかった。

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表 2.7.6.2.11-6　　日本人健康被験者にポサコナゾール新錠剤 D（黄色）200～600 mg 又はプラセボを空腹時に単回経口投与あるいはポサコナゾール静注用溶液 300 mg、プラセボ又は SBECD を空腹時に単回末梢静脈内投与した際の有害事象の内訳（P067 試験、パート 1）

	プラセボ 経口投与 (N=8)		200 mg 経口投与 (N=6)		300 mg 経口投与 (N=6)		400 mg 経口投与 (N=6)		600 mg 経口投与 (N=6)		SBECD 静脈内投与 (N=6)		プラセボ 静脈内投与 (N=4)		300 mg 静脈内投与 (N=6)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
有害事象あり	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(33.3)
有害事象なし	8	(100.0)	5	(83.3)	6	(100.0)	6	(100.0)	6	(100.0)	6	(100.0)	4	(100.0)	4	(66.7)
副作用あり	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(33.3)
副作用なし	8	(100.0)	5	(83.3)	6	(100.0)	6	(100.0)	6	(100.0)	6	(100.0)	4	(100.0)	4	(66.7)
胃腸障害	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(33.3)
悪心	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(33.3)
神経系障害	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
頭痛	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Data source; [資料5.3.3.1.4: P067] 14 3 1 1

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表 2.7.6.2.11-7　　日本人健康被験者にポサコナゾール新錠剤 D（黄色）200 mg、400 mg 又はプラセボを 1 日 1 回 10 日間空腹時に反復経口投与した際の有害事象の内訳（P067 試験、パート 2）

	プラセボ 経口投与 (N=4)		200 mg 経口投与 (N=6)		400 mg 経口投与 (N=6)	
	n	(%)	n	(%)	n	(%)
有害事象あり	1	(25.0)	0	(0.0)	1	(16.7)
有害事象なし	3	(75.0)	6	(100.0)	5	(83.3)
副作用あり	1	(25.0)	0	(0.0)	1	(16.7)
副作用なし	3	(75.0)	6	(100.0)	5	(83.3)
一般・全身障害および投与部位の状態	0	(0.0)	0	(0.0)	1	(16.7)
発熱	0	(0.0)	0	(0.0)	1	(16.7)
臨床検査	1	(25.0)	0	(0.0)	0	(0.0)
アラニン・アミノトランスフェラーゼ増加	1	(25.0)	0	(0.0)	0	(0.0)

Data source; [資料5.3.3.1.4: P067] 14.3.1.2

2.7.6.2.11.5　　結論

1) 日本人健康被験者にポサコナゾール新錠剤 D（黄色）200～600 mg を空腹時に単回経口投与、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及びポサコナゾール新錠剤 D（黄色）200又は400 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後)］空腹時に反復経口投与した際、概して安全で忍容性は良好であった。
2) 日本人健康被験者にポサコナゾール新錠剤 D（黄色）300 mg を空腹時に単回経口投与した際の絶対的バイオアベイラビリティは約60%であった。
3) 日本人健康被験者にポサコナゾール新錠剤 D（黄色）を空腹時に単回経口投与した際の血漿中曝露は、200～600 mg の範囲で、概して用量に比例して増加することが示唆された。
4) 日本人健康被験者にポサコナゾール新錠剤 D（黄色）200又は400 mg を1日1回10日間［1日目は1日2回（初回は空腹時、2回目は規定の夕食摂取後)］空腹時に反復経口投与した際、定常状態の90%に第5日目までに到達した。ポサコナゾール新錠剤 D（黄色）400 mg を1日1回10日間（1日目は1日2回）反復経口投与した際、定常状態の $AUC_{0\text{-}24\ hr}$ の90%信頼区間の下限値は目標曝露量である28800 ng·hr/mL を超えていたが、200 mg の1日1回10日間（1日目は1日2回）反復経口投与ではわずかに下回っていた。
5) 日本人健康被験者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及びポサコナゾール新錠剤 D（黄色）を反復経口投与した際の薬物動態パラメータは、それぞれ非日本人健康被験者（P05637試験又は P06356試験）と類似していたが、ポサコナゾール新錠剤 D（黄色）を空腹時に単回経口投与した際の薬物動態パラメータは、非日本人健康被験者（P05637試験）と比較してやや低かった。

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2.7.6.2.12　非日本人健康被験者を対象とした用量漸増単回経口投与試験（[redacted]-098試験）［参考資料］

治験総括報告書[資料5.3.3.1.5: [redacted]_098]の概要を以下に示す。

2.7.6.2.12.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としたポサコナゾールを用量漸増単回経口投与した際の安全性及び忍容性試験／[redacted]-098試験

治験責任医師／実施医療機関

[redacted]（オランダ）

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

1) 健康被験者にポサコナゾール50、100、200、400、800及び1200 mg を単回経口投与した際のポサコナゾールの安全性及び忍容性を評価する。
2) 健康被験者にポサコナゾールを単回投与した際の薬物動態プロファイルを検討する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール旧錠剤を単回経口投与した際の安全性、忍容性及び薬物動態を評価する、二重盲検、無作為化、プラセボ対照、並行群間、用量漸増単回投与試験であった。各投与群で、被験者9例をポサコナゾール（6例）又はプラセボ（3例）のいずれかに無作為に割り付け、高脂肪食摂取後5分以内に、ポサコナゾール旧錠剤50、100、200、400、800及び1200 mg 又はプラセボを投与した。

投与期間

単回

用法・用量

ポサコナゾール旧錠剤50 mg（50 mg×1錠）、100 mg（100 mg×1錠）、200 mg（100 mg×2錠）、400 mg（100 mg×4錠）、800 mg（100 mg×8錠）及び1200 mg（100 mg×12錠）又はプラセボを高

脂肪食摂取後に単回経口投与した。治験薬の内容を、[表 2.7.6.2.12-1]に示す。

表 2.7.6.2.12-1　治験薬の内容（[redacted]-098 試験）

薬剤	力価	剤形
ポサコナゾール旧錠剤	ポサコナゾール50 mg	錠剤
ポサコナゾール旧錠剤	ポサコナゾール100 mg	錠剤
ポサコナゾール旧錠剤50 mg のプラセボ	-	錠剤
ポサコナゾール旧錠剤100 mg のプラセボ	-	錠剤

診断／選択基準

スクリーニング時に保険数理表に基づく体重の±15%以内の体重で、18歳以上45歳以下の健康な男性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、投与前及び投与後120時間までの規定した時点で採取した。また、尿中薬物濃度測定用検体を、投与前及び投与後48時間までの規定した間隔で採取することとしたが、安定性及び溶解性の問題のため、尿中薬物濃度については報告しなかった。薬物動態パラメータ（$AUC_{0-\infty}$、AUC_{0-last}、C_{max}、T_{max}、k_{el}、$t_{1/2}$、CL/F 及び V_d/F 等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

各投与量の薬物動態パラメータについて要約統計量を算出した。また、1 mg 当たりの曝露量に用量補正後の AUC 及び C_{max} の対数変換値について、処置（用量）を項とする分散分析モデルを用いて解析した。

2.7.6.2.12.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.12-2]及び[表 2.7.6.2.12-3]に示す。

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表 2.7.6.2.12-2　被験者の内訳（[redacted]-098 試験）

	50 mg		100 mg		200 mg		400 mg		800 mg		1200 mg		プラセボ		合計	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	6		6		6		6		6		6		18		54	
内訳																
完了	6	(100.0)	6	(100.0)	6	(100.0)	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)	54	(100.0)
中止	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Data source: [資料5.3.3.1.5: [redacted]_098] Appendix B-4, Subject Listing

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表 2.7.6.2.12-3　　被験者の背景（[redacted]-098 試験）

	n	年齢（歳）	体重（kg）	身長（cm）
ポサコナゾール	36	22.7 ± 4.7 (18 - 44)	78.1 ± 11.1 (53.6 - 102.8)	184.8 ± 6.9 (170 - 199)
プラセボ	18	22.8 ± 5.0 (18 - 41)	75.3 ± 10.1 (57.2 - 101.0)	183.2 ± 6.5 (174 - 200)
全体	54	22.7 ± 4.8 (18 - 44)	77.2 ± 10.8 (53.6 - 102.8)	184.3 ± 6.7 (170 - 200)
算術平均±標準偏差（範囲）				

Data source: [資料5.3.3.1.5: [redacted]_098] Appendix B-4, Demographic profile, Subject listing

2.7.6.2.12.3　　薬物動態の結果

本試験では、ポサコナゾール旧錠剤を投与した被験者36例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール旧錠剤50、100、200、400、800及び1200 mgを高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約並びに C_{max} 及び $AUC_{0-\infty}$の実測値及び用量補正値の算術平均を、それぞれ[表 2.7.6.2.12-4]及び[表 2.7.6.2.12-5]に示す。血漿中ポサコナゾール濃度は50～800 mg で概して用量に比例して増加した。しかし、1200 mgを投与した際の血漿中ポサコナゾール濃度は、800 mg 投与時にみられた濃度以下であったことから、800 mg を超える用量では吸収が飽和したことが示唆された。

経口投与した際、ポサコナゾールは緩やかに吸収され、T_{max} の算術平均は5.8～8.8時間であった。ポサコナゾール200～1200 mg を経口投与した際の $t_{1/2}$の算術平均は約25時間（24～28時間）であった。50及び100 mg 投与時の $t_{1/2}$の算術平均は、それぞれ16時間及び18時間であった。CL/F は用量に依存せず、4.1～6.6 mL/min/kg の範囲であった。V_d/F の算術平均は、6.6～15.0 L/kg で、広範な組織に分布した可能性が示唆された。安定性及び溶解性の問題のため、尿中薬物濃度については報告しなかった。

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表 2.7.6.2.12-4　　健康被験者にポサコナゾール旧錠剤 50、100、200、400、800 及び 1200 mg を高脂肪食摂取後に単回経口投与した際の血漿中薬物動態パラメータの要約（[redacted]-098 試験）

薬物動態パラメータ	算術平均 (%CV, N=6)					
	50 mg	100 mg	200 mg	400 mg	800 mg	1200 mg
体重 (kg)	75.65 (7)	66.63 (12)	85.58 (14)	80.37 (7)	75.98 (13)	85.20 (1)
C_{max} (ng/mL)	113.40 (46)	234.83 (26)	331.83 (21)	610.50 (31)	1319.50 (26)	933.17 (28)
T_{max} (hr)	6.33 (51)	7.33 (36)	5.83 (35)	6.33 (44)	6.17 (46)	8.83 (85)
T_{last} (hr)	62.50 (34)	92.00 (20)	112.00 (17)	116.00 (8)	120.00 (0)	120.00 (0)
$AUC_{0\text{-}last}$ (ng･hr/mL)	2317.14 (50)	6105.50 (28)	10354.03 (30)	19400.96 (33)	46983.74 (40)	41755.00 (42)
$AUC_{0\text{-}\infty}$ (ng･hr/mL)	2501.22 (45)	6356.61 (27)	10895.97 (31)	20263.58 (33)	49841.10 (43)	45260.27 (44)
k_{el} (1/hr)	0.0449 (18)	0.0382 (11)	0.0298 (28)	0.0307 (32)	0.0316 (38)	0.026 (26)
$t_{1/2}$ (hr)	15.86 (18)	18.34 (13)	24.50 (22)	24.10 (24)	24.42 (33)	28.49 (26)
CL/F (mL/min)	389.40 (40)	274.86 (21)	340.62 (40)	363.40 (35)	320.13 (48)	585.17 (73)
CL/F (mL/min/kg)	5.20 (42)	4.21 (27)	4.08 (46)	4.53 (34)	4.28 (49)	6.56 (65)
V_d/F (L)	511.13 (32)	431.26 (20)	674.31 (18)	781.49 (49)	594.10 (19)	1340.77 (58)
V_d/F (L/kg)	6.89 (40)	6.57 (24)	8.05 (24)	9.69 (47)	7.87 (19)	14.97 (49)

CV：変動係数

Data source: [資料5.3.3.1.5: [redacted]_098] Appendix B-2, Table 2

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表 2.7.6.2.12-5　　健康被験者にポサコナゾール旧錠剤 50、100、200、400、800 及び 1200 mg を高脂肪食摂取後に単回経口投与した際の C_{max} 及び $AUC_{0-\infty}$ の用量補正値（[redacted]-098 試験）

用量 (mg)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng･hr/mL)
50	2.27 (46)	50.0 (45)
100	2.35 (26)	63.6 (27)
200	1.66 (21)	54.5 (31)
400	1.53 (31)	50.7 (33)
800	1.65 (26)	62.3 (43)
1200	0.78 (28)	37.7 (44)
算術平均（%CV）、1 mg 当たりの曝露量に用量補正した。n＝6 CV：変動係数		

Data source: [資料5.3.3.1.5: [redacted]_098] Appendix B-2, Section 3.1 Table

2.7.6.2.12.4　　安全性の結果

本試験では、治験薬を投与した全被験者54例を安全性解析対象集団に含めた。健康被験者にポサコナゾール旧錠剤50、100、200、400、800及び1200 mg 又はプラセボ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。54例中27例で有害事象が報告され、その内訳は、ポサコナゾール投与で36例中18例、プラセボ投与で18例中9例であった。最もよくみられた有害事象は、頭痛、傾眠、浮動性めまい及び疲労であった。プラセボ投与の1例で発現した中等度の浮動性めまい1件（投与前に発現したため副作用ではない）を除いて、いずれの有害事象も軽度であり、すべての有害事象は処置なく回復した。ポサコナゾールの用量が50 mg から1200 mg に増加しても、有害事象の発現率に増加はみられなかった。ポサコナゾール投与の被験者のみでみられた疲労を除き、概して、ポサコナゾールを投与した被験者の有害事象の種類や発現率は、プラセボ投与の被験者と類似していた。

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

2.7.6.2.12.5　　結論

1) 健康被験者にポサコナゾール旧錠剤50、100、200、400、800及び1200 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。
2) ポサコナゾール旧錠剤を高脂肪食摂取後に単回経口投与した際、ポサコナゾールは緩やかに吸収され、終末相の $t_{1/2}$ は約25時間であった。
3) ポサコナゾール旧錠剤50～800 mg を高脂肪食摂取後に単回経口投与した際の血漿中ポサコナゾール濃度は概して用量に比例していたが、1200 mg 投与では増加しなかった。

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2.7.6.2.13　非日本人健康被験者を対象とした用量漸増反復経口投与試験（[redacted]-089試験）［参考資料］

治験総括報告書[資料5.3.3.1.6: [redacted]_089]の概要を以下に示す。

2.7.6.2.13.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としたポサコナゾールの安全性及び忍容性を評価する用量漸増反復投与試験／[redacted]-089試験

治験責任医師／実施医療機関

[redacted]（オランダ）

公表文献

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2) Courtney R, Pai S, Laughlin M, et al. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother. 2003; 47: 2788-95.

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

1) 健康被験者にポサコナゾール旧錠剤50、100、200及び400 mg を1日2回反復経口投与した際のポサコナゾールの安全性及び忍容性を評価する。
2) 健康被験者にポサコナゾール旧錠剤を反復投与した際の薬物動態プロファイルを検討する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール旧錠剤を反復経口投与した際の安全性、忍容性及び薬物動態を評価する、二重盲検、無作為化、プラセボ対照、並行群間、用量漸増反復投与試験であった。各投与群でポサコナゾール（9例）又はプラセボ（3例）のうちいずれかに無作為に割り付けた。高脂肪朝食又は標準的夕食摂取後5分以内に、ポサコナゾール旧錠剤50、100、

200及び400 mg 又はプラセボを1日2回14日間投与した。

投与期間

反復（14日間）

用法・用量

ポサコナゾール旧錠剤50 mg（50 mg×1錠）、100 mg（100 mg×1錠）、200 mg（100 mg×2錠）及び400 mg（100 mg×4錠）又はプラセボを1日2回14日間高脂肪朝食又は標準的夕食摂取後に反復経口投与した。治験薬の内容を、[表 2.7.6.2.13-1]に示す。

表 2.7.6.2.13-1　治験薬の内容（[redacted]-089 試験）

薬剤	力価	剤形
ポサコナゾール旧錠剤	ポサコナゾール50 mg	錠剤
ポサコナゾール旧錠剤	ポサコナゾール100 mg	錠剤
ポサコナゾール旧錠剤50 mg のプラセボ	-	錠剤
ポサコナゾール旧錠剤100 mg のプラセボ	-	錠剤

診断／選択基準

スクリーニング時に保険数理表に基づく体重の±15%以内の体重で、18歳以上45歳以下の健康な男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1日目の朝投与前及び投与後24時間、14日目の朝投与前及び投与後120時間までの規定した時点で採取した。さらに3、7、10、11、12及び13日目の朝投与前にも採取した。また、尿中薬物濃度測定用検体を、-1日目の-12～0時間、14日目の0～12時間及び12～24時間の間隔で採取したが、安定性及び溶解性に問題があったため、尿中薬物濃度については報告しなかった。ポサコナゾールの血漿中薬物動態パラメータ（AUC、C_{max}、T_{max} 及び $t_{1/2}$等）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

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各投与量の薬物動態パラメータについて、要約統計量を算出した。また、1 mg 当たりの曝露量に用量補正後の AUC 及び C_{max} の対数変換値について、処置（用量）を項とする分散分析モデルを用いて解析した。

2.7.6.2.13.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.13-2]及び[表 2.7.6.2.13-3]に示す。

表 2.7.6.2.13-2　被験者の内訳（[redacted]-089 試験）

	50 mg		100 mg		200 mg		400 mg		プラセボ		合計	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	9		9		10		9		12		49	
内訳												
完了	9	(100.0)	9	(100.0)	9	(90.0)	9	(100.0)	12	(100.0)	48	(98.0)
中止	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	1	(2.0)
有害事象	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	1	(2.0)

Data source: [資料5.3.3.1.6: [redacted]_089] Appendix 9, Table A-3.1

表 2.7.6.2.13-3　被験者の背景（[redacted]-089 試験）

投与群	パラメータ					
	n	年齢（歳）	体重（kg）	身長（cm）	性別（例）†	人種（例）‡
50 mg	9	22 ± 2.4 (20 - 27)	75 ± 6.9 (68 - 88)	183 ± 7.0 (171 - 191)	0/9	9C
100 mg	9	27 ± 6.9 (19 - 41)	74 ± 14.8 (51 - 96)	182 ± 8.2 (166 - 189)	2/7	9C
200 mg	10	24 ± 3.3 (20 - 31)	80 ± 9.0 (63 - 92)	180 ± 7.7 (165 - 190)	0/10	8C/2A
400 mg	9	24 ±4.1 (20 - 33)	73 ± 10.4 (58 - 87)	180 ± 8.2 (162 - 189)	0/9	9C
プラセボ	12	27 ± 7.1 (20 - 43)	76 ± 11.3 (64 - 100)	182 ± 8.1 (168 - 198)	0/12	10C/1B/1A

算術平均±標準偏差（範囲）
† 女性／男性
‡ C：白人、B：黒人、A：アジア系

Data source: [資料5.3.3.1.6: [redacted]_089] Appendix 9, Table A-2.1

2.7.6.2.13.3　　薬物動態の結果

本試験では、有害事象で中止した1例を除く、ポサコナゾール旧錠剤を投与した被験者36例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール旧錠剤50、100、200及び400 mg を1日2回14日間高脂肪朝食又は標準的夕食摂取後に反復経口投与した際の1日目及び14日目の血漿中薬物動態パラメータの要約を、それぞれ[表 2.7.6.2.13-4]及び[表 2.7.6.2.13-5]に示す。いずれの用量でも、血漿中ポサコナゾール濃度は朝投与後5時間で C_{max} に到達し、その後緩やかに減少した。夜投与（すなわち朝投与後12時間）後も血漿中ポサコナゾール濃度の減少は継続し、1日目の朝投与後から最大16時間まで減少し続けた。その後、血漿中濃度は上昇し、夜投与後約8時間（すなわち朝投与後から約20時間）で C_{max} に到達し、その後明らかな減少は示さなかったことから、ポサコナゾールの蓄積性が示された。各採血時点の血漿中ポサコ

ナゾール濃度のばらつきは中程度であった（変動係数：30%～40%）。C_{trough} の統計解析から、1日2回投与した際、10日目までに定常状態に到達することが示された。

14日目の朝投与後4～6時間、夜投与後9～11時間でそれぞれ C_{max} に到達した。いずれの用量でも、14日目の朝投与後120時間まで（最終採血時点）、血漿中ポサコナゾール濃度は定量可能であった。50～400 mg の用量範囲で、$t_{1/2}$の算術平均は19～31時間で、定常状態の V_d/F の推定値は大きく、算術平均の範囲は343～486 L であった。$t_{1/2}$に基づくと、1日2回反復投与で血漿中ポサコナゾールの AUC は単回投与時の約4倍に増大すると予測されたが、$AUC_{0\text{-}12\ hr}$ の実測値に基づく累積係数（14日目／1日目）は、それよりもやや高かった（算術平均の範囲：6.6～8.3）。

1日目及び14日目の血漿中ポサコナゾール濃度は用量に対して線形性を示した。夜投与後の C_{max} を除き、対数変換した用量補正後の朝投与後の C_{max}、$AUC_{0\text{-}12\ hr}$、$AUC_{12\text{-}24\ hr}$ 及び $AUC_{0\text{-}24\ hr}$ には、用量間で統計的に有意な差はなかった。夜投与後の C_{max} でみられた用量間の差は、統計的にわずかに有意であった（1日目及び14日目で、それぞれ P=0.03及び P=0.04）。しかし、これらの解析では、20%の用量間の差を検出する検出力は35%未満であった。

表 2.7.6.2.13-4　健康被験者にポサコナゾール旧錠剤 50、100、200 及び 400 mg を 1 日 2 回 14 日間食後に反復経口投与した際の 1 日目の血漿中薬物動態パラメータの要約（[redacted]-089 試験）

薬物動態パラメータ	用量（1日2回投与）			
	50 mg	100 mg	200 mg	400 mg
$C_{max}1$ (ng/mL)	108 (33)	271 (35)	368 (33)	761 (32)
$T_{max}1$ (hr)	5 (0)	5 (7)	5 (7)	5 (11)
$C_{max}2$ (ng/mL)	127 (27)	349 (22)	519 (24)	1165 (24)
$T_{max}2$ (hr)	9 (25)	10 (16)	8 (25)	10 (25)
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	687 (31)	1713 (34)	2411 (33)	5031 (30)
$AUC_{12\text{-}24\ hr}$ (ng·hr/mL)	1008 (24)	2663 (28)	4141 (24)	9619 (23)
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	1695 (25)	4376 (30)	6551 (27)	14650 (24)

各投与群9例、算術平均（%CV）
CV：変動係数、$C_{max}1$：朝投与後の C_{max}、$T_{max}1$：朝投与後の T_{max}、$C_{max}2$：夜投与後の C_{max}、$T_{max}2$：夜投与後の T_{max}

Data source: [資料5.3.3.1.6: [redacted]_089] Appendix 7, Table 1

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表 2.7.6.2.13-5 健康被験者にポサコナゾール旧錠剤 50、100、200 及び 400 mg を 1 日 2 回 14 日間食後に反復経口投与した際の 14 日目の血漿中薬物動態パラメータの要約（[redacted]-089 試験）

薬物動態パラメータ	用量（1日2回投与）			
	50 mg	100 mg	200 mg	400 mg
$C_{max}1$ (ng/mL)	457 (38)	1141 (37)	1753 (27)	4150 (20)
$T_{max}1$ (hr)	5 (12)	6 (40)	4 (12)	5 (12)
$C_{max}2$ (ng/mL)	371 (30)	1045 (42)	1358 (27)	3239 (19)
$T_{max}2$ (hr)	9 (34)	11 (16)	10 (19)	9 (32)
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	4454 (37)	11571 (40)	16801 (26)	39206 (20)
$AUC_{12\text{-}24\ hr}$ (ng·hr/mL)	3841 (36)	10206 (40)	14305 (27)	33899 (21)
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	8295 (36)	21778 (40)	31106 (26)	73105 (20)
k_{el} (1/hr)	0.037 (14)	0.030 (19)	0.031 (27)	0.026 (36)
$t_{1/2}$ (hr)	19.2 (16)	24.1 (20)	23.9 (26)	31.0 (46)
CL/F (L/hr)	13.5 (34)	10.3 (32)	13.9 (34)	11.5 (25)
V_d/F (L)	365 (29)	343 (24)	467 (32)	486 (34)
累積係数†	6.6 (29)	6.9 (27)	7.6 (37)	8.3 (32)

各投与群9例、算術平均（%CV）
CV：変動係数、$C_{max}1$：朝投与後の C_{max}、$T_{max}1$：朝投与後の T_{max}、$C_{max}2$：夜投与後の C_{max}、$T_{max}2$：夜投与後の T_{max}
† $AUC_{0\text{-}12\ hr}$ に基づく累積係数（14日目／1日目）

Data source: [資料5.3.3.1.6: [redacted]_089] Appendix 7, Table 2

2.7.6.2.13.4　　安全性の結果

本試験では、治験薬を投与した全被験者49例を安全性解析対象集団に含めた。健康被験者にポサコナゾール旧錠剤50、100、200及び400 mg 又はプラセボを1日2回14日間高脂肪朝食又は標準的夕食摂取後に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、妊娠及び死亡はなかった。抗菌治療を必要とする歯膿瘍の重度の有害事象（副作用ではない）を発現した被験者1例（ポサコナゾール旧錠剤200 mg 1日2回投与）が試験を中止した。49例中42例で有害事象が報告され、その内訳は、ポサコナゾール投与で37例中31例、プラセボ投与で12例中11例であった。このうち、副作用が報告されたのは、ポサコナゾール投与で24例、プラセボ投与で9例であった。ポサコナゾール投与で最もよくみられた有害事象は頭痛及び口内乾燥で、用量の増加に伴い本事象の発現率が上昇する傾向がみられた。

ポサコナゾール100 mg 1日2回投与の1例で、14日目に一過性の軽度の ALT 増加［世界保健機関（WHO）グレード1］が発現したが、その他の肝機能パラメータの上昇はなかった。400 mg 1日2回投与の1例では、14日目に一過性の臨床的に意味のある ALT 増加（WHO グレード2）、並びにγ-グルタミルトランスフェラーゼ（GGT）増加を伴わない軽度の AST 及び LDH 増加（WHO グレード1）がみられた。また、プラセボ投与の1例で臨床的に意味のある ALT 増加（WHO グレード2）、並びに軽度の GGT 上昇（WHO グレード1）及び AST 増加がみられた。これらの被験者でみられた変動は、投与完了4週間以内に基準値内に戻った。その他の臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

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2.7.6.2.13.5　　結論

1) 健康被験者にポサコナゾール旧錠剤50、100、200及び400 mg を1日2回14日間高脂肪朝食又は標準的夕食摂取後に反復経口投与した際、安全で忍容性は良好であった。
2) ポサコナゾール旧錠剤を50～400 mg の用量範囲で1日2回投与した際、ポサコナゾールの定常状態における薬物動態は概して用量比例性を示した。
3) 定常状態の $t_{1/2}$は長く（算術平均：19～31時間）、V_d/F は大きかった（算術平均：343～486 L）。
4) ポサコナゾール旧錠剤を50～400 mg の用量範囲で1日2回高脂肪朝食又は標準的夕食摂取後に投与した際、定常状態での $AUC_{0\text{-}12\ hr}$ の値に基づく累積係数は6.6～8.3であった。

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2.7.6.2.14　非日本人健康被験者を対象とした単回及び反復経口投与試験（P05637試験）［参考資料］

治験総括報告書[資料5.3.3.1.7: P05637]の概要を以下に示す。

2.7.6.2.14.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としたポサコナゾールの新規の固形経口剤の薬物動態を評価する試験／P05637試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

新規の固形経口剤を反復投与した際のポサコナゾールの薬物動態を評価する。

【副次目的】

1)　新規の固形経口剤を単回投与した際のポサコナゾールの薬物動態を評価する。
2)　新規の固形経口剤の安全性及び忍容性を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール新錠剤 C の薬物動態、安全性及び忍容性を評価する、二重盲検、無作為化、プラセボ対照、用量漸増単回及び反復経口投与試験であった。ポサコナゾール新錠剤 C を単回及び反復経口投与するため、合計24例の被験者を2つのコホート［各12例（実薬9例、プラセボ3例)］の1つに無作為に割り付ける計画であったが、実際には25例が組み入れられた。

コホート1では、1日目の朝にポサコナゾール新錠剤 C 200 mg 又はプラセボを単回投与した。6日目にポサコナゾール新錠剤 C 200 mg 又はプラセボを1日2回、7～14日目に1日1回反復経口投与した。また、15～22日目の朝及び夜にポサコナゾール新錠剤 C 200 mg 又はプラセボを1日2回反復経口投与した。

コホート2では、1日目の朝にポサコナゾール新錠剤C 400 mg又はプラセボを単回経口投与した。6日目にポサコナゾール新錠剤 C 400 mg 又はプラセボを1日2回、7～14日目に1日1回反復経口投与した。

投与期間

単回及び反復（コホート1：17日間、コホート2：9日間）

用法・用量

コホート1では、1日目にポサコナゾール新錠剤 C 200 mg（100 mg×2錠）又はプラセボを空腹時に単回経口投与、6日目にポサコナゾール新錠剤 C 200 mg（100 mg×2錠）又はプラセボを1日2回、7～14日目に1日1回、15～22日目に1日2回反復経口投与した。

コホート2では、1日目にポサコナゾール新錠剤 C 400 mg（100 mg を4錠）又はプラセボ（4錠）を空腹時に単回経口投与、6日目にポサコナゾール新錠剤 C 400 mg（100 mg を4錠）又はプラセボ（4錠）を1日2回、7～14日目に1日1回反復経口投与した。治験薬の内容を、[表 2.7.6.2.14-1]に示す。

表 2.7.6.2.14-1　治験薬の内容（P05637 試験）

薬剤	力価	剤形
ポサコナゾール新錠剤 C	ポサコナゾール100 mg	錠剤
ポサコナゾール新錠剤 C のプラセボ	-	錠剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^2以上35 kg/m^2未満で、18歳以上65歳以下の健康な男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1日目の投与前及び投与後120時間まで、並びに6日目の24時間までの規定した時点で採取した。また、トラフの血漿中薬物濃度測定用検体を12日目及び13日目の0時間（投与前）に採取した。さらに、コホート1では、14日目の投与前及び投与後24時間まで、並びに22日目の投与前及び投与後168時間まで、コホート2では、14日目の投与前及び投与後168時間までの規定した時点で採取した。血漿中ポサコナゾールの $AUC_{0-\infty}$、AUC_{0-last}、$AUC_{0-\tau}$、C_{max}、T_{max} 及び累積係数を主要評価薬物動態パラメータとし、可能であれば、CL/F、$t_{1/2}$及び V_d/F も算出した。

【薬力学】

副腎機能を確認するため、コホート1では-1、10及び23日目、コホート2では-1、10及び15日目の

午前7時頃に ACTH（コシントロピン）250 μg を静脈内投与し、投与後60分に血清中コルチゾール及びアルドステロン濃度測定用検体を採取した。さらに、血清中アルドステロン濃度測定用検体を、コホート1では1、11及び24日目、コホート2では1，11及び16日目の午後4時頃に採取した。必要に応じ、これらの検体は副腎ホルモンの追加解析に用いることとした。尿中アルドステロン濃度測定用検体を、コホート1では1～2，11～12及び24～25日目、コホート2では1～2，11～12及び16～17日目に24時間にわたり（午前8時から午後8時）採取した。これらの検体は必要に応じ、電解質の解析にも用いた。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

ポサコナゾールの AUC 及び C_{max} の値を用量ごとに要約した。また、用量比例性の探索的評価のため、用量補正後の AUC 及び C_{max} の対数変換値を解析した。用量比例性の評価には、モデルに基づいた AUC 及び C_{max} の用量間の幾何平均比及びその90%信頼区間を用いた。さらに、時間依存性について、1、14及び22日目（コホート1のみ）の AUC を用いて評価した。

【薬力学】

薬力学的データを一覧表にし、要約した。

【安全性】

有害事象及び安全性パラメータを投与群ごとに要約した。心電図パラメータ、血圧測定及びベースラインからの変動について投与群ごとに要約した。プラセボデータは両コホートを統合した。

2.7.6.2.14.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.14-2]及び[表 2.7.6.2.14-3]に示す。

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表 2.7.6.2.14-2　　被験者の内訳（P05637 試験）

	200 mg		400 mg		プラセボ		合計	
	n	(%)			n	(%)	n	(%)
総被験者数	10		9		6		25	
内訳								
完了	8	(80)	8	(89)	6	(100)	22	(88)
中止	2	(20)	1	(11)	0	(0.0)	3	(12)
有害事象	2†	(20)	1‡	(11)	0	(0.0)	3	(12)

† 被験者1例が肝酵素上昇の副作用により14日目に試験を中止した。他の被験者1例が肝酵素上昇の副作用により22日目に試験を中止した。
‡ 被験者1例が肝酵素上昇の副作用により14日目に試験を中止した。

Data source: [資料5.3.3.1.7: P05637] 14.1.2.2

表 2.7.6.2.14-3　　被験者の背景（P05637 試験）

	200 mg (n=10) (%)	400 mg (n=9) (%)	プラセボ (n=6) (%)	合計 (n=25) (%)
性別（例）				
女性	5 (50)	3 (33)	3 (50)	11 (44)
男性	5 (50)	6 (67)	3 (50)	14 (56)
人種（例）				
白人	10 (100)	9 (100)	6 (100)	25 (100)
民族（例）				
ヒスパニック系又はラテン系	10 (100)	9 (100)	6 (100)	25 (100)
年齢（歳）				
算術平均（標準偏差）	47.7 (8.2)	43.8 (9.9)	46.0 (9.3)	45.9 (8.9)
中央値	46.5	40.0	46.5	44.0
範囲	33 - 59	31 - 56	33 - 56	31 - 59
体重（kg）				
算術平均（標準偏差）	74.85 (14.13)	72.89 (7.61)	71.83 (9.58)	73.42 (10.72)
中央値	71.00	72.00	71.00	71.00
範囲	61.0 - 100.0	61.0 - 86.0	61.0 - 88.0	61.0 - 100.0
身長（cm）				
算術平均（標準偏差）	165.60 (5.62)	168.78 (7.90)	166.17 (8.18)	166.88 (6.98)
中央値	165.00	168.00	167.00	167.00
範囲	156.0 - 175.0	155.0 - 181.0	153.0 - 175.0	153.0 - 181.0

Data source: [資料5.3.3.1.7: P05637] 14.1.1

2.7.6.2.14.3　　薬物動態の結果

本試験では、ポサコナゾール新錠剤 C を投与した被験者19例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール新錠剤 C 200又は400 mg を単回経口投与、並びに200 mg を1日1回及び1日2回又は400 mg を1日1回反復経口投与した際の血漿中薬物動態パラメータの要約を、それぞれ[表 2.7.6.2.14-4]及び[表 2.7.6.2.14-5]に示す。また、単回及び反復経口投与した際の用量補正後のポサコナゾールの曝露量の比較を[表 2.7.6.2.14-6]に示す。ポサコナゾール新錠剤 C 200及び400 mg を空腹時に単回経口投与した際の曝露量は、用量に依存して増加した。1日目の用量補正後のポサコナゾールの曝露量は既存の試験でみられた結果（P04975試験

でポサコナゾール新錠剤100 mg を空腹時に単回投与した際の AUC：11400 ng·hr/mL）と同程度であった。対数変換値に基づくポサコナゾール400 mg 投与時の用量補正後の C_{max} 及び $AUC_{0\text{-}last}$ は、それぞれ200 mg 投与時の値の83%及び91%であった。T_{max} の中央値は、200 mg 投与時で4時間、400 mg 投与時で5時間、範囲はいずれの用量でも3～8時間であった。$t_{1/2}$の算術平均は、200及び400 mg 投与時で類似していた（それぞれ、25時間及び26時間）。200及び400 mg 投与時の C_{max} 及び AUC の変動係数は、それぞれ23%～35%であった。

ポサコナゾール新錠剤 C 200 mg を1日1回及び1日2回並びに400 mg を1日1回8日間反復経口投与した際の投与群間の曝露量は用量に依存して増加した。対数変換値に基づくポサコナゾール400 mg 投与時の用量補正後の C_{max} 及び $AUC_{0\text{-}\tau}$ は、それぞれ200 mg 投与時の値の76%及び81%であった。200 mg を1日1回及び1日2回並びに400 mg を1日1回反復投与した際の累積係数は、それぞれ3.14、4.75及び3.16であった。400 mg を投与した際の曝露量のばらつきは、200 mg 投与時よりも相対的に大きいと考えられた（AUC の変動係数：54%）。

ポサコナゾールの C_{trough} を、12、13及び14日目の投与前（0時間）に測定した。得られた測定値に基づき、ポサコナゾールは13日目（反復経口投与8日目）までには定常状態に到達していると考えられた。

表 2.7.6.2.14-4　健康被験者にポサコナゾール新錠剤 C 200 mg 又は 400 mg を空腹時に単回経口投与した際の血漿中薬物動態パラメータの要約（P05637 試験）

コホート	投与量 (mg)	日	n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{0\text{-}last}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	CL/F (L/hr)	$t_{1/2}$ (hr)
1	200	1	10	778 (29)	4.0 (3-8)	23000 (23)	24000 (23)	8.80 (26)	25.1 (20)
2	400	1	9	1290 (29)	5.0 (3-8)	42800 (35)	46600 (35)‡	9.55 (34)‡	26.1 (22)‡

算術平均（%CV）
CV：変動係数
† 中央値（範囲）
‡ 8例。1例の薬物動態パラメータは算出できなかった。

Data source: [資料5 3 3 1.7: P05637] 16.1.9.2.1 Display A1

表 2.7.6.2.14-5　健康被験者にポサコナゾール新錠剤 C 200 mg を 1 日 1 回及び 1 日 2 回又は 400 mg を 1 日 1 回反復経口投与した際の血漿中薬物動態パラメータの要約（P05637 試験）

コホート	投与量 (mg)	日	n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{0-\tau}$‡ (ng·hr/mL)	C_{avg}§ (ng/mL)	$t_{1/2}$ (hr)	累積係数‖
1	200 QD	6¶	10	818 (26)††	5.0 (3-6)	6740 (21)	-		
		14	8	1800 (31)	5.0 (2-8)	31400 (32)	1310 (32)	-	3.14 (24)
	200 BID	22	8	2980 (38)	4.0 (2-8)	30600 (38)	2550 (38)	31.4 (31)	4.75 (28)
2	400 QD	6¶	9	1370 (36)††	5.0 (3-12)	11400 (35)	-		
		14	8	2940 (46)	5.0 (0-12)	56600 (54)	2360 (54)	26.6 (15)	3.16 (57)

算術平均（%CV）
CV：変動係数、QD：1日1回投与、BID：1日2回投与
† 中央値（範囲）
‡ τ=1日1回投与で24時間、1日2回投与で12時間
§ $AUC_{0-\tau}/\tau$
‖ 1日1回投与では1日目に対する14日目、1日2回投与では6日目に対する22日目の $AUC_{0-\tau}$ の比
¶ コホート1及び2の6日目の200 mg 1日2回及び400 mg 1日2回負荷投与
†† 200 mg 1日2回及び400 mg 1日2回投与前の濃度は、それぞれ C_{max} の1%～5%及び1%～9%であった。

Data source: [資料5.3.3.1.7: P05637] 16.1.9.2.1 Display A1, 16.1.9.2.2 Display A1

表 2.7.6.2.14-6　健康被験者にポサコナゾール新錠剤 C を単回及び反復経口投与した際の用量補正後のポサコナゾールの曝露量の比較（P05637 試験）

日	薬物動態パラメータ	n (200 mg)	n (400 mg)	比較†	幾何平均比 (%)‡	90%信頼区間 (%)
1	C_{max}	10	9	400 mg/200 mg	83	65, 106
	$AUC_{0\text{-last}}$	10	9	400 mg/200 mg	91	72, 114
	$AUC_{0-\infty}$	10	8	400 mg/200 mg	94	74, 121
14	C_{max}	8	8	400 mg/200 mg	76	51, 114
	$AUC_{0-\tau}$	8	8	400 mg/200 mg	81	52, 126

† 対数変換した用量補正済みデータに基づいて、処置を項とする一元配置分散分析を用いて比較した。
‡ モデルに基づく幾何平均比

Data source: [資料5.3.3.1.7: P05637] 16.1.9.2.3

2.7.6.2.14.4　薬力学の結果

本試験では、治験薬を投与した全被験者25例を薬力学解析対象集団に含めた。副腎機能に対するポサコナゾールの影響を確認するため、血清中アルドステロン濃度を測定した。本分析の定量下限値は、55 pmol/L であった。ポサコナゾール200及び400 mg を投与した際の血清中アルドステロン濃度の算術平均及び中央値は、プラセボ投与時と比べると低く、ポサコナゾール投与終了後に、血清中アルドステロン濃度は増加し始めた。

また、標準的な ACTH 負荷試験を実施し、副腎機能及び ACTH の蓄積を評価した。ポサコナゾール新錠剤 C 200 mg、400 mg 又はプラセボを1日1回又は1日2回反復経口投与した際に、-1日目の ACTH 負荷投与後の血清中アルドステロン濃度の算術平均及び中央値は、いずれの処置でも、ベースライン値（ACTH 負荷投与前）と比較して3～4倍であった。10日目のポサコナゾール400 mg 投与の血清中アルドステロン濃度の算術平均及び中央値のベースライン値及び ACTH 負荷投与後の値は、ポサコナゾール200 mg 又はプラセボ投与のそれぞれ約3分の1であった。

ポサコナゾール新錠剤C 200 mgを1日1回反復経口投与後に1日2回反復経口投与した際の23日目の血清中アルドステロン濃度のベースライン値及びACTH負荷投与後の値は低く、ポサコナゾール400 mg 1日1回（反復投与1日目のみ1日2回）反復経口投与後3日目（10日目）の値と類似していた。ポサコナゾール新錠剤C 400 mgを投与した際の15日目の血清アルドステロン濃度のベースライン値及びACTH負荷投与後の値は、算術平均は10日目と15日目で類似していたが、中央値は、15日目のACTH負荷投与後の値が定量下限未満まで低下した。以上のことから、特にACTH負荷投与後、副腎機能は低下し、アルドステロンの産生が低下することが示唆された。

一方、血清中コルチゾール濃度の算術平均及び中央値は、ポサコナゾール200 mg、400 mg及びプラセボのすべての処置で、ACTH負荷投与による測定を行ったいずれの試験日についても、ベースライン値及びACTH負荷投与後の値は類似していた。このことから、経口剤として投与した際、ポサコナゾールは、コルチゾール産生に関して、副腎機能に大きく影響しないことが示唆された。

2.7.6.2.14.5　安全性の結果

本試験では、治験薬を投与した全被験者25例を安全性解析対象集団に含めた。健康被験者にポサコナゾール新錠剤C 200 mgを1日1回及び1日2回並びに400 mgを1日1回（反復投与1日目のみ1日2回）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、妊娠及び死亡はなかった。有害事象により中止した被験者は3例（200 mg投与：2例及び400 mg投与：1例）であり、いずれも肝酵素上昇（AST及びALT値）によるものであった。

25例中12例で有害事象が報告され、その内訳は、コホート1のポサコナゾール200 mg 1日1回又は1日2回投与で10例中6例、コホート2の400 mg 1日1回（反復投与1日目のみ1日2回）投与で9例中5例、プラセボ投与で6例中1例であった。いずれの有害事象も軽度であった。このうち11例が副作用と判定された。最もよくみられた副作用は、肝酵素上昇（AST及びALT値）で、コホート1のポサコナゾール200 mg 1日1回又は1日2回投与で10例中5例、コホート2の400 mg 1日1回（反復投与1日目のみ1日2回）投与で9例中1例に、10日目以降に報告された。いずれの肝酵素上昇も軽度であった。臨床検査値の異常値がみられたが、明らかな傾向はなく、基準値上限の3倍を超える増加はなかった。いずれの投与群のバイタルサイン又は心電図にも臨床的に意味のある一貫した変化はなかった。

2.7.6.2.14.6　結論

1) 健康被験者にポサコナゾール新錠剤Cを経口投与した際、曝露量は用量に依存して増加し、用量が200 mgから400 mgに2倍になると、1日目及び14日目の曝露量はそれぞれ1.9倍及び1.8倍に増加した。
2) 1日目の用量補正後のポサコナゾールの曝露量は既存の試験でみられた結果（P04975試験でポサコナゾール新錠剤C 100 mgを空腹時に単回経口投与した際のAUC：11400 ng·hr/mL）と同程度であった。

3) 健康被験者にポサコナゾール新錠剤 C 200 mg を1日1回及び1日2回並びに400 mg を1日1回（反復投与1日目のみ1日2回）反復経口投与した際、安全で忍容性は良好であった。軽度の肝酵素上昇が200 mg を1日1回及び1日2回並びに400 mg を1日1回投与した10日目以降にみられたが、一過性の事象であった。
4) ポサコナゾール新錠剤 C 200 mg を1日1回及び1日2回並びに400 mg を1日1回（反復投与1日目のみ1日2回）反復経口投与した際、血清中アルドステロン値が低下したことから、用量が多いあるいは投与期間が長い場合、プラセボと比べ血清中アルドステロン濃度が大きく低下する傾向がみられた。
5) ポサコナゾール新錠剤 C 200 mg 1日1回及び1日2回反復経口投与、400 mg 1日1回（反復投与1日目のみ1日2回）反復経口投与並びにプラセボ投与時の ACTH 負荷反応の影響から、ポサコナゾール経口剤は、コルチゾール産生に関して、副腎機能に影響しないことが示唆された。

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2.7.6.2.15　非日本人健康被験者を対象とした単回及び反復静脈内投与試験（P04985試験）［参考資料］

治験総括報告書[資料5.3.3.1.8: P04985]の概要を以下に示す。

2.7.6.2.15.1　試験方法

治験実施計画書標題／番号

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を投与した際の薬物動態及び安全性評価試験／P04985試験

治験責任医師／実施医療機関

[redacted]（スイス）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

健康被験者を対象として、ポサコナゾール静注用溶液を単回及び反復末梢静脈内投与した際の薬物動態を評価する。

【副次目的】

1) 健康被験者を対象として、ポサコナゾール静注用溶液を単回及び反復末梢静脈内投与した際の安全性及び忍容性を評価する。
2) 健康被験者を対象として、ポサコナゾール静注用溶液及び新錠剤Cの、ポサコナゾール経口懸濁液に対する相対的バイオアベイラビリティを評価する。
3) 健康被験者を対象として、ポサコナゾール静注用溶液が副腎機能に及ぼす影響を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール静注用溶液を投与した際の薬物動態、安全性及び忍容性を評価する、二重盲検（処置A及びB）及び非盲検（処置C及びD）、無作為化、プラセボ対照（処置A及びB）、用量漸増単回及び反復投与試験であった。また、ポサコナゾール経口懸濁液に対する静注用溶液及び新錠剤Cの相対的バイオアベイラビリティも比較する。

本試験では、以下のとおり投与する予定であった。コホート1では、12例にポサコナゾール静注

用溶液200 mg（9例）又はプラセボ（3例）を空腹時に1日目は1日1回、6日目は1日2回、以降8日間（7～14日目）は1日1回反復末梢静脈内投与する（処置 A)。コホート2として別の被験者12例にポサコナゾール静注用溶液400 mg（9例）又はプラセボ（3例）を空腹時に1日目は1日1回、6日目は1日2回、以降8日間は1日1回反復末梢静脈内投与する（処置 B)。さらにコホート2では、ポサコナゾール静注用溶液400 mg 又はプラセボを投与した被験者に、2週間のウォッシュアウト後、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する（処置 C)。その後、更に2週間のウォッシュアウトを設け、ポサコナゾール新錠剤 C 400 mg を空腹時に単回経口投与する（処置 D)。

しかし、本試験はコホート1でポサコナゾール200 mg 単回末梢静脈内投与後に認められた注入部位の不耐容により早期中止に至った。コホート1に処置 A の単回末梢静脈内投与（1日目）のみ行い、処置 B、C 及び D は行わなかった。

投与期間

処置 A：単回

用法・用量

処置 A は10時間絶食後、ポサコナゾール静注用溶液200 mg 又はプラセボを90分かけて単回末梢静脈内投与した。

治験薬の内容を、[表 2.7.6.2.15-1]に示す。

表 2.7.6.2.15-1　治験薬の内容（P04985 試験）

治験薬	力価	剤形
ポサコナゾール静注用溶液	ポサコナゾール18 mg/mL	注射剤
ポサコナゾール静注用溶液のプラセボ（5%ブドウ糖注射液）	-	注射剤
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤
ポサコナゾール新錠剤 C	ポサコナゾール100 mg	錠剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^{2}以上35 kg/m^{2}以下で、18歳以上65歳以下の健康な男性又は女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を処置 A の投与前及び投与後120時間までの規定した時点で採取した。ポサコナゾールの薬物動態パラメータ（C_{max}、T_{max}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}24\,hr}$、$AUC_{0\text{-}\infty}$、k_{el}、$t_{1/2}$、CL 及び V_d）を算出した。

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【薬力学】

処置 A の投与開始前（-1日目）に、ACTH 負荷試験を実施し、血漿中コルチゾール濃度を測定して副腎機能を評価した。また、処置 A の投与開始前及び投与開始8時間後に血液検体、投与開始後24時間までの蓄尿を行い、血漿中及び尿中アルドステロン濃度を測定した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

ポサコナゾールの各検体採取時点の血漿中濃度データ及び薬物動態パラメータの要約統計量（平均値、標準偏差及び変動係数等）を示した。

【薬力学】

血漿中アルドステロン濃度の要約統計量を示した。ACTH 負荷後の血漿中コルチゾール及び血漿中アルドステロン濃度の変化量の要約統計量を示した。

【安全性】

処置 A の有害事象及び安全性の評価項目を要約した。心電図、バイタルサイン及びそれぞれのベースラインからの変化量を要約した。有害事象が認められた被験者数、有害事象の発現率及び有害事象による中止を集計した。臨床検査値を一覧で示し、基準値を外れた値に印を付けた。被験者ごとのバイタルサイン、心電図及び注入部位反応の評価を一覧で示した。

2.7.6.2.15.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.15-2]及び[表 2.7.6.2.15-3]に示す。

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表 2.7.6.2.15-2　被験者の内訳（コホート 1、P04985 試験）

	ポサコナゾール 静注用溶液200 mg		プラセボ		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	9	(100)	3	(100)	12	(100)
内訳						
完了	0	(0)	0	(0)	0	(0)
中止	9	(100)	3	(100)	12	(100)
試験の中止	9	(100)	3	(100)	12	(100)

Data source: [資料5.3.3.1.8: P04985] 14.1.2.2

表 2.7.6.2.15-3　被験者の背景（コホート 1、P04985 試験）

	ポサコナゾール 静注用溶液200 mg		プラセボ		合計	
	n	(%)	n	(%)	n	(%)
総被験者数	9		3		12	
性別						
男性	7	(78)	2	(67)	9	(75)
女性	2	(22)	1	(33)	3	(25)
年齢（歳）						
算術平均	50.4		55.3		51.7	
標準偏差	13.2		8.6		12.0	
中央値	51.0		57.0		51.5	
範囲	30 - 65		46 - 63		30 - 65	
18～65歳未満	7	(78)	3	(100)	10	(83)
65歳以上	2	(22)	0	(0)	2	(17)
体重（kg）						
算術平均	76.01		73.87		75.48	
標準偏差	11.24		7.96		10.21	
中央値	75.60		77.10		76.35	
範囲	60.1 - 98.8		64.8 - 79.7		60.1 - 98.8	
身長（cm）						
算術平均	176.11		168.67		174.25	
標準偏差	10.54		7.77		10.15	
中央値	180.00		171.00		174.50	
範囲	160.0 - 190.0		160.0 - 175.0		160.0 - 190.0	
人種						
白人	8	(89)	3	(100)	11	(92)
混血	1	(11)	0	(0)	1	(8)
民族						
非ヒスパニック系又は非ラテン系	9	(100)	3	(100)	12	(100)

Data source: [資料5.3.3.1.8: P04985] 14.1.1

2.7.6.2.15.3　薬物動態の結果

本試験では、ポサコナゾール静注用溶液を投与した被験者9例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール静注用溶液200 mg を空腹時に単回末梢

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静脈内投与した際の血漿中薬物動態パラメータの要約を[表 2.7.6.2.15-4]に示す。

ポサコナゾール200 mg を単回末梢静脈内投与した際、投与後1.00時間（中央値）で C_{max} に到達し、その後、急速に低下した後、緩徐に上昇し、大部分の被験者で2つ目のわずかなピークが認められた。$t_{1/2}$の算術平均は24.3時間であった。ポサコナゾール200 mg を単回末梢静脈内投与した際の薬物動態パラメータのばらつきはいずれも小さかった。

1例の被験者でポサコナゾールの末梢静脈内投与中に血管外への漏出が疑われ、他の被験者よりも C_{max} は低く、T_{max} は遅かったが、この被験者を除外しても、ポサコナゾールの薬物動態パラメータの要約統計量への影響はわずかであった。

なお、本試験は早期中止となったため、ポサコナゾール静注用溶液400 mg、新錠剤 C 及び経口懸濁液を投与した際の薬物動態は得られなかった。そのため、経口懸濁液に対する静注用溶液及び新錠剤 C の相対的バイオアベイラビリティは評価できなかった。

表 2.7.6.2.15-4　健康被験者にポサコナゾール静注用溶液 200 mg を空腹時に単回末梢静脈内投与した際の血漿中薬物動態パラメータの要約（P04985 試験、コホート 1）

n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-24 hr}}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	k_{el} (1/hr)	$t_{1/2}$ (hr)	CL (L/hr)	V_d (L)
9	1470 (24)	1.00 (1.00 - 4.00)	27000 (23)	13500 (16)	28100 (26)	0.0297 (21)	24.3 (22)	7.46 (20)	254 (17)

算術平均（%CV）
CV：変動係数
† 中央値（範囲）

Data source: [資料5.3.3.1.8: P04985] 16.1.9.2.1 Table 1

2.7.6.2.15.4　薬力学の結果

本試験では、治験薬を投与した被験者12例から得られたデータを用いてポサコナゾールの副腎機能に及ぼす影響を評価した。健康被験者にポサコナゾール200 mg を空腹時に単回末梢静脈内投与した際の血漿中アルドステロン濃度（pmol/L）の要約を[表 2.7.6.2.15-5]に示す。

ポサコナゾール投与後8時間の血漿中アルドステロン濃度は、ベースラインと比較して数値的に低かったが、プラセボ投与後8時間では血漿中アルドステロン濃度に顕著な影響は認められなかった。

また、ベースライン時に ACTH 負荷試験を実施したが、いずれの被験者でも ACTH 負荷に対して十分なアルドステロン及びコルチゾールの反応が認められた。

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表 2.7.6.2.15-5　健康被験者にポサコナゾール静注用溶液 200 mg を空腹時に単回末梢静脈内投与した際の血漿中アルドステロン濃度（pmol/L）の要約（P04985 試験、コホート 1）

臨床検査	ポサコナゾール200 mg（n = 9）		プラセボ（n = 3）	
アルドステロン	ベースライン（-1日目の朝）	1日目（投与後8時間時点）	ベースライン（-1日目の朝）	1日目（投与後8時間時点）
算術平均	394.2	270.6	476.2	492.8
標準偏差	101.1	127.2	193.7	81.2
中央値	385.6	224.7	413.3	479.9
最小値	277	169	322	419
最大値	619	571	694	580

Data source: [資料5.3.3.1.8: P04985] 14.3.5.3

2.7.6.2.15.5　安全性の結果

本試験では、治験薬を投与した全被験者12例を安全性解析対象集団に含めた。健康被験者9例にポサコナゾール200 mg、3例にプラセボを単回末梢静脈投与した際、重篤な有害事象、妊娠及び死亡はなかった。治験薬を投与された12例中4例に合計9件の有害事象が認められ、軽度の有害事象が3例に5件認められ、中等度の有害事象が2例に3件認められ、このうち注入部位血腫2件（プラセボの2例）、末梢性浮腫1件（ポサコナゾール200 mgの1例）、注入部位疼痛1件（ポサコナゾール200 mgの1例）、肝機能検査異常1件（ポサコナゾール200 mg の1例）、頭痛1件（プラセボの1例）の合計6件は副作用と判定された。注入部位の有害事象は、いずれも投与開始後5～22時間の間に認められた。

注入部位の不耐容は、低 pH（約2.6）の注射液を90分かけて末梢静脈内投与したことに関連する刺激感に起因する可能性が考えられた。注入部位の不耐容により、本試験は早期中止された。注入部位反応は投与後3～36日で回復した。

肝機能検査異常（ALT が基準値上限の約9倍に上昇）は中等度と判断されたが、投与経路特異的な事象とは考えられなかった。また、薬物動態パラメータ及び曝露量との関連はみられなかった。その他、肝機能検査異常を除く臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.15.6　結論

1) 健康被験者にポサコナゾール静注用溶液200 mg を空腹時に単回末梢静脈内投与した際、血漿中のポサコナゾール濃度は急速に低下した後、緩徐に上昇し、大部分の被験者で2つ目のピークが認められた。また、薬物動態パラメータのばらつきは小さかった。
2) ポサコナゾール投与後の血漿中アルドステロン濃度は、ベースラインと比較して数値的に低かったが、プラセボ投与後では血漿中アルドステロン濃度に顕著な影響は認められなかった。この可逆的な変化の持続期間は、ポサコナゾール末梢静脈内投与時と経口投与時で同程度であった。
3) ポサコナゾールを末梢静脈投与した健康被験者に認められた注入部位の不耐容により、本

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試験は早期に中止した。注入部位の不耐容は、低 pH の注射液を90分かけて末梢静脈内投与したことに関連する刺激感による可能性が高いと考えられる。

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2.7.6.2.16　非日本人健康被験者を対象とした単回及び反復静脈内投与試験（P06356試験）［参考資料］

治験総括報告書[資料5.3.3.1.9: P06356]の概要を以下に示す。

2.7.6.2.16.1　試験方法

治験実施計画書標題／番号

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末梢静脈内投与の安全性及び薬物動態を検討する試験／P06356試験

治験責任医師／実施医療機関

[redacted]（オランダ）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

ポサコナゾール静注用溶液を末梢静脈内単回及び反復投与したときの安全性及び忍容性を検討する。

【副次目的】

ポサコナゾール静注用溶液の薬物動態及び代謝物プロファイルを解明する。

【探索的目的】

ポサコナゾール静注用溶液が副腎機能に及ぼす影響を検討する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール静注用溶液の安全性、忍容性及び薬物動態を検討する、二重盲検、無作為化、2パート、プラセボ対照、用量漸増単回及び反復末梢静脈内投与試験であった。

パート1（単回）：合計72例の健康被験者を各12例（実薬9例及びプラセボ3例）から構成される6コホートの1つに無作為に割り付けし、SBECD（ポサコナゾール非含有、コホート1）又はポサコナゾール静注用溶液（コホート2～6）及びプラセボ（5%ブドウ糖注射液）を単回末梢静脈内投与した。ポサコナゾールの用量範囲は、0（SBECD）、50、100、200、250及び300 mg であった。

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パート2（反復）：合計48例の健康被験者を各12例（実薬9例及びプラセボ3例）から構成される4コホートの1つに無作為に割り付けし、1日目に12時間間隔で2回、2～10日目に朝に1回、SBECD（ポサコナゾール非含有、コホート7）又はポサコナゾール静注用溶液（コホート8～10）及びプラセボ（5%ブドウ糖注射液）を末梢静脈内投与する予定であり、計画されていたポサコナゾールの用量範囲は、0（SBECD）、100、200及び300 mg であった。しかしながら、パート2は、反復投与後の注入部位の有害事象により、100 mg 投与後に早期に中止した。そのため、パート2に組み入れられた実被験者数は18例であった。

投与期間

パート1：単回

パート2：反復（10日間）

用法・用量

パート1では、SBECD（ポサコナゾール非含有、コホート1）又はポサコナゾール静注用溶液（50、100、200、250及び300 mg、コホート2～6）及びプラセボ（5%ブドウ糖注射液、全コホート）を30分かけて末梢静脈内投与した。パート2では、SBECD（ポサコナゾール非含有、コホート7）又はポサコナゾール静注用溶液（100、200及び300 mg、コホート8～10）及びプラセボ（5%ブドウ糖注射液、全コホート）を30分かけて1日1回（1日目は1日2回）10日間反復末梢静脈内投与する予定であった。

治験薬の内容を、[表 2.7.6.2.16-1]に示す。

表 2.7.6.2.16-1　治験薬の内容（P06356 試験）

薬剤	力価	剤形
ポサコナゾール静注用溶液	ポサコナゾール18 mg/mL	注射剤
SBECD（静注用溶媒）	-	注射剤
ポサコナゾール静注用溶液のプラセボ（5%ブドウ糖注射液）	-	注射剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^{2}以上35 kg/m^{2}以下で、18歳以上65歳以下の健康な男性及び女性

評価基準

【薬物動態】

パート1：各コホートから、血漿中薬物濃度測定用検体を、1日目の投与開始後168時間までの規定した時点で採取した。用量群ごとの各被験者の血漿中ポサコナゾール濃度データを用いて、単回投与時の C_{max}、T_{max}、$AUC_{0\text{-}last}$、$AUC_{0\text{-}\infty}$、k_{el}、$t_{1/2}$、CL 及び V_d を算出した。

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パート2：血漿中薬物濃度測定用検体を、1日目の投与開始後12時間まで、及び10日目の投与開始後168時間までの規定した時点、さらに8日目及び9日目の投与前に、定常状態評価用検体を採取する予定であり、初回及び反復投与後の薬物動態パラメータの要約、用量比例性及び定常状態到達時間の評価を計画していた。しかし、反復投与後の注入部位の有害事象により、100 mg の投与後に早期に中止となったため、100 mg 初回投与後の薬物動態パラメータの要約のみを行った。

【安全性】

パート1及び2でバイタルサイン、身体所見、心電図、心エコーによる駆出率の測定及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。注入部位反応を SPCT の重症度を判定する半定量的スコアリング尺度を用いてモニタリングした。パート2で、ACTH 負荷試験実施後の血漿中コルチゾール濃度及び血漿中アルドステロン濃度、並びに血漿中アルドステロン濃度及び尿中アルドステロン濃度を測定する予定であったが、パート2のポサコナゾール反復投与を中止したため、評価しなかった。

統計計画及び解析

【薬物動態】

薬物動態パラメータは、用量群ごとに要約統計量を用いて要約した。

パート1：用量比例性を評価するために、用量を項とする分散分析モデルを用い、用量補正した AUC 及び C_{max} の対数変換値を解析した。この分散分析モデルによる解析は検討した全用量による2用量のすべての組合せで行い、それぞれの幾何平均比（高用量／低用量）の推定値とその90%信頼区間を提示した。

さらに、用量比例性を評価するために、パワーモデルも適用した。反応変数を C_{max}、$AUC_{0-\infty}$又は AUC_{0-last} の対数変換値とし、共変量を用量の対数変換値としたパワーモデルを用いた。本モデルの傾きの推定値及び90%信頼区間を算出した。本モデルにより最高用量の C_{max}、$AUC_{0-\infty}$及び AUC_{0-last} が最低用量との比較で何倍上昇したかとその90%信頼区間を算出した。

【安全性】

安全性データを用量群ごとに要約した。

2.7.6.2.16.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.16-2]、[表 2.7.6.2.16-3]、[表 2.7.6.2.16-4]及び[表 2.7.6.2.16-5]に示す。

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表 2.7.6.2.16-2　　被験者の内訳（P06356 試験、パート 1）

	プラセボ 単回投与		SBECD 単回投与		ポサコナゾール 50 mg 単回投与		ポサコナゾール 100 mg 単回投与		ポサコナゾール 200 mg 単回投与		ポサコナゾール 250 mg 単回投与		ポサコナゾール 300 mg 単回投与		合計	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	18	(100)	9	(100)	9	(100)	9	(100)	9	(100)	9	(100)	9	(100)	72	(100)
内訳																
完了	18	(100)	9	(100)	9	(100)	9	(100)	9	(100)	9	(100)	9	(100)	72	(100)
中止	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)

Data source: [資料5 3 3 1 9: P06356] 14.1.2.2

表 2.7.6.2.16-3　　被験者の内訳（P06356 試験、パート 2）

	プラセボ 反復投与		SBECD 反復投与		ポサコナゾール 100 mg 反復投与		合計	
	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	4	(100)	9	(100)	5	(100)	18	(100)
内訳								
完了	2	(50)	8	(89)	0	(0)	10	(56)
中止	2	(50)	1	(11)	5	(100)	8	(44)
有害事象	1	(25)	1	(11)	2	(40)	4	(22)
運用上の中止	1	(25)	0	(0)	3	(60)	4	(22)

Data source: [資料5.3.3.1.9: P06356] 14.1.2.2

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表 2.7.6.2.16-4　　被験者の背景（P06356 試験、パート 1）

	プラセボ 単回投与		SBECD 単回投与		ポサコナゾール 50 mg 単回投与		ポサコナゾール 100 mg 単回投与	
	n	(%)	n	(%)	n	(%)	n	(%)
総被験者数	18	(100)	9	(100)	9	(100)	9	(100)
性別								
男性	5	(28)	4	(44)	4	(44)	6	(67)
女性	13	(72)	5	(56)	5	(56)	3	(33)
年齢								
18～65歳未満	18	(100)	8	(89)	9	(100)	9	(100)
65歳以上	0	(0)	1	(11)	0	(0)	0	(0)
算術平均	38.6		33.4		31.3		32.4	
標準偏差	19.0		15.5		13.3		14.3	
中央値	35.0		28.0		29.0		28.0	
範囲	18 - 63		18 - 65		21 - 58		21 - 64	
体重（kg）								
算術平均	70.44		77.30		81.59		70.74	
標準偏差	12.09		10.37		13.69		8.92	
中央値	67.80		79.20		83.30		71.20	
範囲	55.6 - 99.5		58.0 - 89.2		63.6 - 108.6		57.9 - 87.0	
身長（cm）								
算術平均	171.65		175.48		178.23		176.82	
標準偏差	6.98		8.13		7.96		8.74	
中央値	172.25		175.50		176.50		178.00	
範囲	160.5 - 187.7		164.0 - 189.3		166.5 - 188.7		163.0 - 187.5	
BMI（kg/m^2）								
算術平均	23.83		25.13		25.70		22.62	
標準偏差	3.16		3.34		3.95		2.18	
中央値	23.40		25.50		24.90		22.20	
範囲	19.2 - 29.0		18.8 - 28.6		19.8 - 31.1		20.6 - 27.5	
肘幅（cm）								
算術平均	6.68		6.72		6.88		7.26	
標準偏差	0.52		0.45		0.41		0.74	
中央値	6.60		6.90		6.90		7.30	
範囲	6.0 - 8.0		5.9 - 7.2		6.2 - 7.5		6.3 - 8.4	
人種								
白人	17	(94)	9	(100)	8	(89)	9	(100)
アジア人	0	(0)	0	(0)	0	(0)	0	(0)
黒人又はアフリカ系アメリカ人	0	(0)	0	(0)	1	(11)	0	(0)
多人種	1	(6)	0	(0)	0	(0)	0	(0)
民族								
非ヒスパニック系又は非ラテン系	18	(100)	9	(100)	9	(100)	9	(100)

Data source: [資料5.3.3.1.9: P06356] 14.1.1

表 2.7.6.2.16-4　　被験者の背景（P06356 試験、パート 1）（続き）

	ポサコナゾール 200 mg 単回投与		ポサコナゾール 250 mg 単回投与		ポサコナゾール 300 mg 単回投与	
	n	(%)	n	(%)	n	(%)
総被験者数	9	(100)	9	(100)	9	(100)
性別						
男性	4	(44)	4	(44)	6	(67)
女性	5	(56)	5	(56)	3	(33)
年齢						
18～65歳未満	9	(100)	9	(100)	9	(100)
算術平均	29.1		42.7		24.9	
標準偏差	10.9		17.4		6.0	
中央値	27.0		42.0		22.0	
範囲	19 - 56		19 - 64		20 - 37	
体重（kg）						
算術平均	73.72		74.78		72.46	
標準偏差	9.04		11.52		7.32	
中央値	72.90		78.30		74.30	
範囲	57.5 - 92.0		57.4 - 89.0		54.3 - 78.2	
身長（cm）						
算術平均	176.40		171.89		178.48	
標準偏差	11.35		6.73		7.86	
中央値	175.00		170.40		183.20	
範囲	161.0 - 196.0		162.5 - 184.5		166.0 - 186.9	
BMI（kg/m^2）						
算術平均	23.87		25.29		22.79	
標準偏差	3.77		3.47		2.57	
中央値	23.20		24.90		21.90	
範囲	20.4 - 31.6		19.8 - 31.2		19.7 - 26.4	
肘幅（cm）						
算術平均	6.79		6.77		6.64	
標準偏差	0.55		0.40		0.50	
中央値	6.70		6.80		6.70	
範囲	6.2 - 7.8		6.1 - 7.3		5.9 - 7.2	
人種						
白人	8	(89)	9	(100)	8	(89)
アジア人	1	(11)	0	(0)	0	(0)
黒人又はアフリカ系アメリカ人	0	(0)	0	(0)	1	(11)
民族						
非ヒスパニック系又は非ラテン系	9	(100)	9	(100)	9	(100)

Data source: [資料5.3.3.1.9: P06356] 14.1.1

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表 2.7.6.2.16-5　　被験者の背景（P06356 試験、パート 2）

	プラセボ 反復投与 n	(%)	SBECD 反復投与 n	(%)	ポサコナゾール 100 mg 反復投与 n	(%)
総被験者数	4		9		5	
性別						
男性	3	(75)	6	(67)	4	(80)
女性	1	(25)	3	(33)	1	(20)
年齢						
18～65歳未満	4	(100)	9	(100)	5	(100)
算術平均	51.8		42.6		40.2	
標準偏差	19.3		19.4		14.2	
中央値	60.0		39.0		40.0	
範囲	23 - 64		21 - 64		19 - 57	
体重（kg）						
算術平均	71.98		73.71		85.00	
標準偏差	13.67		12.08		16.32	
中央値	73.30		72.90		86.10	
範囲	57.2 - 84.1		65.0 - 103.7		65.5 - 102.4	
身長（cm）						
算術平均	177.05		177.33		179.74	
標準偏差	16.05		15.45		10.33	
中央値	180.80		176.50		179.00	
範囲	154.5 - 192.1		152.2 - 197.0		165.4 - 193.1	
BMI（kg/m^2）						
算術平均	22.88		23.56		26.26	
標準偏差	2.15		3.23		4.48	
中央値	23.40		21.80		26.60	
範囲	19.9 - 24.8		20.0 - 28.1		20.9 - 33.0	
肘幅（cm）						
算術平均	6.95		6.82		7.24	
標準偏差	0.67		0.78		0.68	
中央値	7.15		6.50		7.50	
範囲	6.0 - 7.5		5.7 - 7.9		6.3 - 8.0	
人種						
白人	4	(100)	8	(89)	5	(100)
多人種	0	(0)	1	(11)	0	(0)
民族						
ヒスパニック系又はラテン系	0	(0)	1	(11)	0	(0)
非ヒスパニック系又は非ラテン系	4	(100)	8	(89)	5	(100)

Data source: [資料5.3.3.1.9: P06356] 14.1.1

2.7.6.2.16.3　　薬物動態の結果

本試験のパート1では、ポサコナゾールを投与した45例、本試験のパート2では、ポサコナゾール100 mg を投与した5例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者に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ときの血漿中薬物動態パラメータの要約及び用量比例性の評価の結果を、それぞれ[表 2.7.6.2.16-6]及び[表 2.7.6.2.16-7]に示す。

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表 2.7.6.2.16-6　　健康被験者にポサコナゾール静注用溶液 50～300 mg を単回末梢静脈内投与した際の血漿中薬物動態パラメータの要約（P06356 試験）

用量 (mg)	コホート	n	k_{el} (1/hr)	$t_{1/2}$ (hr)	T_{max}† (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}last}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	V_d (L)	CL (L/hr)
50	2	9	0.0410 (34)	18.7 (34)	0.6 (0.5 - 0.7)	313 (30)	4620 (31)	4890 (30)	294 (39)	10.9 (25)
100	3	9	0.0360 (14)	19.6 (16)	0.5 (0.5 - 0.5)	1330 (27)	10800 (27)	11200 (26)	262 (22)	9.40 (23)
200	4	9	0.0307 (23)	23.6 (23)	0.5 (0.5 - 24)‡	2250 (29)	34600 (52)	35400 (50)	226 (38)	6.54 (32)
250	5	9	0.0279 (21)	26.0 (23)	0.5 (0.5 - 0.5)	2260 (26)	40600 (39)	41500 (41)	245 (33)	6.68 (29)
300	6	9	0.0292 (20)	24.6 (20)	0.5 (0.5 - 1.0)	2840 (30)	45500 (26)	46400 (26)	236 (17)	6.90 (27)

算術平均（%CV）
CV：変動係数
† 中央値（範囲）、30分間投与
‡ 被験者1例の C_{max} は24時間時点に採取した検体で示されたため、本被験者の T_{max} は24時間である。

Data source: [資料5.3.3.1.9: P06356] Table 16-2, Table 16-3, Table 16-4, Table 16-5, Table 16-6

健康被験者に対してポサコナゾール静注用溶液50～300 mg を単回末梢静脈内投与した際のポサコナゾールの平均曝露量（$AUC_{0\text{-}\infty}$）は4890～46400 ng·hr/mL であった。ポサコナゾール静注用溶液50～300 mg を単回末梢静脈内投与した際、ポサコナゾールは体内から緩徐に消失した。ポサコナゾールの $t_{1/2}$の算術平均は、高用量（200 mg 以上）（範囲：23.6～26.0時間）の方が低用量（範囲：18.7～19.6時間）より長かった。CL の算術平均は、200 mg 以上（範囲：6.54～6.90 L/hr）の方が低用量（範囲：9.40～10.9 L/hr）より低値を示した。

V_d の算術平均は、200 mg 以上（範囲：226～245 L）の方が低用量（範囲：262～294 L）より小さかった。ポサコナゾールが血漿中に検出されたのは、低用量（50 mg 及び100 mg）では投与開始後120時間までであったのに対し、高用量では投与開始後168時間までであった。ポサコナゾールを50～300 mg の用量で30分かけて単回末梢静脈内投与した際の C_{max} の算術平均は313～2840 ng/mL であり、そのばらつきは中程度であった（変動係数の範囲：26%～30%）。探索的な用量比例性を評価するパワーモデルで得られた傾きの推定値及び90%信頼区間を[表 2.7.6.2.16-7]に示す。パワーモデルで得られた C_{max}、$AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$の傾きの推定値（90%信頼区間）は、それぞれ1.159（1.018, 1.300）、1.328（1.215, 1.441）及び1.302（1.191, 1.414）であった。用量比例性の評価結果から、C_{max}、$AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$は用量比例性を上回る増加を示したが、この用量比例性を上回る増加は主に200 mg を下回る用量でみられており、臨床的に重要な用量である200～300 mg ではその程度はより小さかった。

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表 2.7.6.2.16-7　　健康被験者にポサコナゾール静注用溶液を 50～300 mg の用量範囲で単回末梢静脈内投与した際のポサコナゾールの用量比例性の評価（P06356 試験）

薬物動態パラメータ	傾き	90%信頼区間		用量範囲	幾何平均比	90%信頼区間	
		下限値	上限値		300 mg / 50 mg	下限値	上限値
C_{max}	1.159	1.018	1.300	50～300 mg（6倍）	7.979	6.197	10.27
$AUC_{0\text{-last}}$	1.328	1.215	1.441		10.80	8.824	13.21
$AUC_{0\text{-}\infty}$	1.302	1.191	1.414		10.32	8.452	12.59

Data source: [資料5.3.3.1.9: P06356] Table 11-3

パート2は、反復投与後の注入部位の有害事象により、100 mg 投与後に早期に中止となったため、反復投与時のポサコナゾールの薬物動態は評価できなかった。[表 2.7.6.2.16-8]にポサコナゾール静注用溶液100 mg 初回投与後の血漿中薬物動態パラメータのみを要約した。

表 2.7.6.2.16-8　　健康被験者にポサコナゾール静注用溶液 100 mg 初回投与後の血漿中薬物動態パラメータの要約（P06356 試験）

用量 (mg)	コホート	n	k_{el} (1/hr)	$t_{1/2}$ (hr)	T_{max}† (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	V_d (L)	CL (L/hr)
100	8	5	0.0268 (20)	26.9 (23)	0.50 (0.50-0.60)	1000 (41)	34500 (33)	35300 (34)	113 (12)	3.05 (26)

算術平均（%CV）
CV：変動係数
†　中央値（範囲）、30分間投与

Data source: [資料5.3.3.1.9: P06356] Table 16-7

2.7.6.2.16.4　　安全性の結果

本試験では、治験薬を投与した全被験者90例を安全性解析対象集団に含めた。重篤な有害事象、妊娠及び死亡はなかった。

パート1で、健康被験者にポサコナゾール静注用溶液を300 mg までの用量で30分かけて単回末梢静脈内投与した際、安全で忍容性は良好であった。パート1の単回末梢静脈内投与後、72例中29例で有害事象が報告され、このうち13例が副作用であった。すべての有害事象は軽度又は中等度と判定された。最もよくみられた有害事象は注入部位反応、鼻咽頭炎及び頭痛であった。注入部位反応は、SBECD のみ含有する治験薬を単回投与された9例中2例及びポサコナゾールを含有する治験薬を単回投与された45例中7例に認められた。注入部位の有害事象（注入部位反応、血栓性静脈炎及び注入部位異常感覚）は、SBECD 投与後に9例中2例、ポサコナゾール静注用溶液50 mg 投与後に9例中1例、200 mg 投与後に9例中2例、250 mg 投与後に9例中2例、並びに300 mg 投与後に9例中3例で報告された。

パート2では、健康被験者に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後、血栓性静脈炎（SPCT スコアリング尺度で評価し、注入部位の有害事象として報告）が発現し、忍容性は良好ではなかった。パート2の反復末梢静脈内投与後、18例中13例で有害事象が報告

され、このうち11例が副作用であった。すべての有害事象は軽度又は中等度と判定された。最もよくみられた有害事象は注入部位反応、血栓性静脈炎及び頭痛であった。注入部位の有害事象（注入部位反応及び血栓性静脈炎）は、プラセボ投与後に4例中1例、SBECD 投与後に9例中3例、ポサコナゾール静注用溶液100 mg 投与後に5例中4例で報告された。治験担当医師は、有害事象の血栓性静脈炎により、4例（プラセボ：1例、SBECD：1例、ポサコナゾール100 mg：2例）の治験薬投与を中止した。

ポサコナゾール静注用溶液を100 mgの用量で30分かけて反復末梢静脈内投与したときの血栓性静脈炎の発現頻度が高かったため、治験依頼者は本試験のパート2を中止し、コホート9及び10に対する投与（ポサコナゾール静注用溶液200 mg 及び300 mg を反復末梢静脈内投与）は実施しなかった。ただし、ポサコナゾール静注用溶液を200 mg を上回る用量（すなわち、250 mg 及び300 mg）で単回末梢静脈内投与したときの安全性を評価するために、パート1は継続した。

本試験で注入部位反応の他に臨床的に意味のある有害事象は報告されなかった。本試験で臨床的に懸念される駆出率低下及び肝機能検査異常は認められなかった。概して、駆出率、臨床検査値、バイタルサイン及び心電図所見に、治験薬投与及び用量と関連する傾向は認められなかった。

2.7.6.2.16.5　　結論

1) パート1で健康被験者にポサコナゾール静注用溶液を300 mg までの用量で30分かけて末梢静脈内単回投与した際、安全で忍容性は良好であった。血栓性静脈炎（SPCT スコアリング尺度で評価し、注入部位の有害事象として報告）は、SBECD のみを投与された9例中2例及びポサコナゾールを投与された45例中7例で報告された。また、注入部位異常感覚が1例で報告された。
2) パート2では、健康被験者に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後、血栓性静脈炎（SPCT スコアリング尺度で評価し、注入部位の有害事象として報告）が5例中4例で発現し、忍容性は良好ではなかった。
3) ポサコナゾール静注用溶液を50～300 mg の用量で単回静脈内投与した際、C_{max}、$AUC_{0\text{-}last}$ 及び $AUC_{0\text{-}\infty}$は用量比例を上回る増加を示した。この用量比例性を上回る曝露量の増加は主に200 mg を下回る用量でみられており、臨床的に重要な用量である200～300 mg ではその程度はより小さかった。

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2.7.6.2.17　非日本人健康被験者を対象に肺上皮被覆液及び肺胞上皮細胞内の薬物動態を評価した反復経口投与試験（P04547試験）［参考資料］

治験総括報告書[資料5.3.3.1.10: P04547]の概要を以下に示す。

2.7.6.2.17.1　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象としたポサコナゾールを反復経口投与した際の血漿、肺上皮被覆液及び肺胞上皮細胞中濃度を評価する非盲検試験／P04547試験

治験責任医師／実施医療機関

Jeffrey Austin Golden, MD / University of California（米国）

治験期間

2006年3月6日～2006年12月5日

開発の相

第Ⅰ相

目的

【主要目的】

健康被験者にポサコナゾールを1日2回反復経口投与した際の規定した時点での血漿、肺上皮被覆液（ELF）及び肺胞上皮細胞（AC）中濃度を測定する。

【副次目的】

健康被験者にポサコナゾールを1日2回反復経口投与した際の安全性及び忍容性を評価する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾール経口懸濁液400 mg を8日間（計14回）反復投与した際の薬物動態及び薬力学パラメータを評価する、非盲検、反復投与試験であった。25例の被験者を1:1:1:1:1の割合で、気管支鏡検査法及び気管支肺胞洗浄の実施スケジュールごとに分けた5つの処置群のうち1つに割り付けた。これらの検査は14回の治験薬の投与後に実施された。肺専門医の指示の下、気管支鏡検査法及び気管支肺胞洗浄を用いて ELF 及び AC を採取した。

投与期間

反復（8日間）

用法・用量

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ポサコナゾール経口懸濁液400 mg を1日2回7日間（1日目は夜に1日1回投与）高脂肪食摂取後に反復経口投与し、8日目は朝に1日1回空腹時に経口投与した。治験薬の内容を、[表 2.7.6.2.17-1]に示す。

表 2.7.6.2.17-1　治験薬の内容（P04547 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤

診断／選択基準

スクリーニング時に BMI が18 kg/m^{2}以上29 kg/m^{2}以下で、21歳以上55歳以下の健康な男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1日目の投与前並びに8日目の投与前及び投与後24時間までの規定した時点で採取した。また、8日目に ELF 中及び AC 中薬物濃度測定用検体を、第1群は投与後3時間、第2群は投与後5時間、第3群は投与後8時間、第4群は投与後12時間、第5群は投与後24時間の時点で採取した。血漿、ELF 及び AC それぞれの薬物動態パラメータ［C_{max}、T_{max}、AUC、C_{min}及び$t_{1/2}$（可能な場合）］を算出した。血漿、ELF 及び AC 中の C_{max}、AUC 及び濃度データを用いて、薬物動態／薬力学パラメータ［C_{max}/90%以上の株の発育を阻止する濃度（MIC_{90}）、AUC/MIC_{90}及びMIC_{90}を超える濃度を維持している持続時間（time-above-MIC_{90}）］を算出した。MIC_{90}については、Schering Plough Research Institute データベースの *Aspergillus* 属に対するポサコナゾールのMIC_{90}の値を使用した。遊離体（非結合型）及び総薬物（非結合型及び結合型）濃度に基づいて、血漿中ポサコナゾールの薬物動態／薬力学パラメータを算出した。

各分析方法については、[資料5.3.3.1.10: P04547]を参照すること。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

1回以上の治験薬の投与を受け、ベースライン以降の有効な薬物動態データが1つ以上あるすべての被験者について薬物動態解析を実施した。血漿中薬物動態パラメータは各被験者の血漿中濃度推移に基づき算出し、ELF 及び AC 中薬物動態パラメータは各採取時点の ELF 及び AC 中ポサ

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コナゾール濃度を平均したデータを用いて算出した。

血漿、ELF 及び AC 中薬物濃度、薬物動態パラメータ及び薬物動態／薬力学パラメータの要約統計量を示した。ELF 及び AC 中ポサコナゾール濃度の散布図、並びに平均血漿中ポサコナゾール濃度－時間プロットを示した。

【安全性】

有害事象について、器官別大分類及び基本語ごとに要約し、程度及び治験薬との因果関係も示した。有害事象発現例数、特定の有害事象の発現及び有害事象による中止例について表に示した。

心電図、臨床検査、バイタルサイン及び身体所見のデータを一覧にした。臨床検査の結果について要約統計量を用いて要約した。

2.7.6.2.17.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.17-2]及び[表 2.7.6.2.17-3]に示す。

表 2.7.6.2.17-2　　被験者の内訳（P04547 試験）

	n	(%)
総被験者数	25	
内訳		
完了	21	(84)
中止	4	(16)
有害事象	2	(8)
同意撤回	2†	(8)
† 被験者1例がすべての投与を受けた後、同意を撤回し、別の被験者1例が3回投与を受けた後、同意を撤回した。		

Data source: [資料5.3.3.1.10: P04547] 16.2.4, 16.2.7.3, 16.2.10

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表 2.7.6.2.17-3　　被験者の背景（P04547 試験）

	ポサコナゾール400 mg 1日2回 n=25 (%)
性別（例）	
女性	10 (40)
男性	15 (60)
人種（例）	
白人	17 (68)
非白人	8 (32)
アメリカ系インディアン又はアラスカ原住民	1 (4)
アジア系	4 (16)
黒人又はアフリカ系アメリカ人	1 (4)
混血	2 (8)
民族（例）	
ヒスパニック系又はラテン系	5 (20)
非ヒスパニック系又は非ラテン系	4 (16)
非ヒスパニック系、非ラテン系又は非日本人	16 (64)
年齢（歳）	
算術平均（標準偏差）	30.4 (7.9)
中央値	27.0
範囲	21 - 47
18～65歳未満	25 (100)
体重（kg）	
算術平均（標準偏差）	66.11 (10.00)
中央値	67.60
範囲	48.8 - 84.0
身長（cm）	
算術平均（標準偏差）	168.48 (7.77)
中央値	167.60
範囲	153.7 - 181.6
BMI（kg/m^2）	
算術平均（標準偏差）	23.23 (2.73)
中央値	22.50
範囲	18.3 - 27.8

Data source: [資料5 3 3 1 10: P04547] 14.1.1

2.7.6.2.17.3　　薬物動態の結果

本試験では、試験を中止した被験者4例を除く21例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール経口懸濁液400 mg を1日2回8日間高脂肪食摂取後に反復経口投与（1日目及び8日目は1日1回投与。8日目朝のみ空腹時投与）した際の8日目の血漿、ELF 及び AC 中ポサコナゾールの薬物動態パラメータの要約を[表 2.7.6.2.17-4]に示す。ポサコナゾール400 mg を1日2回高脂肪食摂取後に反復経口投与した際、血漿中ポサコナゾール濃度は投与後3時間（T_{max} の中央値）で C_{max} に到達した。平均血漿中ポサコナゾール濃度は12時間の投与間隔を通して *Aspergillus* 属に対する MIC_{90}（500 ng/mL）を超え、投与終了後24時間でもこの MIC_{90}を超えていた。2例の被験者で血漿中濃度が MIC_{90}を超えなかったが、AC 中ポサコナゾール濃度は MIC_{90}よりも極めて高かった。

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ELF 及び AC 中のポサコナゾール濃度は投与後5時間に C_{max} に到達した。血漿及び ELF 中ポサコナゾール濃度は類似していたが、AC 中ポサコナゾール濃度は、血漿中濃度と比べ、かなり高く、AUC の比（ELF／血漿及び AC／血漿）は、それぞれ0.836及び32.6であった。これは、ポサコナゾールの親油性及び高い膜透過性と一貫していると考えられる。また、AC 中ポサコナゾール濃度は、12時間の投与間隔を通して、投与終了後24時間まで *Aspergillus* 属に対する MIC_{90}より極めて高かった。血漿、ELF 及び AC の AUC/MIC_{90}の比はそれぞれ、88、73及び2860であった［AUC には $AUC_{0\text{-}24\ hr}$（$AUC_{0\text{-}12\ hr}$×2）を用いた］。

血漿、ELF 及び AC 中のポサコナゾール濃度は比較的平坦な推移を示しており、ポサコナゾールの濃度が維持され、消失が遅いことが示唆された。

表 2.7.6.2.17-4　健康被験者にポサコナゾール経口懸濁液 400 mg を 1 日 2 回（1 日目及び 8 日目は 1 日 1 回）8 日間高脂肪食摂取後に反復経口投与した際の 8 日目の血漿、ELF 及び AC 中ポサコナゾールの薬物動態パラメータの要約（P04547 試験）

薬物動態パラメータ (n=21)	検体		
	血漿	ELF†	AC†
T_{max} (hr)	3.00 (0.00-12.0)‡	5.00	5.00
C_{max} (ng/mL)	2080 (45)	1860	87700
C_{min} (ng/mL)	1540 (52)	1020	46200
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	21900 (47)	18300	715000
Time-above-MIC_{90} (hr)	24.0 (2.39-24.0)‡	24.0	24.0
C_{max}/MIC_{90}	4.15 (45)	3.72	175
AUC§/MIC_{90}	87.6 (47)	73.2	2860
非結合型の C_{max}/MIC_{90}	0.0623 (45)	-	-
非結合型の AUC§/MIC_{90}	1.31 (47)	-	-
AUC の血漿に対する比	-	0.836	32.6

Aspergillus 属に対する MIC_{90}は500 ng/mL、ポサコナゾールの血漿中蛋白との非結合率は1.5%（結合率は98 5%）。
算術平均（%CV）
AC：（気管支肺胞洗浄液の遠心分離で得られた）肺胞上皮細胞、CV：変動係数、ELF：肺上皮被覆液（気管支肺胞洗浄液から肺胞上皮細胞を遠心分離した上清）
† 各被験者から得られたすべての薬物濃度を統合して得られた1つの薬物濃度推移に基づき算出した薬物動態パラメータ
‡ 中央値（範囲）
§ $AUC_{0\text{-}24\ hr}$（$AUC_{0\text{-}12\ hr}$×2）に基づく

Data source: [資料5.3.3.1.10: P04547] 16.1.9.2 Table 3, Table 4

2.7.6.2.17.4　安全性の結果

本試験では、治験薬を投与した全被験者25例を安全性解析対象集団に含めた。健康被験者にポサコナゾール経口懸濁液400 mg を1日2回（1日目及び8日目は1日1回）8日間高脂肪食摂取後に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、妊娠及び死亡はなかった。被験者1例が下痢、発熱、悪寒、疲労及び食欲不振の有害事象、別の被験者1例が、疲労、眼瞼浮腫及び呼吸時疼痛の有害事象により試験を中止した。25例中17例で有害事象が報告された。重度の不安1件（気管支鏡検査法及び気管支肺胞洗浄実施前に発現し、副作用ではないと判定）を除き、ほとんどの有害事象は軽度又は中等度と判定された。2例以上で報告された有害事象は、疲労（3

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例)、頭痛（3例)、悪心（3例)、下痢（2例)、呼吸時疼痛（2例）及び発熱（2例）であった。25例中9例で副作用が報告された。いずれの副作用も軽度又は中等度と判定された。2例以上の被験者で報告された副作用は、疲労（3例)、悪心（3例)、下痢（2例）及び頭痛（2例）であった。臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.17.5　　結論

1) 健康被験者にポサコナゾール経口懸濁液400 mg を1日2回（1日目及び8日目は1日1回）8日間高脂肪食摂取後に反復経口投与した際、安全で忍容性は良好であった。
2) 平均血漿中ポサコナゾール濃度は12時間の投与間隔を通して *Aspergillus* 属に対するポサコナゾールの MIC_{90}（500 ng/mL）を超え、投与終了後24時間でもこの MIC_{90}を超えていた。
3) AUC の比（ELF／血漿及び AC／血漿）は、それぞれ0.836及び32.6であった。
4) 血漿、ELF 及び AC の AUC/MIC_{90}の比はそれぞれ、88、73及び2860であった［AUC には $AUC_{0\text{-}24\ hr}$（$AUC_{0\text{-}12\ hr}$×2）を用いた］。

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2.7.6.2.18　非日本人健康被験者を対象に皮膚中薬物濃度を評価した反復経口投与試験（P05270試験）［参考資料］

治験総括報告書[資料5.3.3.1.11: P05270]の概要を以下に示す。

2.7.6.2.18.1　試験方法

治験実施計画書標題／番号

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400 mgを1日2回反復投与した際のポサコナゾールの皮膚中濃度を評価する非盲検試験／P05270試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

【主要目的】

ポサコナゾール400 mgを1日2回反復投与した際のポサコナゾールの皮膚中濃度を評価する。

【副次目的】

1) ポサコナゾールの皮膚中濃度及び血漿中濃度を比較する。
2) 血漿及び皮膚検体の C_{max}/MIC_{90}、AUC/MIC_{90}及び time-above-MIC_{90}を算出し、薬物動態／薬力学を探索的に検討する。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾールを反復投与した際のポサコナゾールの皮膚中濃度を評価する、非盲検、無作為化、反復投与試験であった。投与24時間前に入所させ、ポサコナゾール経口懸濁液400 mgを高脂肪食摂取後に初回投与し、続く14回の投与を被験者自身で実施するよう指導した。7日目に再来所させ、7日目の夜及び8日目の朝に高脂肪食摂取後、治験薬を投与した。

投与期間

反復（8日間）

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用法・用量

ポサコナゾール経口懸濁液400 mg を1日2回8日間（8日目は朝投与のみ）食後に反復経口投与した。治験薬の内容を、[表 2.7.6.2.18-1]に示す。

表 2.7.6.2.18-1　治験薬の内容（P05270 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤

診断／選択基準

スクリーニング時に BMI が18 kg/m^2以上30 kg/m^2以下で、18歳以上60歳以下の健康な男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1日目の初回投与及び8日目の最終投与前及び投与後12時間までの規定した時点で採取した。また、皮膚中薬物濃度測定用検体を、以下の5群のうち1つに被験者を無作為に割り付け、採取した。

- 第1群：初回投与直前及び最終投与直前（0時間）
- 第2群：初回投与後3時間及び最終投与後3時間
- 第3群：初回投与後5時間及び最終投与後5時間
- 第4群：初回投与後8時間及び最終投与後8時間
- 第5群：初回投与後12時間及び最終投与後12時間

ポサコナゾールの血漿中及び皮膚中薬物動態パラメータ［C_{max}、T_{max}、$AUC_{0\text{-}12\ hr}$、C_{min}、$t_{1/2}$（可能な場合）］を算出した。C_{max}、$AUC_{0\text{-}12\ hr}$及び濃度データから薬物動態／薬力学パラメータ（血漿中及び皮膚中の C_{max}/MIC_{90}、$AUC_{0\text{-}12\ hr}/MIC_{90}$及び time-above-$MIC_{90}$）を算出した。$MIC_{90}$については、Schering Plough Research Institute データベースの *Aspergillus* 属に対するポサコナゾールのMIC_{90}の値を使用した。血漿中の薬物動態／薬力学パラメータは、遊離体（非結合型）及び総薬物（非結合型及び結合型）濃度に基づいて算出することとした。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

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統計計画及び解析

【薬物動態】

血漿中及び皮膚中薬物濃度、薬物動態パラメータ並びに薬物動態／薬力学パラメータの要約統計量を算出した。また、適切な場合、データを図示した。必要に応じ、追加の解析を実施することとした。

2.7.6.2.18.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.18-2]及び[表 2.7.6.2.18-3]に示す。

表 2.7.6.2.18-2　　被験者の内訳（P05270 試験）

	n	(%)
総被験者数	30	(100)
内訳		
完了	27	(90)
中止	3	(10)
有害事象	2†	(7)
同意撤回	1	(3)

† 被験者1例が ALT 及び AST 上昇、もう1例が ALT 上昇の副作用により、7日目の朝投与後に試験を中止した。

Data source: [資料5.3.3.1.11: P05270] 14.1.2.2, 16.2.5.1, 16.2.7.2

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表 2.7.6.2.18-3　　被験者の背景（P05270 試験）

	合計 n = 30 (%)
性別（例）	
女性	10 (33)
男性	20 (67)
人種（例）	
白人	16 (53)
非白人	14 (47)
アジア系	1 (3)
黒人又はアフリカ系アメリカ人	13 (43)
年齢（歳）	
算術平均（標準偏差）	37.7 (11.9)
中央値	36.5
範囲	18 - 60
18～65歳未満	30 (100)
体重（kg）	
算術平均（標準偏差）	79.06 (12.96)
中央値	80.00
範囲	49.8 - 100.0
身長（cm）	
算術平均（標準偏差）	174.40 (9.96)
中央値	177.80
範囲	149.0 - 189.5
BMI（kg/m^2）	
算術平均（標準偏差）	25.85 (2.68)
中央値	25.90
範囲	21.5 - 29.7

Data source: [資料5.3.3.1.11: P05270] 14.1.1

2.7.6.2.18.3　　薬物動態の結果

本試験では、被験者30例から得られた血漿中薬物濃度データを薬物動態解析に含めた。健康被験者にポサコナゾール経口懸濁液400 mg を1日2回（8日目は1日1回）8日間食後に反復経口投与した際の1日目及び8日目の血漿中及び皮膚中薬物動態パラメータの要約を[表 2.7.6.2.18-4]に示す。ポサコナゾール400 mg を1日2回食後反復経口投与した際、8日目では投与後5時間（中央値）で C_{max} に到達した。12時間の投与間隔を通してポサコナゾールの平均血漿中濃度は *Aspergillus* 属に対する MIC_{90}（500 ng/mL）を超えた。

また、皮膚中のポサコナゾールに関しては、8日目では投与後3時間で最高皮膚中濃度に到達した。12時間の投与間隔を通してポサコナゾールの皮膚中濃度は MIC_{90}（500 ng/mL）より数倍高かった。8日目の血漿中及び皮膚中の $AUC_{0\text{-}12\ hr}/MIC_{90}$の比は、それぞれ37.3及び46.8であった。

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表 2.7.6.2.18-4　健康被験者にポサコナゾール経口懸濁液 400 mg を 1 日 2 回（8 日目は 1 日 1 回）8 日間食後に反復経口投与した際の 1 日目及び 8 日目の血漿中及び皮膚中薬物動態パラメータの要約（P05270 試験）

薬物動態パラメータ	血漿		皮膚†‡	
	算術平均（%CV）			
	1日目(n=30)	8日目(n=27)	1日目	8日目
T_{max} (hr)	8.00 (3.00 - 12.0)§	5.00 (3.00 - 12.0)§	12.0	3.00
C_{max} (ng/mL)	453 (46)	1740 (51)	328	2610
C_{min} (ng/mL)	-	1360 (56)	-	1500
$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	3630 (46)	18600 (53)	1760	23400
Time-above-MIC_{90} (hr)	0.00 (0.00 - 9.53)§	12.0 (0.121 - 12.0)§	0.00	12.0
C_{max}/MIC_{90}	0.906 (46)	3.47 (51)	0.657	5.22
$AUC_{0\text{-}12\ hr}/MIC_{90}$	7.26 (46)	37.3 (53)	3.52	46.8
$AUC_{0\text{-}24\ hr}$‖$/MIC_{90}$	14.5 (46)	74.6 (53)	7.04	93.5
非結合型の C_{max}/MIC_{90}	0.0136 (46)	0.0521 (51)	-	-
非結合型の $AUC_{0\text{-}12\ hr}/MIC_{90}$	0.109 (46)	0.559 (53)	-	-
非結合型の $AUC_{0\text{-}24\ hr}$‖$/MIC_{90}$	0.218 (46)	1.12 (53)	-	-
AUC の血漿に対する比	-	-	0.485	1.26

Aspergillus 属に対する MIC_{90}は500 ng/mL、ポサコナゾールの血漿中蛋白との非結合率は1.5%（結合率は98.5%）
CV：変動係数
† 各被験者から得られたすべての薬物濃度を統合して得られた1つの薬物濃度推移に基づき算出した薬物動態パラメータ
‡ C_{max} 及び AUC の単位：ng/g 及び ng·hr/g
§ 中央値（範囲）
‖ $AUC_{0\text{-}24\ hr}$ は $AUC_{0\text{-}12\ hr}$×2に基づく

Data source: [資料5.3.3.1.11: P05270] 14.2.2 Table 3, Table 4, Table 5, Table 6, Table 7

2.7.6.2.18.4　安全性の結果

本試験では、治験薬を投与した全被験者30例を安全性解析対象集団に含めた。健康被験者にポサコナゾール経口懸濁液400 mg を1日2回8日間食後に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、妊娠及び死亡はなかった。2例の被験者が副作用により7日目の朝投与後に中止した（1例は ALT 及び AST 上昇、別の1例は ALT 上昇）。30例中17例で有害事象が報告され、このうち11例が副作用であり、いずれも軽度又は中等度であった。最もよくみられた有害事象は、胃腸障害で、本分類で最もよくみられた有害事象は白色便であった。その他の臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。試験中、いずれの時点でも QTc の延長（男性で450 msec 超、女性で470 msec 超）を示した被験者はなかった。

2.7.6.2.18.5　結論

1) 健康被験者にポサコナゾール経口懸濁液400 mg を1日2回8日間食後に反復経口投与した際、安全で忍容性は良好であった。
2) 健康被験者にポサコナゾール経口懸濁液400 mg を1日2回8日間食後に反復経口投与した際、12時間の投与間隔を通して8日目のポサコナゾールの平均血漿中濃度及び皮膚中濃度は *Aspergillus* 属に対する MIC_{90}（500 ng/mL）を超えた。
3) 8日目の皮膚中ポサコナゾール濃度は、血漿中濃度よりも高かった。

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4)　8日目の血漿中及び皮膚中の $AUC_{0\text{-}12\ hr}/MIC_{90}$の比は、それぞれ37.3及び46.8であった。

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2.7.6.2.19　　非日本人健康被験者を対象としたマスバランス試験（C[redacted]-104試験）［参考資料］

治験総括報告書[資料5.3.3.1.12: C[redacted]_104]の概要を以下に示す。

2.7.6.2.19.1　　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象とした^{14}C-ポサコナゾール経口懸濁液を単回投与した際の吸収、代謝及び排泄を評価する試験／C[redacted]-104試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

健康被験者に^{14}C-ポサコナゾール経口懸濁液409 mg を高脂肪食摂取後に単回経口投与した際の吸収、代謝及び排泄の特徴を明らかにする。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾールの吸収、分布、代謝及び排泄を評価する、非盲検、単回経口投与試験であった。^{14}C-ポサコナゾール経口懸濁液約409 mg（約79.3 μCi）を高脂肪食摂取後に単回経口投与した。

投与期間

単回

用法・用量

^{14}C-ポサコナゾール経口懸濁液約409 mg（約79.3 μCi）を高脂肪食摂取後に単回経口投与した。治験薬の内容を、[表 2.7.6.2.19-1]に示す。

表 2.7.6.2.19-1　治験薬の内容（C[redacted]-104 試験）

薬剤	力価	剤形
^{14}C-ポサコナゾール経口懸濁液	ポサコナゾール409 mg（79.3 μCi）／被験者	液剤

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診断／選択基準

スクリーニング時に保険数理表に基づく体重の±15%以内の体重で、18歳以上45歳以下の健康な男性

評価基準

【薬物動態】

血漿中ポサコナゾール並びに血中及び血漿中総放射能濃度測定用検体を投与前及び投与後168時間までの規定した時点で採取した。さらに、代謝物プロファイル検討用血液検体を投与後48時間までの規定した時点で採取した。総放射能及びポサコナゾール測定並びに代謝物プロファイル検討用尿検体を投与前及び投与後168時間までの規定した間隔で採取した。また、総放射能測定及び代謝プロファイル検討用糞検体を、投与前及び投与後168時間まで採取した。薬物動態パラメータ［C_{max}、T_{max}、$AUC_{0\text{-}24\ hr}$、$AUC_{0\text{-}last}$及び総排泄量等］を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

薬物動態パラメータの要約統計量を示した。

2.7.6.2.19.2　　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.19-2]及び[表 2.7.6.2.19-3]に示す。

表 2.7.6.2.19-2　　被験者の内訳（C[redacted]-104 試験）

	n	(%)
総被験者数	8	
内訳		
完了	8	(100)
中止	0	(0.0)

Data source: [資料5.3.3.1.12: C[redacted]_104] 16.2.1 Subject Listing

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表 2.7.6.2.19-3　　被験者の背景（C[redacted]-104 試験）

	n	(%)
総被験者数	8	
性別		
男性	8	(100.0)
年齢（歳）		
算術平均	36.5	
標準偏差	5.1	
中央値	37	
範囲	26 - 44	
身長（inch †）		
算術平均	68.8	
標準偏差	2.5	
中央値	69.0	
範囲	65.0 - 72.0	
体重（lb ‡）		
算術平均	164.9	
標準偏差	17.2	
中央値	164.5	
範囲	141 - 190	
体格§		
中	7	(87.5)
大	1	(12.5)
人種		
黒人	1	(12.5)
白人	2	(25.0)
ヒスパニック	5	(62.5)

† 1 inch = 2.54 cm
‡ 1 lb = 0.4536 kg
§ [資料5.3.3.1.12: C[redacted]_104] 16.1.1 Protocol Appendix B

Data source: [資料5.3.3.1.12: C[redacted]_104] 16.2.1

2.7.6.2.19.3　　薬物動態の結果

本試験では、^{14}C-ポサコナゾール経口懸濁液を投与した被験者8例から得られた薬物濃度データを薬物動態解析に含めた。健康被験者に^{14}C-ポサコナゾール経口懸濁液409 mg を高脂肪食摂取後に単回経口投与した際の血漿中ポサコナゾール並びに血漿中及び血中総放射能の薬物動態パラメータの要約を[表 2.7.6.2.19-4]に示す。血漿中ポサコナゾール及び総放射能の $AUC_{0\text{-}24\ hr}$ の値の比較から、血漿中の薬物由来の放射能の63%がポサコナゾール（未変化体）であることが示された。

血漿中及び血中総放射能の曝露量（$AUC_{0\text{-}24\ hr}$）の比較から、血漿中総放射能は、血中総放射能より46%高いことが示された（血漿中総放射能に対する血中総放射能の個々値の比は、0.348～0.713の範囲であった）。さらに、血漿中の薬物由来の放射能濃度推移は、血中での推移と類似していた。以上の結果から、薬物由来の放射能が赤血球中にわずかに分配されることが示唆された。

投与した放射能の9.73%が尿中に排泄された。ポサコナゾールの未変化体は全被験者の尿中に検出されたが、その尿中排泄率は投与量の約0.22%にすぎなかった。また、ポサコナゾールの腎クリアランス（CL_r）の算術平均は約0.42 mL/min で、全身クリアランスの算術平均（220 mL/min）と比べるとわずかであった。

平均総放射能排泄率は投与した放射能の80.4%（範囲：42.4%～111%）で、尿中には9.73%（範

囲：4.36%～13.6%）、糞中には70.6%（範囲：38.0%～101%）が排泄された。

いずれの被験者でも、長時間にわたって尿中及び糞中へ放射能が排泄され、投与後120～144時間及び144～168時間の尿中及び糞中の累積放射能排泄率の算術平均は、それぞれ投与放射能の約4.1%及び2.7%であった。

糞中への放射能の排泄は投与後168時間においても8例全例で検出可能であった。被験者3例の糞中総放射能排泄率（算術平均：48.4%）は他の5例（算術平均：84.0%）と比べ、有意に低く、糞中への放射能の排泄は一定していなかった。投与放射能の排泄が不完全であったのは、検体採取期間が短かったことによる可能性が考えられ、10日間以上採取期間を延長すれば改善した可能性がある。

代謝物プロファイルの評価から、血漿中の薬物由来放射能の主成分はポサコナゾール（未変化体）であり（血漿中総放射能の76.5%）、血漿中の主要な代謝物は、ポサコナゾールのグルクロン酸抱合体であった（血漿中総放射能の23.5%）。

尿中代謝物は主にグルクロン酸抱合体で、ポサコナゾールの未変化体はわずかであった。糞中にはほとんど未変化体として排泄された。

表 2.7.6.2.19-4 健康被験者に ^{14}C-ポサコナゾール経口懸濁液 409 mg を高脂肪食摂取後に単回経口投与した際の血漿中ポサコナゾール並びに血漿中及び血中総放射能の薬物動態パラメータの要約（C[redacted]-104 試験）

薬物動態パラメータ	血漿中ポサコナゾール	血漿中総放射能	全血中総放射能
C_{max} (ng/mL 又は ng Eq/g)	739 (25)	1135 (26)	768 (20)
T_{max} (hr)	7.88 (46)	8.50 (17)	8.00 (19)
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL 又は ng Eq·hr/g)	11911 (21)	19124 (24)	13137 (18)
$AUC_{0\text{-}last}$ (ng·hr/mL 又は ng Eq·hr/g)	32118 (31)	34324 (39)	23475 (36)
T_{last} (hr)	165 (5)	48 (27)	46.5 (26)
$t_{1/2}$ (hr)	31.1 (24)	-	-
CL/F (mL/min)	220 (26)	-	-

n=8、算術平均（%CV）
CV：変動係数

Data source: [資料5.3.3.1.12: C[redacted]_104] 16.2.4

2.7.6.2.19.4　安全性の結果

本試験では、治験薬を投与した全被験者8例を安全性解析対象集団に含めた。健康被験者に^{14}C-ポサコナゾール経口懸濁液409 mg（79.3 μCi）を高脂肪食摂取後に単回投与した際、安全で、忍容性は良好であった。有害事象及び死亡はなかった。臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.19.5　結論

1) 健康被験者に^{14}C-ポサコナゾール経口懸濁液409 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。

2) ^{14}C-ポサコナゾールは緩やかに吸収及び消失し、薬物由来の放射能は主に糞中に排泄（投与した放射能の約71%）され、尿中にはわずかに排泄された（投与した放射能の約10%）。
3) 血漿中の薬物由来の放射能のほとんど（76.5%）はポサコナゾールの未変化体であった。主要な血漿中代謝物は、ポサコナゾールのグルクロン酸抱合体のみであった。
4) ポサコナゾールは未変化体として糞中に排泄された。尿中代謝物は主にグルクロン酸抱合体で、尿中に排泄されたポサコナゾールの未変化体はわずかであった。

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2.7.6.2.20　　非日本人健康被験者を対象としたマスバランス試験（P02418試験）［参考資料］

治験総括報告書[資料5.3.3.1.13: P02418]の概要を以下に示す。

2.7.6.2.20.1　　試験方法

治験実施計画書標題／番号

非日本人健康被験者を対象とした^{14}C-ポサコナゾール経口懸濁液を単回投与した際の吸収、代謝及び排泄を評価する試験／P02418試験

治験責任医師／実施医療機関

[redacted]（米国）

治験期間

20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日

開発の相

第Ⅰ相

目的

健康被験者に^{14}C-ポサコナゾール経口懸濁液399 mg を高脂肪食摂取後に単回経口投与した際の吸収、代謝及び排泄の特徴を明らかにする。

試験デザイン

本試験は、健康被験者を対象とした、ポサコナゾールの吸収、分布、代謝及び排泄を評価する、非盲検、単回投与試験であった。10時間絶食後、高脂肪食を20分以内に摂取し、その後5分以内に、10 mL の^{14}C-ポサコナゾール経口懸濁液399 mg（81.7 μCi）を単回投与した。

投与期間

単回

用法・用量

^{14}C-ポサコナゾール経口懸濁液399 mg（81.7 μCi）を高脂肪食摂取後に単回経口投与した。治験薬の内容を、[表 2.7.6.2.20-1]に示す。

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表 2.7.6.2.20-1　治験薬の内容（P02418 試験）

薬剤	力価	剤形
^{14}C-ポサコナゾール経口懸濁液	ポサコナゾール399 mg (81.7 μCi)／被験者	液剤

診断／選択基準

スクリーニング時に BMI が19 kg/m^{2}以上27 kg/m^{2}以下で、18歳以上45歳以下の健康な男性

評価基準

【薬物動態】

血漿中ポサコナゾール並びに血中及び血漿中総放射能濃度測定用検体を投与前及び投与後336時間（15日目）までの規定した時点又は投与放射能の90%が排泄された時点まで採取した。さらに、代謝物プロファイル検討用血液検体（20 mL）を投与後24時間までの規定した時点で採取した。総放射能及びポサコナゾール測定用尿検体を投与前及び投与後336時間（15日目）までの規定した間隔で採取した。また、総放射能測定及び代謝物プロファイル検討用糞検体を、投与前及び投与後336時間（15日目）までの規定した間隔で採取した。薬物動態パラメータ（C_{max}、T_{max}、AUC、$t_{1/2}$、1日排泄量、総排泄量、CL/F、CL_r及びV_d/F）を算出した。

【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

要約統計量を示した。

2.7.6.2.20.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.20-2]及び[表 2.7.6.2.20-3]に示す。

表 2.7.6.2.20-2　被験者の内訳（P02418 試験）

	n	(%)
総被験者数	8	
内訳		
完了	8	(100)
中止	0	(0.0)

Data source: [資料5.3.3.1.13: P02418] 16.2.1 page 264

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表 2.7.6.2.20-3　　被験者の背景（P02418 試験）

	合計	
	n	(%)
総被験者数	8	
性別		
男性	8	(100)
年齢		
算術平均	28.4	
標準偏差	8.1	
中央値	25.0	
範囲	22 - 43	
身長（cm）		
算術平均	175.44	
標準偏差	7.41	
中央値	174.25	
範囲	167.0 - 187.5	
体重（kg）		
算術平均	72.65	
標準偏差	8.09	
中央値	70.20	
範囲	61.8 - 87.8	
BMI		
算術平均	23.556	
標準偏差	1.412	
中央値	23.973	
範囲	21.57 - 25.02	
人種		
白人	8	(100)

Data source: [資料5.3.3.1.13: P02418] 16 2 1 page 262-263

2.7.6.2.20.3　　薬物動態の結果

本試験では、^{14}C-ポサコナゾール経口懸濁液を投与した被験者8例から得られた薬物濃度データを用いて薬物動態解析を実施した。健康被験者に^{14}C-ポサコナゾール経口懸濁液399 mg（81.7 μCi）を高脂肪食摂取後に単回経口投与した際のポサコナゾール及び血漿中総放射能の薬物動態パラメータの要約を[表 2.7.6.2.20-4]に示す。ポサコナゾールは経口投与後、緩やかに吸収された。C_{max}（算術平均：654 ng/mL）に、投与後約9時間で到達した（T_{max} の中央値：10時間、範囲：6～12時間）。その後、ポサコナゾール濃度は緩やかに低下し、$t_{1/2}$の算術平均は約20時間、CL は16.3 L/hr（272 mL/min）であった。ポサコナゾールの血漿中曝露量は総放射能の血漿中曝露量の約半分であったことから、血漿中には代謝物が存在することが示唆された。血中総放射能濃度はほとんどが LLOQ を下回ったため、血中の薬物動態パラメータを算出しなかった。投与放射能に対する投与後336時間までの平均排泄率は、尿中で14.0%、糞中で76.9%、総排泄率は91.1%であった。尿中に排泄された未変化体はわずかな量であった。CL_r は CL/F と比べ、極めて小さかった。

血漿中総放射能の主な成分はポサコナゾールであった。また、主な血漿中代謝物はポサコナゾールのモノグルクロン酸抱合体で、血漿中総放射能の18%～28%であった。投与後24時間の血漿中ではジグルクロン酸抱合体及び酸化代謝物がみられ、それぞれ血漿中総放射能の9%及び8%であった。尿中には、2種類のモノグルクロン酸抱合体及び1種類のジグルクロン酸抱合体が検出された

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が、合わせても投与量の4%未満であった。その他の尿中放射能は、多数の酸化代謝物か未知のピークであった。糞中には主に未変化体として排泄され（糞中総放射能の94%、投与量の66%）、わずかに酸化代謝物もみられた。

表 2.7.6.2.20-4　健康被験者に ^{14}C-ポサコナゾール経口懸濁液 399 mg（81.7 μCi）を単回経口投与した際のポサコナゾール及び血漿中総放射能の薬物動態パラメータの要約（P02418 試験）

薬物動態パラメータ	ポサコナゾール	(%CV)	血漿中総放射能	(%CV)
C_{max} (ng/mL 又は ng Eq/g)	654	(19)	1260	(18)
T_{max}† (hr)	9.25 [10 (6-12)]	(26)	11.0 [10 (8-16)]	(22)
$t_{1/2}$ (hr)	20	(19)	-	-
$AUC_{0\text{-}24\ hr}$ (ng·hr/mL 又は ng Eq·hr/g)	10300	(22)	21300	(21)
$AUC_{0\text{-}last}$ (ng·hr/mL 又は ng Eq·hr/g)	26000	(26)	48100	(31)
$AUC_{0\text{-}\infty}$ (ng·hr/mL 又は ng Eq·hr/g)	26100	(26)	-	-
未変化体の $AUC_{0\text{-}24\ hr}$ ／総放射能の $AUC_{0\text{-}24\ hr}$ (%)	48	(14)	-	-
T_{last} (hr)	183	(14)	66	(26)
CL/F (L/hr)	16.3	(30)	-	-
V_d/F (L)	465	(31)	-	-
CL_r (L/hr)	0.0114‡	(76)	-	-

N=8、算術平均（%CV）
CV：変動係数
† 算術平均［中央値（範囲）］
‡ N=3

Data source: [資料5.3.3.1.13: P02418] 16 2 5 1 Table 1, Table 2

2.7.6.2.20.4　安全性の結果

本試験では、治験薬を投与した全被験者8例を安全性解析対象集団に含めた。健康被験者に ^{14}C-ポサコナゾール経口懸濁液399 mg（81.7 μCi）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。8例中3例で有害事象が報告され、いずれの有害事象も1件ずつであった。中等度の不安1件を除き、いずれも軽度で、有害事象を治療するための併用薬は必要なかった。また、副作用と判定された有害事象はなかった。臨床検査、バイタルサイン又は心電図に臨床的に意味のある一貫した変化はなかった。

2.7.6.2.20.5　結論

1) 健康被験者に^{14}C-ポサコナゾール経口懸濁液399 mg（81.7 μCi）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。
2) ポサコナゾールは緩やかに吸収及び消失した。薬物由来の放射能は、主に糞中に排泄され（77%）、尿中にはわずかに排泄された（14%）。

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3) 血漿中総放射能の主な化合物はポサコナゾールで、主な代謝物はポサコナゾールのモノグルクロン酸抱合体であった。
4) 尿中には、2種類のモノグルクロン酸抱合体及び1種類のジグルクロン酸抱合体並びに多数の酸化代謝物が検出された。
5) 糞中には主に未変化体として排泄され、わずかに酸化代謝物もみられた。

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2.7.6.2.21　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/[redacted]-421試験）［参考資料］

治験総括報告書[資料5.3.3.2.1: C[redacted]_421]の概要を以下に示す。

2.7.6.2.21.1　試験方法

治験実施計画書標題／番号

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/[redacted]-421試験

治験責任医師／実施医療機関

施設1：[redacted]（米国）
施設3：[redacted]（米国）

公表文献

1) Ezzet F, Wexler D, Courtney R, et al. The Pharmacokinetics of posaconazole in neutropenic oncology patients. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Dec 16-19; Chicago, IL; Abstract 26.
2) Ezzet F, Courtney R, Wexler D, et al. The impact of time-dependent clinical symptoms on pharmacokinetics: an application of posaconazole in neutropenic oncology patients. 4th International Symposium on Measurement and Kinetics of in Vivo Drug Effects; 2002 Apr 24-27; Leiden, Holland.

治験期間

19[redacted]年[redacted]月[redacted]日～19[redacted]年[redacted]月[redacted]日

開発の相

後期第Ⅰ相

目的

1) 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を対象として、ポサコナゾール経口懸濁液を反復経口投与した際の薬物動態プロファイル、用量反応性及び安全性を評価する。
2) 高用量化学療法又は骨髄移植を受け好中球が減少しており、かつフルコナゾール抵抗性カンジダ属のコロニー形成が認められた患者を対象として、ポサコナゾール経口懸濁液を反復経口投与した際の有効性を予備的に評価する。

試験デザイン

本試験は、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を対象とした、ポサコナゾール経口懸濁液の薬物動態を評価する、非盲検、多施設共同、用量漸増反復投与試験であった。朝食摂取後にポサコナゾール経口懸濁液200 mg を1日1回又は400 mg を1日1回7～14日間、若しくは食後に200 mg を1日4回7～14日間反復経口投与した。

なお、本試験ではポサコナゾール経口懸濁液を反復経口投与した際の有効性を予備的に評価することを計画したが、実施しなかった。

投与期間

反復（7～14日間）

用法・用量

グループⅠ及びⅡではいずれも、ポサコナゾール経口懸濁液を1日1回7～14日間朝食摂取後に反復経口投与した。グループⅢでは、ポサコナゾールを1日4回7～14日間食後に反復経口投与した。

グループⅠ：ポサコナゾール経口懸濁液200 mg を1日1回7～14日間朝食摂取後に反復経口投与

グループⅡ：ポサコナゾール経口懸濁液400 mg を1日1回7～14日間朝食摂取後に反復経口投与

グループⅢ：ポサコナゾール経口懸濁液200 mg を1日4回7～14日間食後に反復経口投与

治験薬の内容を、[表 2.7.6.2.21-1]に示す。

表 2.7.6.2.21-1　治験薬の内容（C/[redacted]-421 試験）

薬剤	力価	剤形
ポサコナゾール経口懸濁液	ポサコナゾール40 mg/mL	液剤

診断／選択基準

スクリーニング時に18歳以上65歳以下で、フルコナゾール抵抗性カンジダ属のコロニー形成が認められ、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男性及び女性

評価基準

【薬物動態】

血漿中薬物濃度測定用検体を、1日目及び最終投与日（投与7～14日目）の各投与前及び各投与後24時間までの規定した時点で頻回採取した。2日目から最終投与日の前日の投与までは投与前のみ採取した（グループⅢは各投与日の1回目の投与前のみ）。血漿中ポサコナゾールの薬物動態パラメータ（C_{max}、$AUC_{0\text{-}24\ hr}$、$AUC_{0\text{-}12\ hr}$、T_{max}及び累積係数等）を算出した。

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【安全性】

バイタルサイン、身体所見、心電図及び臨床検査（血液学的検査、血液生化学検査及び尿検査）により、安全性及び忍容性を評価した。有害事象は治験期間を通して収集した。

統計計画及び解析

【薬物動態】

対数変換して計算した $AUC_{0\text{-}24\ hr}$ の幾何平均比（200 mg 1日4回／400 mg 1日1回、200 mg 1日4回／200 mg 1日1回）の点推定値及び信頼区間を算出した。

【安全性】

有害事象について一覧にし、表に示した。臨床的に適切な場合、臨床検査値、心電図及びバイタルサインの要約統計量も算出した。

2.7.6.2.21.2　被験者の内訳及び背景

本試験の被験者の内訳及び背景を、[表 2.7.6.2.21-2]及び[表 2.7.6.2.21-3]に示す。

表 2.7.6.2.21-2　被験者の内訳（C/[redacted]-421 試験）

	合計	
	n	(%)
総被験者数	31	
内訳		
完了	27	(87.1)
中止	4	(12.9)
管理手続上の理由	1	(3.2)
同意の撤回	1	(3.2)
試験とは関連のない理由	1†	(3.2)
効果不十分	1‡	(3.2)

† 被験者1例が試験とは関連のない理由により試験を中止し、最終投与日の18日後に死亡した。
‡ 被験者1例が効果不十分により試験を中止し、最終投与の30日目以降に死亡した。

Data source: [資料5.3.3.2.1: C[redacted]_421] 10.1, 12.3.1, Appendix 9 Table A-3.1

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表 2.7.6.2.21-3　　被験者の背景（C/[redacted]-421 試験）

	合計	
	n	(%)
総被験者数	31	
年齢（歳）		
被験者数	31	
算術平均	51.90	
標準偏差	9.86	
中央値	51	
範囲	26 - 66	
性別		
女性	15	(48.4)
男性	16	(51.6)
人種		
白人	28	(90.3)
黒人	3	(9.7)
体重（lb †）		
被験者数	30§	
算術平均	167.60	
標準偏差	36.00	
中央値	170	
範囲	105 - 241	
身長（inch ‡）		
被験者数	29‖	
算術平均	66.03	
標準偏差	3.56	
中央値	65	
範囲	61 - 74	
BMI（kg/m^2）		
被験者数	28¶	
算術平均	26.85	
標準偏差	4.51	
中央値	25	
範囲	18 - 36	

† 1 lb = 0.4536 kg
‡ 1 inch = 2 54 cm
§ 被験者1例のデータを入手できなかった。
‖ 被験者2例のデータを入手できなかった。
¶ 被験者3例について算出できなかった。

Data source: [資料5.3.3.2.1: C[redacted]_421] Appendix 9 Table A-2.1

2.7.6.2.21.3　　薬物動態の結果

本試験では、ポサコナゾール経口懸濁液を投与した31例から得られた血漿中薬物濃度データを薬物動態解析に含めた。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1日1回朝食摂取後に、若しくは200 mg を1日4回食後に7～14日間反復経口投与した際の頻回採血を行った1日目及び最終検体採取日（最終検体採取日：7～14日目）の血漿中薬物動態パラメータの要約を[表 2.7.6.2.21-4]に示す。

投与1日目の1日1回投与時の C_{max} 及び AUC は200 mg と400 mg の用量間で用量比よりも小さい増加を示し、400 mg の1日1回投与時と200 mg の1日4回投与時の $AUC_{0\text{-}24\ hr}$ の算術平均は類似して

いた。T_{max} の算術平均は1日1回投与時ではいずれの用量でも約8時間であったが、1日4回投与時では初回投与後約20時間であった。

最終検体採取日の1日1回投与時の C_{max} 及び AUC は200 mg と400 mg の用量間で用量比よりも小さい増加を示した。検討した用法用量において、$AUC_{0\text{-}24\ hr}$ は200 mg の1日4回投与時で最も高かった［幾何平均比（90%信頼区間）：200 mg 1日4回／400 mg 1日1回1.73（1.10, 2.70）、200 mg 1日4回／200 mg 1日1回2.48（1.51, 4.07）］。また、ポサコナゾールの C_{trough} の推移から、検討した用法用量では、いずれも最終投与日までには定常状態に到達することが示唆された。定常状態での累積係数は2.4～3.9の範囲で、いずれの用法用量でもポサコナゾールは血漿中に蓄積することが示唆された。

表 2.7.6.2.21-4　高用量化学療法又は骨髄移植を受けた好中球減少患者にポサコナゾールの経口懸濁液 200 mg 又は 400 mg を 1 日 1 回朝食摂取後に、若しくは 200 mg を 1 日 4 回食後に反復経口投与した際の 1 日目及び最終検体採取日（投与 7～14 日目）の血漿中薬物動態パラメータの要約（C/[redacted]-421 試験）

投与群	検体採取日	N	C_{max} (ng/mL)	T_{max} (hr)	T_{last} (hr)	$AUC_{0\text{-}12\ hr}$ (ng·hr/mL)	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	累積係数
グループⅠ	1日目	7†	118 (62)	7.6 (39)	24 (3)	949 (53)	1960 (57)	-
	最終検体採取日	7†	263 (77)	3.9 (43)	22 (20)	2381 (65)	4402 (66)	2.7 (75)‡
グループⅡ	1日目	15	186 (68)	8.2 (62)	24 (3)	1438 (67)	2959 (68)	-
	最終検体採取日	14§	352 (47)	6.5 (56)	24 (3)	3344(49)	6192 (47)	2.4 (58)
グループⅢ	1日目	8	209 (28)	19.8 (37)	24 (2)	1049 (45)	3015 (38)	-
	最終検体採取日	8‖	548 (30)	9.4 (103)	20 (35)	4846 (29)¶	9705 (28)¶	3.9 (53)¶

算術平均（%CV）
グループⅠ：ポサコナゾール経口懸濁液200 mg を1日1回7～14日間朝食摂取後に反復経口投与
グループⅡ：ポサコナゾール経口懸濁液400 mg を1日1回7～14日間朝食摂取後に反復経口投与
グループⅢ：ポサコナゾール経口懸濁液200 mg を1日4回7～14日間食後に反復経口投与
CV：変動係数
† 被験者1例の1日目の検体を採取しなかった。別の1例の最終投与日の検体を採取しなかった。
‡ n=6
§ 被験者1例の最終検体採取日の検体を採取しなかった。
‖ 被験者1例は14日目に血漿中薬物濃度測定用検体を採取した後も投与を継続した。
¶ 被験者1例の T_{last} は6時間であったため、AUC 及び累積係数は n=7。

Data source: [資料5.3.3.2.1: C[redacted]_421] Table 11, Table12

2.7.6.2.21.4　安全性の結果

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。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。発現率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。

2.7.6.2.21.5　　結論

1) 高用量化学療法又は骨髄移植を受けた好中球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1日4回食後に7～14日間反復経口投与した際の安全性が確認された。
2) 高用量化学療法又は骨髄移植を受けた好中球減少患者にポサコナゾール200 mg 又は400 mg を1日1回反復経口投与した際、定常状態の AUC は用量に依存した増加を示した。
3) ポサコナゾール200 mg を1日4回食後に反復経口投与した際の定常状態の $AUC_{0\text{-}24\ hr}$ の幾何平均は、400 mg を1日1回又は200 mg を1日1回投与時より高くそれぞれの1.73倍及び2.48倍に相当した。

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2.7.6.2.22　侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症が確認又は予測される患者並びに同種造血幹細胞移植後の移植片対宿主病の治療又は予防患者）を対象としたポサコナゾール新錠剤予防投与の海外後期第Ⅰ相／第Ⅲ相、2パート、非盲検、非対照、多施設共同試験（P05615試験）［評価資料］

治験総括報告書[資料5.3.3.2.2: P05615]の概要を以下に示す。

2.7.6.2.22.1　試験方法の概要

治験実施計画書標題

侵襲性真菌症のハイリスク患者を対象としたポサコナゾール新錠剤の薬物動態及び安全性を評価する試験

実施医療機関

海外多施設共同（米国を含む計15ヵ国の42施設）

治験期間

2009年7月20日～2012年2月24日

開発の相

後期第Ⅰ相／第Ⅲ相

投与期間

8日間以上最長28日間投与した。ただし、投与期間中に急性骨髄性白血病（AML）又は骨髄異形成症候群（MDS）の治療に付随して発現した好中球減少症が回復し、抗真菌薬による予防投与を継続不要と判断した場合は、その時点までとした。

目的

【主要目的】

侵襲性真菌症のハイリスク患者におけるポサコナゾール新錠剤の薬物動態プロファイルを評価する。

【副次目的】

1) 侵襲性真菌症のハイリスク患者におけるポサコナゾール新錠剤の安全性及び消化器に対する忍容性を評価する。
2) 侵襲性真菌症のハイリスク患者にポサコナゾール新錠剤を投与した際の定常状態到達時のポサコナゾールの曝露量を評価する。

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治験デザイン

P05615試験は、侵襲性真菌症のハイリスク患者［血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症が確認又は予測される患者並びに同種造血幹細胞移植（HSCT）後の移植片対宿主病（GVHD）の治療又は予防患者］を対象に、ポサコナゾール新錠剤を予防投与した際の薬物動態及び安全性を評価する後期第Ⅰ相／第Ⅲ相、2パート、非盲検、非対照、多施設共同試験である。

P05615試験は、後期第Ⅰ相となるパート1A 及びパート1B 並びに第Ⅲ相となるパート2の3つで構成された。パート1A 及び1B では、AML 又は MDS に対して化学療法を受けている好中球減少症患者を組み入れ、2種類の用量におけるポサコナゾール新錠剤の薬物動態及び安全性を評価した。パート2では、パート1A 及び1B で対象とした好中球減少症患者に加え、同種 HSCT 患者を組み入れ、ポサコナゾール新錠剤の薬物動態及び安全性を評価した。パート2の用量は、パート1A 又は1B で達成した曝露量及び安全性に基づき決定した[図 2.7.6.2.22-1]。

パート1A から開始し、ポサコナゾール新錠剤200 mg を治験薬投与1日目は1日2回、2日目以降は1日1回経口投与した。パート1A における用量の安全性は治験依頼者が評価した。パート1B では、ポサコナゾール新錠剤300 mg を治験薬投与1日目は1日2回、2日目以降は1日1回経口投与した。パート1A 及び1B における安全性及び用量の妥当性を治験依頼者が評価し、その後データモニタリング委員会による安全性の評価を経た結果、パート2では、治験実施計画書で定めた目標曝露量を達成したパート1B と同様の用法・用量で投与した。

P05615試験の各評価期間を以下に示す。また、治験の構成を[図 2.7.6.2.22-1]に、評価期間の略図を[図 2.7.6.2.22-2]に示す。

- 治療期
  - (1) 治験薬投与開始から最終投与6日後まで（Treatment Phase）
  - (2) 治験薬投与開始から最終投与7日後まで（Exposure Phase）（治療失敗の評価）
- 追跡調査期（Follow-up Phase）
  - (1) 治験薬最終投与7日後（有効性及び安全性の評価）
  - (2) 治験薬投与65日後（生存の評価）

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図 2.7.6.2.22-1　　治験の構成（P05615 試験）

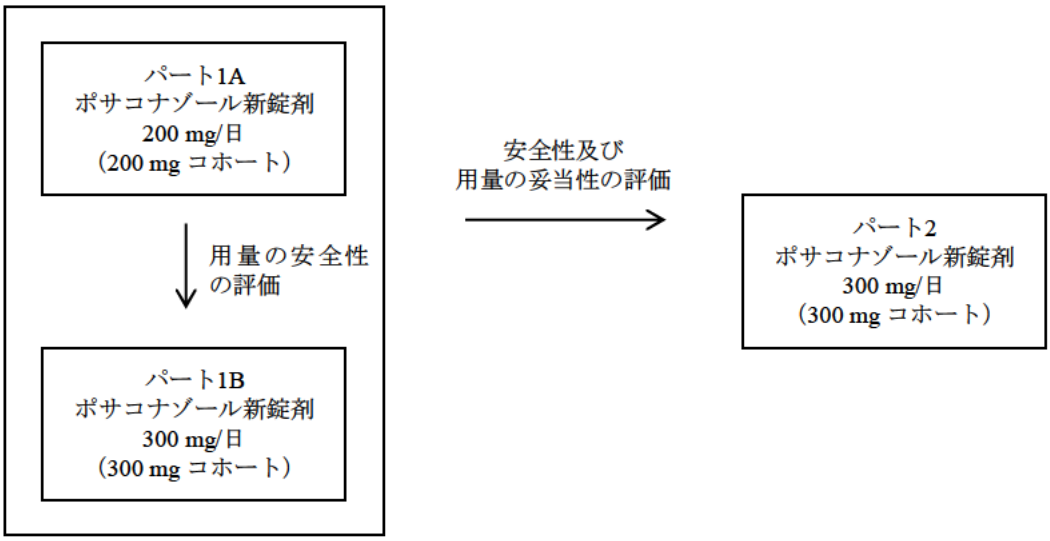
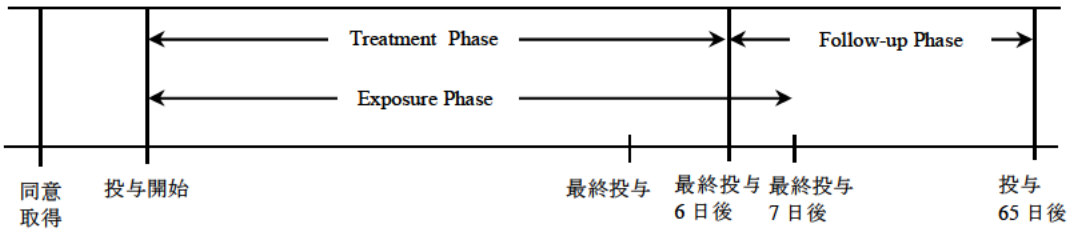


図 2.7.6.2.22-2　　評価期間の略図（P05615 試験）



用法・用量

- パート1A（ポサコナゾール新錠剤200 mg コホート）
  ポサコナゾール新錠剤 C 200 mg を治験薬投与1日目は1日2回、2日目以降は1日1回経口投与した。
- パート1B 及びパート2（ポサコナゾール新錠剤300 mg コホート）
  ポサコナゾール新錠剤［パート1B では新錠剤 C、パート2では新錠剤 D（緑色）］300 mg を治験薬投与1日目は1日2回、2日目以降は1日1回経口投与した。

いずれの場合も、食事条件を規定せず投与した。

主な診断／選択基準

- 18歳以上で体重が34 kg を超える患者（性別及び人種／民族不問）
- 以下のいずれかの理由により、3～5日以内に7日間以上持続する可能性がある好中球減少症［好中球絶対数（ANC）<500/mm^3（0.5×10^9/L）］の発症が見込まれる患者又はベースライ

ン時に好中球減少症と診断され、7日間以上持続する可能性がある患者

a) 初発 AML に対する強力な標準的寛解導入化学療法、アントラサイクリン系又はその他の認められたレジメン（ほかの治験薬を除く）の投与
b) 初回再発の AML に対する再寛解導入化学療法の投与
c) AML に移行した MDS 又は急性転化した慢性骨髄性白血病以外の二次性 AML に対する骨髄抑制導入療法の投与

- パート2では、上記の診断基準に加え、HSCT 後に生着し、GVHD の予防又は治療で免疫抑制療法［ステロイド、タクロリムス、シクロスポリン、ミコフェノール酸モフェチル及び抗胸腺細胞グロブリン（ATG）］を受けている患者も組入れ可とした。

評価基準

パート1A（対象：AML/MDS 患者）をポサコナゾール新錠剤200 mg コホート、パート1B 及びパート2の併合（対象：AML/MDS 患者及び HSCT 患者）をポサコナゾール新錠剤300 mg コホートとした。

【有効性】

有効性の主要評価項目及び重要な副次評価項目は設定しなかった。

有効性のその他の副次評価項目として以下を評価した。

- 治験薬投与開始から最終投与7日後まで（Exposure Phase）の治療失敗率
  以下の場合を治療失敗とした。
  (1) ポサコナゾール新錠剤200 mg コホート：侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例†）の発症
  (2) ポサコナゾール新錠剤300 mg コホート：侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例／疑い例†）の発症

† European Organization for Research and Treatment of Cancer/Mycosis Study Group（EORTC-MSG）の診断基準（2008年版）に基づき、治験担当医師は侵襲性真菌症の確定診断例／臨床診断例／疑い例／侵襲性真菌症なしに分類し、治療失敗例を判定した。
なお、治験実施計画書の初版では侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例）の発症を評価することとしていたが、パート1A（200 mg コホート）のデータ収集終了後の治験実施計画書の改訂において、侵襲性真菌症の臨床症状の評価に疑い例を追加した。このため、パート1B 及びパート2（300 mg コホート）では、侵襲性真菌症の疑い例が、治療失敗の判定及び治験の中止基準に含まれた。

- 治験薬投与65日後の生存率

【薬物動態】

頻回採血のデータを基にした薬物動態（Serial PK）評価及び C_{min} の推移を基にした薬物動態（C_{min} PK）評価を以下の通り実施した。なお、治験薬投与8日目には、ポサコナゾールの血漿中濃度は定常状態に到達していると想定して評価した。

1)　Serial PK 評価

治験薬投与1日目及び8日目の、以下のポサコナゾールの薬物動態パラメータを評価した。

- C_{min}
- C_{max}
- T_{max}
- $AUC_{0-\tau}$
- C_{avg}
- $C_{12\ hr}$
- CL/F
- C_{max} に基づく累計係数（R）

2)　C_{min} PK 評価

治験薬投与8～28日目のポサコナゾールの C_{min} を評価した。

【安全性】

有害事象、臨床検査値、バイタルサイン及び心電図を評価した。また、Hy's law［ALT 又は AST が基準範囲上限（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］に該当する被験者を特に注目してモニタリングした。有害事象は、同意取得から治験薬最終投与7日後までの各評価時点で得られた事象を収集し、治験薬最終投与後30日間追跡した。有害事象及び臨床検査値の程度（Grade）は CTCAE を用いて評価し、治験担当医師が程度［4段階 : 軽度（Grade 1）、中等度（Grade 2）、重度（Grade 3）、生命を脅かす（Grade 4）］を判定した。有害事象名は、治験担当医師が症例報告書に記載した事象名を MedDRA v15.0の器官別大分類及び基本語で読み替えた。

統計計画及び解析

以下の項目は、コホート別（ポサコナゾール新錠剤200 mg コホート又は300 mg コホート）及び基礎疾患別（AML/MDS 患者又は AML/MDS 患者及び HSCT 患者）に解析した。

【有効性】

有効性解析対象集団は、治験薬を1回以上投与されたすべての被験者（All Treated Subjects）とした。

治験薬投与開始から治験薬最終投与7日後まで（Exposure Phase）の治療失敗率及び治験薬投与65日後の生存率を、記述統計量を用いて被験者全体及び基礎疾患別に要約した。

【薬物動態】

薬物動態解析対象集団は、Serial PK 評価対象集団及び C_{min} PK 評価対象集団の2つで構成され、[2.7.6.3.3.2.2 項]で記載する1例を除き、薬物動態のデータが得られたすべての被験者を解析対象集団とした。

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パート1では、ポサコナゾールの目標曝露量を以下に設定した。

1) 90%以上の被験者で定常状態の C_{avg} が500 ng/mL 以上又は定常状態の投与後24時間までの血漿中濃度－時間曲線下面積（$AUC_{0\text{-}24\ hr}$）が12,000 ng·hr/mL 以上。
2) 定常状態の C_{avg} が3,750 ng/mL を超える被験者又は定常状態の $AUC_{0\text{-}24\ hr}$ が90,000 ng·hr/mL を超える被験者がいない。
3) 定常状態の C_{avg} の算術平均が2,500 ng/mL 以下又は $AUC_{0\text{-}24\ hr}$ の算術平均が59,000 ng·hr/mL 以下。

定常状態の C_{avg} 及び C_{min} を被験者全体及び基礎疾患別に要約した。また、これらの薬物動態パラメータの分布を評価した。

【安全性】

安全性解析対象集団は、治験薬を1回以上投与されたすべての被験者（All Treated Subjects）とした。

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。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は、この期間外であっても、同意取得後に有害事象として報告された事象はすべて集計した。また、臨床検査値、バイタルサイン及び心電図を集計した。

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2.7.6.2.22.2　　被験者の内訳及び背景

2.7.6.2.22.2.1　　被験者の内訳

2.7.6.2.22.2.1.1　　ポサコナゾール新錠剤200 mg 及び300 mg コホート併合

AML/MDS 患者を対象としたポサコナゾール新錠剤200 mg コホート及び AML/MDS 患者並びに HSCT 患者を対象としたポサコナゾール新錠剤300 mg コホート併合の治験薬投与開始から最終投与6日後まで（Treatment Phase）の被験者の内訳を[表 2.7.6.2.22-1]に、治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）の被験者の内訳を[表 2.7.6.2.22-2]に示す。

ポサコナゾール新錠剤200 mg 及び300 mg コホート併合では、治験薬を1回以上投与されたすべての被験者は合計230例で、そのうち治験薬投与開始から最終投与6日後まで（Treatment Phase）の完了例は78%（179/230例）、早期中止例は22%（51/230例）であった。中止理由は、有害事象15%（34/230例）、治療失敗3%（7/230例）、同意撤回1%（2/230例）及びプロトコール不遵守3%（8/230例）であった。

治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）への移行例は229例で、Follow-up Phase 完了例は90%（207/229例）であった。

表 2.7.6.2.22-1　　被験者の内訳：
治験薬投与開始から最終投与 6 日後まで（Treatment Phase）
（ポサコナゾール新錠剤 200 mg 及び 300 mg コホート併合）
（All Treated Subjects）（P05615 試験）

Subject Disposition- Treatment Phase	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort and 300 mg Cohort Combined n=230
Treated	230 (100)
Discontinued Treatment Phase	51 (22)
Adverse Event	34 (15)
Treatment Failure†	7 (3)
Subject Withdrew Consent	2 (1)
Non-compliance with the Protocol	8 (3)
Completed Treatment Phase	179 (78)

POS：ポサコナゾール
† 治療失敗=効果不十分により早期中止した被験者
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
・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

表 2.7.6.2.22-2　　被験者の内訳：
治験薬最終投与 7 日後から治験薬投与 65 日後まで（Follow-up Phase）
（ポサコナゾール新錠剤 200 mg 及び 300 mg コホート併合）
（All Treated Subjects）（P05615 試験）

Subject Disposition- Follow-up Phase	Number of Treated Subjects (%) All Treated Subjects That Entered the Follow-up Phase POS 200 mg Cohort and 300 mg Cohort Combined n=229
Entered Follow-up	229 (100)
Discontinued Follow-up	22 (10)
Adverse Event	20 (9)
Subject Withdrew Consent	2 (1)
Completed Follow-Up	207 (90)
Never Entered Follow-Up	1

POS：ポサコナゾール
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
・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

2.7.6.2.22.2.1.2　　ポサコナゾール新錠剤200 mg コホート

AML/MDS 患者を対象としたポサコナゾール新錠剤200 mg コホートの治験薬投与開始から最終投与6日後まで（Treatment Phase）の被験者の内訳を[表 2.7.6.2.22-3]に、治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）の被験者の内訳を[表 2.7.6.2.22-4]に示す。

ポサコナゾール新錠剤200 mg コホートでは、治験薬を1回以上投与された被験者は20例で、そのうち治験薬投与開始から最終投与6日後まで（Treatment Phase）の完了例は80%（16/20例）、早期中止例は20%（4/20例）であった。中止理由は、有害事象10%（2/20例）、治療失敗5%（1/20例）及びプロトコール不遵守5%（1/20例）であった。

治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）への移行例は20例で、Follow-up Phase 完了例は90%（18/20例）であった。

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表 2.7.6.2.22-3　　被験者の内訳：
治験薬投与開始から最終投与 6 日後まで（Treatment Phase）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

Subject Disposition- Treatment Phase	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20
Treated	20 (100)
Discontinued Treatment Phase	4 (20)
Adverse Event	2 (10)
Treatment Failure†	1 (5)
Non-compliance with the Protocol	1 (5)
Completed Treatment Phase	16 (80)

POS：ポサコナゾール
† 治療失敗=効果不十分により早期中止した被験者
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

表 2.7.6.2.22-4　　被験者の内訳：
治験薬最終投与 7 日後から治験薬投与 65 日後まで（Follow-up Phase）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

Subject Disposition- Follow-up Phase	Number of Treated Subjects (%) All Treated Subjects That Entered Follow-up Phase POS 200 mg Cohort n=20
Entered Follow-up	20 (100)
Discontinued Follow-up	2 (10)
Adverse Event	2 (10)
Completed Follow-up	18 (90)

POS：ポサコナゾール
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

2.7.6.2.22.2.1.3　　ポサコナゾール新錠剤300 mg コホート

AML/MDS 患者及び HSCT 患者を対象としたポサコナゾール新錠剤300 mg コホートの治験薬投与開始から最終投与6日後まで（Treatment Phase）の被験者の内訳を[表 2.7.6.2.22-5]に、治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）の被験者の内訳を[表 2.7.6.2.22-6]に示す。

ポサコナゾール新錠剤300 mg コホートでは、治験薬を1回以上投与された被験者は210例で、そのうち治験薬投与開始から最終投与6日後まで（Treatment Phase）の完了例は78%（163/210例）、早期中止例は22%（47/210例）であった。中止理由は、有害事象15%（32/210例）、治療失敗3%（6/210例）、同意撤回1%（2/210例）及びプロトコール不遵守3%（7/210例）であった。

治験薬最終投与7日後から治験薬投与65日後まで（Follow-up Phase）への移行例は209例で、Follow-up Phase 完了例は90%（189/209例）であった。

表 2.7.6.2.22-5　　被験者の内訳：
治験薬投与開始から最終投与 6 日後まで（Treatment Phase）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

Subject Disposition- Treatment Phase	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
Treated	210 (100)
Discontinued Treatment Phase	47 (22)
Adverse Event	32 (15)
Treatment Failure†	6 (3)
Subject Withdrew Consent	2 (1)
Non-compliance with the Protocol	7 (3)
Completed Treatment Phase	163 (78)

POS：ポサコナゾール
† 治療失敗=効果不十分により早期中止した被験者
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

表 2.7.6.2.22-6　　被験者の内訳：
治験薬最終投与 7 日後から治験薬投与 65 日後まで（Follow-up Phase）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

Subject Disposition- Follow-up Phase	Number of Treated Subjects (%) All Treated Subjects That Entered the Follow-up Phase POS 300 mg Cohort n=209
Entered Follow-up	209 (100)
Discontinued Follow-up	20 (10)
Adverse Event	18 (9)
Subject Withdrew Consent	2 (1)
Completed Follow-up	189 (90)
Never Entered Follow-Up	1

POS：ポサコナゾール
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

2.7.6.2.22.2.2　　解析対象集団

治験薬を1回以上投与されたすべての被験者（All Treated Subjects）は、ポサコナゾール新錠剤200 mg コホートで20例、ポサコナゾール新錠剤300 mg コホートで210例であった。

ポサコナゾール新錠剤200 mg コホート20例のうち、C_{min} PK 評価対象集団は19例、Serial PK 評価対象集団は18例であった。

ポサコナゾール新錠剤300 mg コホート210例のうち、C_{min} PK 評価対象集団は187例（AML/MDS 患者：108例、HSCT 患者：79例）、Serial PK 評価対象集団は50例（AML/MDS 患者：34例、HSCT 患者：16例）であった。なお、C_{min} PK 評価対象集団の HSCT 患者1例は誤って解析から除外され

たため、C_{min} PK 評価対象集団での薬物動態の結果は、当該被験者を除いた186例で解析した。また、データベース固定後に AML/MDS 患者1例が HSCT 患者に該当することが判明した。当該被験者は、C_{min} PK 評価対象集団及び Serial PK 評価対象集団の HSCT 患者に含まれた。

2.7.6.2.22.2.3　人口統計学的特性及びベースライン特性

2.7.6.2.22.2.3.1　ポサコナゾール新錠剤200 mg コホート

AML/MDS 患者を対象としたポサコナゾール新錠剤200 mg コホートの被験者の背景因子を[表 2.7.6.2.22-7]に示す。

ポサコナゾール新錠剤200 mg コホートに組み入れられた20例の平均年齢は51.0歳（範囲：30～69歳）で、65歳以上の被験者の割合は15%（3/20例）であった。性別は男性60%（12/20例）及び女性40%（8/20例）で、平均体重は76 kg であった。被験者の多くは白人で95%（19/20例）であった。

治療歴に基づくベースライン時の基礎疾患別の被験者の割合は、初発 AML が65%（13/20例）、初回再発 AML が20%（4/20例）及び MDS が15%（3/20例）であった。

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表 2.7.6.2.22-7　　被験者の背景因子
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20
Sex (n, %)	
Female	8 (40)
Male	12 (60)
Race (n, %)	
White	19 (95)
Non-White	1 (5)
Asian	1 (5)
Ethnicity (n, %)	
Hispanic or Latino	7 (35)
Not Hispanic or Latino	13 (65)
Age (years)	
Mean (SD)	51.0 (13.2)
Median	53.5
Range (minimum - maximum)	30 - 69
Age (n, %)	
18 - < 65 years	17 (85)
≥65 years	3 (15)
Weight (kg)	
Mean (SD)	76.04 (12.70)
Median	77.00
Range (minimum - maximum)	54.2 – 99.4
Primary Diagnosis at Study Entry† (n, %)	
Acute Myelogenous Leukemia (New Diagnosis)	13 (65)
Acute Myelogenous Leukemia (First Relapse)	4 (20)
Myelodysplastic Syndromes	3 (15)
Hematopoietic stem cell transplant	0

POS：ポサコナゾール、SD：標準偏差
† 被験者の治療歴に基づく
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

2.7.6.2.22.2.3.2　　ポサコナゾール新錠剤300 mg コホート

AML/MDS 患者及び HSCT 患者を対象としたポサコナゾール新錠剤300 mg コホートの被験者の背景因子を[表 2.7.6.2.22-8]に示す。

ポサコナゾール新錠剤300 mg コホートに組み入れられた210例の平均年齢は51.0歳（範囲：19～78歳）で、65歳以上の被験者の割合は17%（35/210例）であった。性別は男性62%（131/210例）及び女性38%（79/210例）で、平均体重は77 kg であった。被験者の多くは白人で93%（196/210例）であった。

治療歴に基づくベースライン時の基礎疾患別の被験者の割合は、初発 AML が46%（97/210例）、初回再発 AML が8%（16/210例）、MDS が3%（6/210例）及び HSCT が43%（91/210例）であった。

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表 2.7.6.2.22-8　　被験者の背景因子

（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
Sex (n, %)	
Female	79 (38)
Male	131 (62)
Race (n, %)	
White	196 (93)
Non-White	14 (7)
Asian	2 (1)
Black or African American	2 (1)
Multiracial	6 (3)
Native Hawaiian or Other Pacific Islander	4 (2)
Ethnicity (n, %)	
Hispanic or Latino	25 (12)
Not Hispanic or Latino	181 (86)
Missing	4 (2)
Age (years)	
Mean (SD)	51.0 (14.1)
Median	54.0
Range (minimum - maximum)	19-78
Age (n, %)	
18 - < 65 years	175 (83)
≥65 years	35 (17)
Weight (kg)	
Mean (SD)	77.15 (18.14)
Median	75.00
Range (minimum - maximum)	45.0-172.4
Primary Diagnosis at Study Entry (n, %)	
Acute Myelogenous Leukemia (New Diagnosis)†	97 (46)
Acute Myelogenous Leukemia (First Relapse)	16 (8)
Myelodysplastic Syndromes‡	6 (3)
Hematopoietic stem cell transplant	91 (43)

POS：ポサコナゾール、SD：標準偏差
† 肥満細胞症に対する化学療法による好中球減少症で組み入れられた被験者が1例いた。肥満細胞症と急性骨髄性白血病（AML）は、化学療法及び化学療法による好中球減少症の罹病期間が類似しているため、当該被験者の基礎疾患は初発 AML に分類した。
‡ 骨髄異形成症候群（MDS）に分類した6例のうち、その後の調査で MDS は既往歴と判明した被験者が1例いた。当該被験者は造血幹細胞移植（HSCT）を経て胃の移植片対宿主病（GVHD）を発症し、ベースライン時は GVHD に対する免疫抑制療法を受けていた。化学療法による好中球減少症は認められていないことから、本表では MDS に分類したが、薬物動態の集計解析では、HSCT に分類した。
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

2.7.6.2.22.2.4　　曝露期間

2.7.6.2.22.2.4.1　　ポサコナゾール新錠剤200 mg コホート

ポサコナゾール新錠剤200 mg コホートで治験薬が投与された20例での曝露期間の中央値は22日（範囲：9～29日）であった。

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2.7.6.2.22.2.4.2　　ポサコナゾール新錠剤300 mg コホート

ポサコナゾール新錠剤300 mg コホートで治験薬が投与された210例での曝露期間の中央値は28日（範囲：1～30日）であった。

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2.7.6.2.22.3　　有効性の結果

2.7.6.2.22.3.1　　ポサコナゾール新錠剤200 mg コホート

ポサコナゾール新錠剤200 mg コホートの治験薬投与開始から最終投与7日後まで（Exposure Phase）の治療失敗率［侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例）の発症率］は10%（2/20例）であった。2例とも確定診断例であった。

治験薬投与65日後の生存率は90%（18/20例）、死亡率は10%（2/20例）であった。

2.7.6.2.22.3.2　　ポサコナゾール新錠剤300 mg コホート

ポサコナゾール新錠剤300 mg コホートの治験薬投与開始から最終投与7日後まで（Exposure Phase）の治療失敗率［侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例／疑い例）の発症率］は5%（10/210例）であった。その内訳は、確定診断例1例（AML 患者）、臨床診断例0例、疑い例9例（AML/MDS 患者 8例、HSCT 患者 1例）であった。

治験薬投与65日後の生存率は90%（190/210例）であり、その内訳はAML/MDS 患者が92%（109/119例）、HSCT 患者が89%（81/91例）であった。死亡率は9%（18/210例）で、同意撤回のため、生存確認情報なしが1%（2/210例）であった。

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2.7.6.2.22.4　　薬物動態の結果

本試験の薬物動態のより詳細な結果については[資料5.3.3.2.2: P05615]を参照のこと。

2.7.6.2.22.4.1　　Serial PK 評価対象集団での薬物動態の結果

2.7.6.2.22.4.1.1　　ポサコナゾール新錠剤200 mg コホート

AML/MDS 患者にポサコナゾール新錠剤200 mg を単回及び反復投与した際の薬物動態パラメータの算術平均（変動係数）を[表 2.7.6.2.22-9]に示す。

ポサコナゾール新錠剤200 mg コホートの Serial PK 評価対象集団における治験薬投与8日目の T_{max} の中央値は4時間で、定常状態の C_{avg} の算術平均は981 ng/mL であった。定常状態の C_{avg} は378 ng/mL から1830 ng/mL の範囲であり、2500 ng/mL 以上の被験者はいなかった。

表 2.7.6.2.22-9　AML/MDS 患者にポサコナゾール 200 mg を単回及び反復投与した際のポサコナゾールの薬物動態パラメータ
（ポサコナゾール新錠剤 200 mg コホート）（Serial PK 評価対象集団）（P05615 試験）

Day	n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{0-\tau}$ (ng·hr/mL)	C_{avg}‡ (ng/mL)	C_{min} (ng/mL)	C_{12hr} (ng/mL)	CL/F (L/hr)	R§
1	18	652 (33)	4 (1.9-4.1)	4670 (33)	-	-	316 (30)	-	-
8	18	1310 (47)	4 (2.0-8.1)	23500 (49)	981 (48)	812 (55)	995 (46)	10.9 (53)	2.22 (59)

算術平均（%CV）
CV：変動係数、gCV：幾何変動係数、AML：急性骨髄性白血病、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
τ：投与間隔（治験薬投与1日目は12時間、治験薬投与8日目は24時間）
† 中央値（最小値－最大値）
‡ $C_{avg}=AUC_{0-\tau}/\tau$
§ $R=C_{max\ Day\ 8}/C_{max\ Day\ 1}$
注：治験薬投与8日目の C_{max}、$AUC_{0-24\ hr}$、C_{avg} 及び C_{min} の幾何平均（%gCV）は、それぞれ1180 ng/mL（52%）、20800 ng·hr/mL（56%）、869 ng/mL（56%）及び687 ng/mL（70%）であった。

2.7.6.2.22.4.1.1.1　　C_{avg} 及び C_{min} の分布評価

AML/MDS 患者にポサコナゾール新錠剤200 mg を反復投与した際の定常状態の C_{avg} 及び C_{min} の分布を[表 2.7.6.2.22-10]に示す。

ポサコナゾール新錠剤200 mg コホートの Serial PK 評価対象集団における定常状態の C_{avg} が200 ng/mL 以上500 ng/mL 未満の被験者は17%（3/18例）で、500 ng/mL 以上2500 ng/mL 未満の被験者は83%（15/18例）であった。定常状態の C_{avg} が2500 ng/mL 以上の被験者はいなかった。また、C_{min} が200 ng/mL 以上500 ng/mL 未満の被験者は33%（6/18例）で、500 ng/mL 以上2500 ng/mL 未満の被験者は67%（12/18例）であった。C_{min} が2500 ng/mL 以上の被験者はいなかった。

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表 2.7.6.2.22-10　AML/MDS 患者にポサコナゾール 200 mg を反復投与した際の定常状態での C_{avg} 及び C_{min} の分布
（ポサコナゾール新錠剤 200 mg コホート）（Serial PK 評価対象集団）（P05615 試験）

Disease State of Subjects	AML/MDS	
	C_{avg}	C_{min}
n	18	18
n (%) of subjects: C_{avg} or C_{min} ≥200 ng/mL and <500 ng/mL	3 (17%)	6 (33%)
n (%) of subjects: C_{avg} or C_{min} ≥500 ng/mL and <2500 ng/mL	15 (83%)	12 (67%)
n (%) of subjects: C_{avg} or C_{min} ≥2500 ng/mL and <3750 ng/mL	0	0
n (%) of subjects: C_{avg} or C_{min} ≥3750 ng/mL	0	0

AML：急性骨髄性白血病、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
$C_{avg}=AUC_{0\text{-}24\ hr}/24$、$C_{min}$：治験薬投与8日目における C_{min} の実測値

2.7.6.2.22.4.1.2　　ポサコナゾール新錠剤300 mg コホート

AML/MDS 患者及び HSCT 患者にポサコナゾール新錠剤300 mg を単回及び反復投与した際の薬物動態パラメータの算術平均（変動係数）を[表 2.7.6.2.22-11]に示す。

ポサコナゾール新錠剤300 mg コホートの Serial PK 評価対象集団における治験薬投与8日目の T_{max} の中央値は4時間で、定常状態の C_{avg} の算術平均は1580 ng/mL であった。定常状態の C_{avg} は510 ng/mL から3450 ng/mL の範囲であり、3750 ng/mL 以上の被験者はいなかった。

表 2.7.6.2.22-11　AML/MDS 患者及び HSCT 患者にポサコナゾール 300 mg を単回及び反復投与した際のポサコナゾールの薬物動態パラメータ
（ポサコナゾール新錠剤 300 mg コホート）（Serial PK 評価対象集団）（P05615 試験）

Day	n	Disease	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{0-\tau}$ (ng·hr/mL)	C_{avg}‡ (ng/mL)	C_{min} (ng/mL)	C_{12hr} (ng/mL)	CL/F (L/hr)	R§
1	50	AML/MDS + HSCT	908 (39)	4 (1.8-12.0)	6730 (40)	-	-	523 (50)	-	-
8	50	AML/MDS + HSCT	2090 (38)	4 (1.3-8.3)	37900 (42)	1580 (42)	1310 (50)	1550‖ (41)	9.39 (45)	2.51 (40)
1	17	HSCT	1030 (48)	6 (2.0-12.0)	7900 (49)	-	-	674 (54)	-	-
	33	AML/MDS	845 (29)	4 (1.8-8.1)	6130 (27)	-	-	445 (32)	-	-
8	17	HSCT	2390 (43)	4.1 (2.0-8.3)	44800 (45)	1870 (45)	1540 (49)	1900¶ (41)	8.11 (46)	2.69 (46)
	33	AML/MDS	1930 (32)	2.2 (1.3-8.1)	34300 (36)	1440 (36)	1190 (47)	1380 (35)	10.1 (43)	2.41 (35)

算術平均（%CV）
CV：変動係数、gCV：幾何変動係数、AML：急性骨髄性白血病、HSCT：造血幹細胞移植、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
τ：投与間隔（治験薬投与1日目は12時間、治験薬投与8日目は24時間）
† 中央値（最小値－最大値）
‡ $C_{avg} = AUC_{0-\tau}/\tau$
§ $R=C_{max\ Day\ 8}/C_{max\ Day\ 1}$
‖ n = 49
¶ n = 16
注：ポサコナゾール新錠剤300 mg コホートの治験薬投与8日目の C_{max}、$AUC_{0\text{-}24\ hr}$、C_{avg} 及び C_{min} の幾何平均（%gCV）は、それぞれ1950 ng/mL（40%）、34800 ng·hr/mL（44%）、1460 ng/mL（44%）及び1160 ng/mL（56%）であった。基礎疾患別では、AML/MDS 患者でそれぞれ1840 ng/mL（35%）、32100 ng·hr/mL（40%）、1340 ng/mL（40%）及び1060 ng/mL（55%）であり、HSCT 患者でそれぞれ2180 ng/mL（48%）、40600 ng·hr/mL（49%）、1700 ng/mL（49%）及び1380 ng/mL（52%）であった。

2.7.6.2.22.4.1.2.1　C_{avg} 及び C_{min} の分布評価

AML/MDS 患者及び HSCT 患者にポサコナゾール新錠剤300 mg を反復投与した際の基礎疾患別の定常状態の C_{avg} 及び C_{min} の分布を[表 2.7.6.2.22-12]に示す。

ポサコナゾール新錠剤300 mg コホートの Serial PK 評価対象集団における定常状態の C_{avg} は、500 ng/mL 以上2500 ng/mL 未満の被験者は90%（45/50例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は10%（5/50例）であり、500 ng/mL 未満の被験者及び3750 ng/mL 以上の被験者はいなかった。

基礎疾患別の内訳では、AML/MDS 患者33例のうち、定常状態の C_{avg} が500 ng/mL 以上2500 ng/mL 未満の被験者は97%（32/33例）で、2500 ng/mL 以上3750 ng/mL 未満の被験者は3%（1/33例）であった。一方、HSCT 患者17例のうち、定常状態の C_{avg} が500 ng/mL 以上2500 ng/mL 未満の被験者は76%（13/17例）で、2500 ng/mL 以上3750 ng/mL 未満の被験者は24%（4/17例）であった。

また、C_{min} については、200 ng/mL 以上500 ng/mL 未満の被験者は6%（3/50例）、500 ng/mL 以上2500 ng/mL 未満の被験者は88%（44/50例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は6%（3/50例）であった。3650 ng/mL を超え、3750 ng/mL 未満の範囲には被験者はいなかった。

基礎疾患別の内訳では、AML/MDS 患者33例のうち、C_{min} が200 ng/mL 以上500 ng/mL 未満の被

験者は9%（3/33例）、500 ng/mL 以上2500 ng/mL 未満の被験者は88%（29/33例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は3%（1/33例）であった。一方、HSCT 患者17例のうち、C_{min} が500 ng/mL 以上2500 ng/mL 未満の被験者は88%（15/17例）で、2500 ng/mL 以上3750 ng/mL 未満の被験者は12%（2/17例）であった。

表 2.7.6.2.22-12　AML/MDS 患者及び HSCT 患者にポサコナゾール 300 mg を反復投与した際の定常状態での C_{avg} 及び C_{min} の分布（基礎疾患別）
（ポサコナゾール新錠剤 300 mg コホート）（Serial PK 評価対象集団）（P05615 試験）

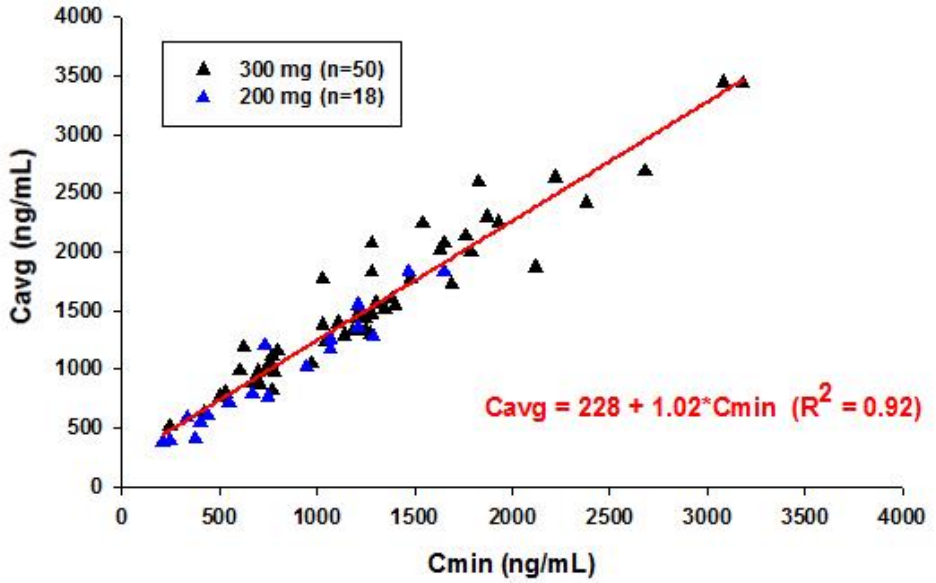
Disease State of Subjects	AML/MDS + HSCT	AML/MDS	HSCT
n	50	33	17
C_{avg}			
n (%) of subjects: C_{avg} ≥200 ng/mL and <500 ng/mL	0	0	0
n (%) of subjects: C_{avg} ≥500 ng/mL and <2500 ng/mL	45 (90%)	32 (97%)	13 (76%)
n (%) of subjects: C_{avg} ≥2500 ng/mL and <3750 ng/mL	5 (10%)	1 (3%)	4 (24%)
n (%) of subjects: C_{avg} ≥3750 ng/mL	0	0	0
C_{min}			
n (%) of subjects: C_{min} ≥200 ng/mL and <500 ng/mL	3 (6%)	3 (9%)	0
n (%) of subjects: C_{min} ≥500 ng/mL and <2500 ng/mL	44 (88%)	29 (88%)	15 (88%)
n (%) of subjects: C_{min} ≥2500 ng/mL and <3750 ng/mL	3 (6%)	1 (3%)	2 (12%)
n (%) of subjects: C_{min} ≥3750 ng/mL	0	0	0

AML：急性骨髄性白血病、HSCT：造血幹細胞移植、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
$C_{avg}=AUC_{0\text{-}24\ hr}/24$、$C_{min}$：治験薬投与8日目における C_{min} の実測値

2.7.6.2.22.4.2　C_{min} PK 評価対象集団での薬物動態の結果

AML/MDS 患者及び HSCT 患者にポサコナゾール新錠剤200 mg 又は300 mg を反復投与した際の Serial PK 評価対象集団の治験薬投与8日目における各被験者で得られた C_{avg} 及び C_{min} の実測値の分布を[図 2.7.6.2.22-3]に示す。C_{avg} と C_{min} の実測値の間に強い相関が認められ（$R^2 = 0.92$）、C_{min} から予測した C_{avg}（pC_{avg}）算出するための関係式（$pC_{avg}= 228 + 1.02 \times$ 平均 C_{min}；なお、平均 C_{min} は治験薬投与8～28日目の C_{min} の算術平均）が得られた。

図 2.7.6.2.22-3　　AML/MDS 患者及び HSCT 患者にポサコナゾール 200 mg 又は 300 mg を反復投与した際の治験薬投与 8 日目の C_{avg} 及び C_{min} の実測値の分布
（ポサコナゾール新錠剤 200／300 mg コホート）（Serial PK 評価対象集団）（P05615 試験）



AML：急性骨髄性白血病、HSCT：造血幹細胞移植、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
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1日2回、2日目以降は1日1回経口投与
$C_{avg}=AUC_{0\text{-}24\ hr}/24$

C_{min} PK 評価対象集団205例（ポサコナゾール新錠剤200 mg コホート：19例、300 mg コホート：186例）から得られた pC_{avg} の算術平均（変動係数）は、200 mg コホートで1010 ng/mL (41%)、300 mg コホートで1970 ng/mL (56%)であり[表 2.7.6.2.22-13]、Serial PK 評価対象集団の C_{avg} の算術平均（200 mg コホート：981 ng/mL、300 mg コホート：1580 ng/mL）と比べて同程度又はやや高い傾向にあった。

ポサコナゾール新錠剤300 mg コホートの C_{min} PK 評価対象集団では、pC_{avg} が200 ng/mL 以上500 ng/mL 未満の被験者は0.5%（1/186例）で、500 ng/mL 以上2500 ng/mL 未満の被験者は81%（151/186例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は15%（27/186例）であった。pC_{avg} が3750 ng/mL 以上の被験者は4%（7/186例）であった。基礎疾患別の内訳は、AML/MDS 患者では、pC_{avg} が200 ng/mL 以上500 ng/mL 未満の被験者は1%（1/107例）、500 ng/mL 以上2500 ng/mL 未満の被験者は90%（96/107例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は8%（9/107例）であった。pC_{avg} が3750 ng/mL 以上の被験者は、1%（1/107例）認められた。HSCT 患者では、pC_{avg} が500 ng/mL 以上2500 ng/mL 未満の被験者は70%（55/79例）で、2500 ng/mL 以上3750 ng/mL 未満の被験者は23%（18/79例）であった。pC_{avg} が3750 ng/mL 以上の被験者は8%（6/79例）であった[表 2.7.6.2.22-14]。

また、ポサコナゾール新錠剤300 mg コホートの C_{min} PK 評価対象集団で、平均 C_{min} が200 ng/mL 以上500 ng/mL 未満の被験者は5%（10/186例）で、500 ng/mL 以上2500 ng/mL 未満の被験者は81%

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（151/186例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は10%（19/186例）であった。平均 C_{min} が3750 ng/mL 以上の被験者は3%（6/186例）であった。基礎疾患別にみると、AML/MDS 患者では、平均 C_{min} が200 ng/mL 以上500 ng/mL 未満の被験者は7%（8/107例）、500 ng/mL 以上2500 ng/mL 未満の被験者は87%（93/107例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は6%（6/107例）であった。平均 C_{min} が3750 ng/mL 以上の被験者はいなかった。HSCT 患者では、平均 C_{min} が200 ng/mL 以上500 ng/mL 未満の被験者は3%（2/79例）で、500 ng/mL 以上2500 ng/mL 未満の被験者は73%（58/79例）、2500 ng/mL 以上3750 ng/mL 未満の被験者は16%（13/79例）であった。平均 C_{min} が3750 ng/mL 以上の被験者は8%（6/79例）であった [表 2.7.6.2.22-14]。

表 2.7.6.2.22-13　AML/MDS 患者及び HSCT 患者にポサコナゾール 200 mg 又は 300 mg を反復投与した際の平均 C_{min} 及び予測 C_{avg}（pC_{avg}）
（ポサコナゾール新錠剤 200／300 mg コホート）（C_{min} PK 評価対象集団）（P05615 試験）

Treatment	n	Disease	平均 C_{min} (ng/mL)		pC_{avg} (ng/mL)	
			AM (%CV)	Range	AM (%CV)	Range
200 mg	19	AML/MDS	771 (53)	306-1470	1010 (41)	539-1720
300 mg	186	AML/MDS + HSCT	1720 (64)	210-9140	1970 (56)	442-9520
	107	AML/MDS	1430 (48)	210-3680	1680 (41)	442-3970
	79	HSCT	2110 (66)	445-9140	2370 (60)	680-9520

AM：算術平均、CV：変動係数、gCV：幾何変動係数、平均 C_{min}：治験薬投与8～28日目の C_{min} の算術平均、pC_{avg}：平均 C_{min} に基づく C_{avg} の予測値
AML：急性骨髄性白血病、HSCT：造血幹細胞移植、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
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1日2回、2日目以降は1日1回経口投与
注：ポサコナゾール新錠剤200 mg を投与した際の平均 C_{min} 及び pC_{avg} の幾何平均（%gCV）は、それぞれ668 ng/mL（61%）及び933 ng/mL（43%）であった。
ポサコナゾール新錠剤300 mg を投与した際の平均 C_{min} 及び pC_{avg} の幾何平均（%gCV）は、それぞれ1460 ng/mL（63%）及び1750 ng/mL（52%）であった。
AML/MDS 患者では、ポサコナゾール新錠剤300 mg を投与した際の平均 C_{min} 及び pC_{avg} の幾何平均（%gCV）は、それぞれ1260 ng/mL（58%）及び1540 ng/mL（46%）であった。
HSCT 患者では、ポサコナゾール新錠剤300 mg を投与した際の平均 C_{min} 及び pC_{avg} の幾何平均（%gCV）は、それぞれ1790 ng/mL（61%）及び2080 ng/mL（53%）であった。
注：ポサコナゾール新錠剤300 mg コホートの HSCT 患者1例は、誤って C_{min} PK 評価対象集団から除外された。当該被験者の治験薬投与8日目の C_{min} は934 ng/mL、pC_{avg} は1181 ng/mL であった。

表 2.7.6.2.22-14　AML/MDS 患者及び HSCT 患者にポサコナゾール新錠剤 300 mg を反復投与した際の pC_{avg} の分布（基礎疾患別）
（ポサコナゾール新錠剤 300 mg コホート）（C_{min} PK 評価対象集団）（P05615 試験）

Disease State of Subjects	AML/MDS + HSCT	AML/MDS	HSCT
n	186	107	79
pC_{avg}			
n (%) of subjects: pC_{avg} ≥200 ng/mL and <500 ng/mL	1 (0.5%)	1 (1%)	0
n (%) of subjects: pC_{avg}≥500 ng/mL and <2500 ng/mL	151 (81%)	96 (90%)	55 (70%)
n (%) of subjects: pC_{avg} ≥2500 ng/mL and <3750 ng/mL	27 (15%)	9 (8%)	18 (23%)
n (%) of subjects: pC_{avg} ≥3750 ng/mL	7 (4%)	1 (1%)	6 (8%)
平均 C_{min}			
n (%) of subjects: 平均 C_{min} ≥200 ng/mL and <500 ng/mL	10 (5%)	8 (7%)	2 (3%)
n (%) of subjects: 平均 C_{min} ≥500 ng/mL and <2500 ng/mL	151 (81%)	93 (87%)	58 (73%)
n (%) of subjects: 平均 C_{min} ≥2500 ng/mL and <3750 ng/mL	19 (10%)	6 (6%)	13 (16%)
n (%) of subjects: 平均 C_{min} ≥3750 ng/mL	6 (3%)	0	6 (8%)

平均 C_{min}：治験薬投与8～28日目の C_{min} の算術平均
pC_{avg}: ポサコナゾール新錠剤200 mg 及び300 mg コホートの Serial PK 評価対象集団68例の治験薬投与8日目における C_{min} 及び C_{avg} の実測値に基づく線形回帰モデルより算出した（pC_{avg}=228 + 1.02×平均 C_{min}）
AML：急性骨髄性白血病、HSCT：造血幹細胞移植、MDS：骨髄異形成症候群
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1日2回、2日目以降は1日1回経口投与
注：ポサコナゾール新錠剤300 mg コホートの HSCT 患者1例は、誤って C_{min}PK 評価対象集団から除外された。当該被験者の治験薬投与8日目の C_{min} は934 ng/mL、pC_{avg} は1181 ng/mL であった。

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2.7.6.2.22.5　　安全性の結果

2.7.6.2.22.5.1　　ポサコナゾール新錠剤200 mg コホート

侵襲性真菌症のハイリスク患者（AML/MDS 患者）にポサコナゾール新錠剤200 mg を予防投与した際の安全性の結果を以下に示す。

2.7.6.2.22.5.1.1　　有害事象及び副作用

2.7.6.2.22.5.1.1.1　　有害事象の要約

ポサコナゾール新錠剤200 mg コホートで認められた有害事象の要約を[表 2.7.6.2.22-15]に示す。

有害事象はすべての被験者に認められた。副作用の発現割合は50%（10/20例）であった。

死亡に至った有害事象の発現割合は10%（2/20例）、重篤な有害事象の発現割合は30%（6/20例）、投与中止に至った有害事象の発現割合は15%（3/20例）であった。

表 2.7.6.2.22-15　有害事象の要約
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20
有害事象	20 (100)
副作用	10 (50)
重篤な有害事象	6 (30)
死亡に至った有害事象	2 (10)
重度／生命を脅かす有害事象	15 (75)
投与中止に至った有害事象	3 (15)

POS：ポサコナゾール
注：有害事象、副作用及び重度／生命を脅かす有害事象は、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、重篤な有害事象、死亡に至った有害事象及び投与中止に至った有害事象は、同意取得後に有害事象として報告された事象を集計した。
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

2.7.6.2.22.5.1.1.2　　有害事象

ポサコナゾール新錠剤200 mg コホートで認められたすべての有害事象及び重度／生命を脅かす有害事象発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-16]に示す。

有害事象はすべての被験者に発現した。よくみられた有害事象（発現割合30%以上）は、下痢40%（8/20例）、嘔吐40%（8/20例）、便秘35%（7/20例）、咳嗽35%（7/20例）、発熱性好中球減少症35%（7/20例）、血小板減少症35%（7/20例）、貧血、腹痛、無力症、悪寒、粘膜の炎症、発熱及び鼻出血 各30%（6/20例）であった。

重度／生命を脅かす有害事象の発現割合は75%（15/20例）であった。よくみられた重度／生命を脅かす有害事象（発現割合20%以上）は、血小板減少症35%（7/20例）、貧血25%（5/20例）及び

好中球減少症20%（4/20例）であった。

表 2.7.6.2.22-16　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
Subjects Reporting Any Adverse Event	20 (100)	15 (75)
血液およびリンパ系障害	15 (75)	10 (50)
貧血	6 (30)	5 (25)
凝血異常	1 (5)	0
発熱性好中球減少症	7 (35)	2 (10)
低プロトロンビン血症	1 (5)	0
好中球減少症	4 (20)	4 (20)
血小板減少症	7 (35)	7 (35)
血小板増加症	1 (5)	1 (5)
心臓障害	5 (25)	0
不整脈	1 (5)	0
徐脈	2 (10)	0
頻脈	2 (10)	0
耳および迷路障害	1 (5)	0
耳そう痒症	1 (5)	0
眼障害	3 (15)	0
眼精疲労	1 (5)	0
眼部腫脹	1 (5)	0
眼充血	1 (5)	0
霧視	1 (5)	0
胃腸障害	20 (100)	2 (10)
腹部不快感	1 (5)	0
腹部膨満	2 (10)	0
腹痛	6 (30)	1 (5)
上腹部痛	1 (5)	1 (5)
肛門直腸不快感	1 (5)	0
盲腸炎	1 (5)	0
口唇炎	1 (5)	0
大腸炎	1 (5)	0
便秘	7 (35)	0
下痢	8 (40)	0
消化不良	2 (10)	0
鼓腸	1 (5)	0
胃腸出血	1 (5)	0
歯肉潰瘍	1 (5)	0
血便排泄	1 (5)	0
痔核	2 (10)	0
イレウス	1 (5)	0

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表 2.7.6.2.22-16　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
口唇乾燥	1 (5)	0
メレナ	1 (5)	0
口腔内出血	2 (10)	0
悪心	4 (20)	0
好中球減少性大腸炎	1 (5)	1 (5)
口腔粘膜紅斑	1 (5)	0
口腔内痛	3 (15)	0
直腸出血	2 (10)	0
舌障害	1 (5)	0
嘔吐	8 (40)	0
一般・全身障害および投与部位の状態	18 (90)	4 (20)
適用部位発疹	1 (5)	0
無力症	6 (30)	1 (5)
カテーテル留置部位炎症	1 (5)	0
カテーテル留置部位紅斑	2 (10)	0
カテーテル留置部位静脈炎	1 (5)	0
胸痛	3 (15)	0
悪寒	6 (30)	1 (5)
顔面痛	1 (5)	0
疲労	2 (10)	0
炎症	1 (5)	0
注入部位小水疱	1 (5)	0
粘膜の炎症	6 (30)	2 (10)
末梢性浮腫	2 (10)	0
発熱	6 (30)	1(5)
肝胆道系障害	4 (20)	1 (5)
胆汁うっ滞	2 (10)	0
高ビリルビン血症	2 (10)	1 (5)
免疫系障害	1 (5)	0
薬物過敏症	1 (5)	0
感染症および寄生虫症	10 (50)	4 (20)
アスペルギルス症	1 (5)	1 (5)
感染性胆嚢炎	1 (5)	1 (5)
エンテロバクター性菌血症	1 (5)	0
毛包炎	1 (5)	0
フサリウム感染	1 (5)	0
単純ヘルペス	1 (5)	0
帯状疱疹	1 (5)	0
咽頭炎	1 (5)	0
肺炎	1 (5)	1 (5)
真菌性肺炎	1 (5)	1 (5)
RS ウイルス感染	1 (5)	0
敗血症	1 (5)	1 (5)
敗血症性ショック	1 (5)	1 (5)
レンサ球菌性菌血症	1 (5)	0

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表 2.7.6.2.22-16　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
傷害、中毒および処置合併症	4 (20)	1 (5)
眼窩周囲血腫	1 (5)	0
腰椎穿刺後症候群	1 (5)	0
血小板輸血不応状態	1 (5)	1 (5)
輸血反応	1 (5)	0
臨床検査	7 (35)	2 (10)
アラニンアミノトランスフェラーゼ増加	2 (10)	1 (5)
心電図 QT 延長	1 (5)	0
ヘモグロビン減少	2 (10)	1 (5)
肝酵素上昇	1 (5)	1 (5)
INR 増加	1 (5)	0
肝機能検査異常	1 (5)	0
酸素飽和度低下	1 (5)	0
血小板数減少	1 (5)	0
尿量増加	1 (5)	0
体重減少	1 (5)	0
代謝および栄養障害	11 (55)	4 (20)
食欲減退	4 (20)	1 (5)
脱水	1 (5)	1 (5)
高リン酸塩血症	1 (5)	0
低カルシウム血症	1 (5)	0
低カリウム血症	4 (20)	1 (5)
低マグネシウム血症	2 (10)	0
低ナトリウム血症	1 (5)	1 (5)
低リン酸血症	4 (20)	2 (10)
筋骨格系および結合組織障害	6 (30)	0
筋骨格系胸痛	1 (5)	0
筋骨格痛	1 (5)	0
頚部痛	1 (5)	0
四肢痛	4 (20)	0
顎痛	1 (5)	0
神経系障害	5 (25)	2 (10)
浮動性めまい	1 (5)	1 (5)
ジスキネジー	1 (5)	0
頭痛	4 (20)	0
知覚過敏	1 (5)	0
失神寸前の状態	1 (5)	0
副鼻腔炎に伴う頭痛	1 (5)	1 (5)
精神障害	3 (15)	0
不眠症	3 (15)	0
腎および尿路障害	5 (25)	2 (10)
着色尿	1 (5)	0
排尿困難	1 (5)	0
血尿	2 (10)	0
腎不全	2 (10)	2 (10)

表 2.7.6.2.22-16　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
生殖系および乳房障害	1 (5)	0
外陰腟そう痒症	1 (5)	0
呼吸器、胸郭および縦隔障害	13 (65)	1 (5)
咳嗽	7 (35)	0
呼吸困難	2 (10)	1 (5)
鼻出血	6 (30)	0
肺障害	1 (5)	0
鼻閉	2 (10)	0
胸膜痛	1 (5)	0
肺塞栓症	1 (5)	0
ラ音	1 (5)	0
レチノイン酸症候群	1 (5)	0
鼻漏	1 (5)	0
喘鳴	1 (5)	0
皮膚および皮下組織障害	9 (45)	1 (5)
斑状出血	1 (5)	0
紅斑	1 (5)	0
嵌入爪	1 (5)	0
点状出血	2 (10)	0
そう痒症	1 (5)	0
発疹	5 (25)	0
紅斑性皮疹	1 (5)	1 (5)
全身性皮疹	1 (5)	0
斑状丘疹状皮疹	2 (10)	0
そう痒性皮疹	1 (5)	0
血管障害	9 (45)	1 (5)
高血圧	3 (15)	0
低血圧	4 (20)	1 (5)
血栓性静脈炎	1 (5)	0
表在性血栓性静脈炎	1 (5)	0

POS：ポサコナゾール、INR：国際標準比
注：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有害事象を集計した。
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

2.7.6.2.22.5.1.1.3　副作用

ポサコナゾール新錠剤200 mgコホートで認められたすべての副作用及び重度／生命を脅かす副作用発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-17]に示す。

副作用の発現割合は50%（10/20例）であった。よくみられた副作用（発現割合10%以上）は、下痢15%（3/20例）、発疹15%（3/20例）、腹痛10%（2/20例）、食欲減退10%（2/20例）及び低カリウム血症10%（2/20例）であった。

重度／生命を脅かす副作用の発現割合は30%（6/20例）であった。2例以上に発現した重度／生命を脅かす副作用はなかった。

表 2.7.6.2.22-17　すべての副作用及び重度／生命を脅かす副作用発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
Subjects Reporting Any Adverse Event	10 (50)	6 (30)
心臓障害	2 (10)	0
不整脈	1 (5)	0
頻脈	1 (5)	0
耳および迷路障害	1 (5)	0
耳そう痒症	1 (5)	0
眼障害	1 (5)	0
眼精疲労	1 (5)	0
霧視	1 (5)	0
胃腸障害	5 (25)	1 (5)
腹痛	2 (10)	1 (5)
上腹部痛	1 (5)	1 (5)
下痢	3 (15)	0
消化不良	1 (5)	0
悪心	1 (5)	0
嘔吐	1 (5)	0
一般・全身障害および投与部位の状態	2 (10)	1 (5)
粘膜の炎症	1 (5)	0
発熱	1 (5)	1 (5)
肝胆道系障害	2 (10)	0
胆汁うっ滞	1 (5)	0
高ビリルビン血症	1 (5)	0
臨床検査	5 (25)	2 (10)
アラニンアミノトランスフェラーゼ増加	1 (5)	1 (5)
心電図 QT 延長	1 (5)	0
肝酵素上昇	1 (5)	1 (5)
INR 増加	1 (5)	0
肝機能検査異常	1 (5)	0
代謝および栄養障害	3 (15)	1 (5)
食欲減退	2 (10)	1 (5)
高リン酸塩血症	1 (5)	0
低カリウム血症	2 (10)	1 (5)
低マグネシウム血症	1 (5)	0
低ナトリウム血症	1 (5)	1 (5)
低リン酸血症	1 (5)	0
腎および尿路障害	1 (5)	1 (5)
腎不全	1 (5)	1 (5)

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表 2.7.6.2.22-17　すべての副作用及び重度／生命を脅かす副作用発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20	
	All	Severe/Life-Threatening
皮膚および皮下組織障害	5 (25)	1 (5)
そう痒症	1 (5)	0
発疹	3 (15)	0
紅斑性皮疹	1 (5)	1 (5)
血管障害	1 (5)	0
低血圧	1 (5)	0

POS：ポサコナゾール、INR：国際標準比
注：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副作用を集計した。
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

2.7.6.2.22.5.1.2　死亡

ポサコナゾール新錠剤200 mg コホートでの死亡に至った有害事象の発現割合は10%（2/20例）で、その内訳は真菌性肺炎1例及び副鼻腔炎に伴う頭痛／肺炎／敗血症性ショック1例であった。これらの事象は、いずれも治験担当医師により治験薬との因果関係なしと判定された。

なお、死亡に至った有害事象の一覧は[資料5.3.7.4.1: P05615_death]に、重篤な有害事象（死亡に至った有害事象を含む）の叙述は[資料5.3.3.2.2: P05615] 14.6.3 項に示す。

2.7.6.2.22.5.1.3　重篤な有害事象

ポサコナゾール新錠剤200 mg コホートで認められた重篤な有害事象発現例数について、発現割合0%超の集計表を[付録 2.7.6.2.22-1]に示す。

重篤な有害事象の発現割合は30%（6/20例）であった。重篤な有害事象は、発熱性好中球減少症が10%（2/20例）に認められた以外は、いずれの事象も各1例のみの発現であった。

重篤な副作用は、腎不全が1例で認められた。本事象は加療により、治験薬投与終了後に回復した。

なお、重篤な有害事象の一覧は[資料5.3.7.5.1: P05615_sae]に、重篤な有害事象の叙述は[資料5.3.3.2.2: P05615] 14.6.3 項に、重篤な副作用の叙述は[付録 2.7.6.2.22-3]に示す。

2.7.6.2.22.5.1.4　投与中止に至った有害事象

ポサコナゾール新錠剤200 mg コホートで認められた投与中止に至った有害事象発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-18]に示す。

投与中止に至った有害事象の発現割合は15%（3/20例）であった。そのうち、副作用は、紅斑性

皮疹1例のみであった。本事象は加療により、投与中止後に回復した。ほかの2例のうち真菌性肺炎を発現した1例は死亡し、腹部膨満及びイレウスを発現した1例は投与中止後に回復した。

なお、投与中止に至った有害事象の一覧は[資料5.3.7.6.1: P05615_discon]に示す。

表 2.7.6.2.22-18　投与中止に至った有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 200 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20
Subjects Reporting Any Adverse Event	3 (15)
胃腸障害	1 (5)
腹部膨満	1 (5)
イレウス	1 (5)
感染症および寄生虫症	1 (5)
真菌性肺炎	1 (5)
皮膚および皮下組織障害	1 (5)
紅斑性皮疹	1 (5)

POS：ポサコナゾール
注：同意取得後に有害事象として報告された事象を集計した。
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

2.7.6.2.22.5.1.5　臨床検査値

ポサコナゾール新錠剤200 mg コホートで臨床検査値の変動［Grade 0、1又は2（ベースライン時）から Grade 3又は4（治療期）への変動］が認められた臨床検査項目は、低カリウム血症25%（5/20例）、ALP 5%（1/20例）、ALT 5%（1/20例）、高カリウム血症5%（1/20例）、低ナトリウム血症5%（1/20例）及びクレアチニン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。

2.7.6.2.22.5.1.6　バイタルサイン

ポサコナゾール新錠剤200 mg コホートでは、臨床的に懸念されるバイタルサインの変動は認められなかった。

2.7.6.2.22.5.1.7　心電図

ポサコナゾール新錠剤200 mg コホートでは、Bazett 法及び Fridericia 法の両補正法とも QTc 間隔が500 msec を超えた被験者はいなかった。

2.7.6.2.22.5.2　　ポサコナゾール新錠剤300 mg コホート

侵襲性真菌症のハイリスク患者（AML/MDS 患者及び HSCT 患者）にポサコナゾール新錠剤300 mg を予防投与した際の安全性の結果を以下に示す。

2.7.6.2.22.5.2.1　　有害事象及び副作用

2.7.6.2.22.5.2.1.1　　有害事象の要約

ポサコナゾール新錠剤300 mg コホートで認められた有害事象の要約を[表 2.7.6.2.22-19]に示す。

有害事象の発現割合は99%（207/210例）であった。副作用の発現割合は40%（84/210例）であった。

死亡に至った有害事象の発現割合は9%（18/210例）、重篤な有害事象の発現割合は33%（69/210例）、投与中止に至った有害事象の発現割合は18%（38/210例）であった。

表 2.7.6.2.22-19　有害事象の要約
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
有害事象	207 (99)
副作用	84 (40)
重篤な有害事象	69 (33)
死亡に至った有害事象†	18 (9)
重度／生命を脅かす有害事象	111 (53)
投与中止に至った有害事象	38 (18)

POS：ポサコナゾール
† このほか、有害事象として報告されなかった死亡が2例いた。
注：有害事象、副作用及び重度／生命を脅かす有害事象は、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、重篤な有害事象、死亡に至った有害事象及び投与中止に至った有害事象は、同意取得後に有害事象として報告された事象を集計した。
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

2.7.6.2.22.5.2.1.2　　有害事象

ポサコナゾール新錠剤300 mg コホートで認められた有害事象発現例数について、発現割合5%以上の集計表（基本語別発現割合順）を[表 2.7.6.2.22-20]に、発現割合0%超の集計表を[付録 2.7.6.2.22-2]示す。

有害事象の発現割合は99%（207/210例）であった。よくみられた有害事象（発現割合20%以上）は、下痢29%（61/210例）、発熱28%（59/210例）、悪心27%（56/210例）、低カリウム血症22%（46/210例）及び発熱性好中球減少症20%（42/210例）であった。

重度／生命を脅かす有害事象の発現割合は53%（111/210例）であった。よくみられた重度／生命を脅かす有害事象（発現割合10%以上）は、発熱性好中球減少症14%（30/210例）及び血小板減少症10%（22/210例）であった。

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表 2.7.6.2.22-20　有害事象発現例数（%）
（基本語別発現割合順、発現割合 5%以上）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

Adverse Events	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
下痢	61 (29)
発熱	59 (28)
悪心	56 (27)
低カリウム血症	46 (22)
発熱性好中球減少症	42 (20)
咳嗽	35 (17)
発疹	34 (16)
末梢性浮腫	33 (16)
鼻出血	30 (14)
頭痛	30 (14)
粘膜の炎症	29 (14)
血小板減少症	29 (14)
嘔吐	28 (13)
腹痛	23 (11)
高血圧	23 (11)
貧血	22 (10)
悪寒	22 (10)
無力症	20 (10)
カテーテル留置部位紅斑	20 (10)
便秘	20 (10)
低マグネシウム血症	20 (10)
点状出血	19 (9)
食欲減退	17 (8)
呼吸困難	17 (8)
低リン酸血症	17 (8)
そう痒症	16 (8)
アラニンアミノトランスフェラーゼ増加	15 (7)
不眠症	15 (7)
好中球減少症	15 (7)
上腹部痛	14 (7)
不安	14 (7)
疲労	14 (7)
背部痛	13 (6)
浮動性めまい	13 (6)
消化不良	13 (6)
低カルシウム血症	13 (6)
低血圧	13 (6)
頻脈	13 (6)
アスパラギン酸アミノトランスフェラーゼ増加	12 (6)
紅斑	12 (6)
口腔咽頭痛	12 (6)
排尿困難	11 (5)
痔核	11 (5)
サイトメガロウイルス感染	10 (5)
口内乾燥	10 (5)
四肢痛	10 (5)

POS：ポサコナゾール
注：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有害事象を集計した。
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

2.7.6.2.22.5.2.1.3　　副作用

ポサコナゾール新錠剤300 mgコホートで認められたすべての副作用及び重度／生命を脅かす副作用発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-21]に示す。

副作用の発現割合は40%（84/210例）であった。よくみられた副作用（発現割合5%以上）は、悪心11%（23/210例）及び下痢8%（16/210例）であった。

重度／生命を脅かす副作用の発現割合は9%（19/210例）で、ほとんどが軽度又は中等度の事象であった。

表 2.7.6.2.22-21　すべての副作用及び重度／生命を脅かす副作用発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210	
	All	Severe/Life-Threatening
Subjects Reporting Any Adverse Event	84 (40)	19 (9)
血液およびリンパ系障害	1 (<1)	1 (<1)
好中球減少症	1 (<1)	1 (<1)
心臓障害	4 (2)	0
徐脈	1 (<1)	0
洞性徐脈	2 (1)	0
上室性期外収縮	1 (<1)	0
頻脈	1 (<1)	0
眼障害	1 (<1)	0
黄疸眼	1 (<1)	0
胃腸障害	54 (26)	5 (2)
腹部不快感	2 (1)	0
腹部膨満	3 (1)	0
腹痛	9 (4)	2 (1)
上腹部痛	5 (2)	0
便秘	3 (1)	0
下痢	16 (8)	2 (1)
口内乾燥	2 (1)	0
消化不良	5 (2)	0
鼓腸	4 (2)	0
胃炎	2 (1)	0
胃食道逆流性疾患	1 (<1)	0
口唇乾燥	1 (<1)	0
口腔内潰瘍形成	1 (<1)	0
悪心	23 (11)	1 (<1)
口腔浮腫	1 (<1)	0
口腔障害	1 (<1)	0
嘔吐	9 (4)	0
一般・全身障害および投与部位の状態	5 (2)	1 (<1)
無力症	1 (<1)	0
薬物相互作用	2 (1)	1 (<1)
粘膜の炎症	1 (<1)	0
末梢性浮腫	1 (<1)	0
発熱	2 (1)	0

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表 2.7.6.2.22-21　すべての副作用及び重度／生命を脅かす副作用発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210	
	All	Severe/Life-Threatening
肝胆道系障害	4 (2)	2 (1)
胆汁うっ滞	1 (<1)	0
肝細胞融解性肝炎	1 (<1)	1 (<1)
肝機能異常	1 (<1)	1 (<1)
肝毒性	1 (<1)	0
免疫系障害	1 (<1)	1 (<1)
移植片対宿主病	1 (<1)	1 (<1)
感染症および寄生虫症	3 (1)	0
細菌感染	1 (<1)	0
毛包炎	1 (<1)	0
歯肉膿瘍	1 (<1)	0
喉頭炎	1 (<1)	0
傷害、中毒および処置合併症	1 (<1)	0
擦過傷	1 (<1)	0
臨床検査	28 (13)	8 (4)
アラニンアミノトランスフェラーゼ増加	9 (4)	1 (<1)
アスパラギン酸アミノトランスフェラーゼ増加	8 (4)	1 (<1)
血中アルカリホスファターゼ増加	3 (1)	0
血中ビリルビン増加	3 (1)	2 (1)
血中クレアチニン増加	3 (1)	1 (<1)
血中マグネシウム減少	1 (<1)	0
心電図 QT 延長	2 (1)	1 (<1)
心電図異常 T 波	1 (<1)	0
心電図 T 波逆転	1 (<1)	0
肝酵素上昇	2 (1)	1 (<1)
肝機能検査異常	5 (2)	1 (<1)
血小板数減少	1 (<1)	0
QRS 軸異常	1 (<1)	0
体重減少	1 (<1)	0
白血球数減少	1 (<1)	1 (<1)
代謝および栄養障害	11 (5)	4 (2)
食欲減退	2 (1)	0
低カルシウム血症	3 (1)	0
低カリウム血症	6 (3)	1 (<1)
低マグネシウム血症	3 (1)	0
低ナトリウム血症	1 (<1)	1 (<1)
低リン酸血症	5 (2)	2 (1)
筋骨格系および結合組織障害	2 (1)	0
四肢痛	2 (1)	0
神経系障害	3 (1)	0
失語症	1 (<1)	0
頭痛	2 (1)	0
精神障害	1 (<1)	0
不眠症	1 (<1)	0
腎および尿路障害	1 (<1)	1 (<1)
慢性腎不全	1 (<1)	1 (<1)

表 2.7.6.2.22-21　すべての副作用及び重度／生命を脅かす副作用発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210	
	All	Severe/Life-Threatening
呼吸器、胸郭および縦隔障害	3 (1)	1 (<1)
咳嗽	1 (<1)	0
鼻出血	1 (<1)	0
しゃっくり	1 (<1)	0
胸膜痛	1 (<1)	1 (<1)
湿性咳嗽	1 (<1)	0
皮膚および皮下組織障害	14 (7)	2 (1)
そう痒症	2 (1)	0
発疹	5 (2)	1 (<1)
全身性皮疹	1 (<1)	0
斑状皮疹	2 (1)	0
斑状丘疹状皮疹	2 (1)	0
そう痒性皮疹	2 (1)	1 (<1)
中毒性皮疹	1 (<1)	0
蕁麻疹	1 (<1)	0
血管障害	2 (1)	1 (<1)
高血圧	1 (<1)	1 (<1)
血管炎	1 (<1)	0

POS：ポサコナゾール
注：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副作用を集計した。
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

2.7.6.2.22.5.2.2　死亡

ポサコナゾール新錠剤300 mg での死亡に至った有害事象の発現割合は9%（18/210例）で、いずれも治験担当医師により治験薬との因果関係なしと判定された。2例以上にみられた死亡に至った有害事象は、敗血症1%（3/210例）、敗血症性ショック1%（2/210例）及び多臓器不全1%（2/210例）であった。

このほか、有害事象として報告されなかった死亡が2例いた。いずれも治験薬最終投与30日後以降の死亡であり、治験担当医師により治験薬との因果関係なしと判定された。

なお、死亡に至った有害事象の一覧は[資料5.3.7.4.1: P05615_death]に、重篤な有害事象（死亡に至った有害事象を含む）の叙述は[資料5.3.3.2.2: P05615] 14.8.4 項に示す。

2.7.6.2.22.5.2.3　重篤な有害事象

ポサコナゾール新錠剤300 mg コホートで認められた重篤な有害事象発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-22]に示す。

重篤な有害事象の発現割合は33%（69/210例）であった。よくみられた重篤な有害事象（発現割

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合2%以上）は、発熱性好中球減少症5%（11/210例）、敗血症2%（5/210例）及び下痢2%（4/210例）であった。

重篤な副作用の発現割合は3%（6/210例）で、その内訳は、血中クレアチニン増加1%（2/210例）、薬物相互作用1%（2/210例）、肝機能検査異常1%（2/210例）、肝毒性<1%（1/210例）及び慢性腎不全<1%（1/210例）であった。このうち、投与中止に至った事象は、肝機能検査異常2例及び肝毒性1例であった。また、肝機能検査異常1例が未回復であったほかは、休薬／投与中止又は入院等により回復した。

なお、重篤な有害事象の一覧は[資料5.3.7.5.1: P05615_sae]に、重篤な有害事象の叙述は[資料5.3.3.2.2: P05615] 14.8.4 項に、重篤な副作用の叙述は[付録 2.7.6.2.22-3]に示す。

表 2.7.6.2.22-22　重篤な有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
Subjects Reporting Any Adverse Event	69 (33)
血液およびリンパ系障害	14 (7)
発熱性好中球減少症	11 (5)
微小血管症性溶血性貧血	1 (<1)
脾臓出血	1 (<1)
血小板減少症	1 (<1)
血栓性血小板減少性紫斑病	1 (<1)
心臓障害	6 (3)
心停止	1 (<1)
心不全	1 (<1)
心肺停止	1 (<1)
心血管不全	1 (<1)
左室不全	1 (<1)
心筋虚血	1 (<1)
心膜炎	1 (<1)
胃腸障害	9 (4)
腹水	1 (<1)
下痢	4 (2)
腸炎	1 (<1)
血便排泄	1 (<1)
痔出血	1 (<1)
悪心	1 (<1)
好中球減少性大腸炎	1 (<1)
嘔吐	1 (<1)

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表 2.7.6.2.22-22　重篤な有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
一般・全身障害および投与部位の状態	11 (5)
無力症	1 (<1)
胸痛	1 (<1)
疾患進行	1 (<1)
薬物相互作用	2 (1)
全身性浮腫	1 (<1)
多臓器不全	2 (1)
非心臓性胸痛	1 (<1)
発熱	3 (1)
肝胆道系障害	2 (1)
肝毒性	1 (<1)
黄疸	1 (<1)
免疫系障害	3 (1)
薬物過敏症	1 (<1)
移植片対宿主病	1 (<1)
腸管移植片対宿主病	1 (<1)
感染症および寄生虫症	30 (14)
細菌性敗血症	1 (<1)
クロストリジウム・ディフィシレ大腸炎	1 (<1)
サイトメガロウイルス感染	3 (1)
サイトメガロウイルス血症	2 (1)
医療機器関連感染	1 (<1)
クレブシエラ感染	2 (1)
下気道感染	1 (<1)
真菌性下気道感染	1 (<1)
肺感染	1 (<1)
好中球減少性敗血症	1 (<1)
肺炎	2 (1)
細菌性肺炎	1 (<1)
RS ウイルス肺炎	1 (<1)
シュードモナス性敗血症	2 (1)
気道感染	1 (<1)
敗血症	5 (2)
敗血症性ショック	2 (1)
ブドウ球菌性敗血症	1 (<1)
レンサ球菌性敗血症	1 (<1)
ウイルス感染	1 (<1)
接合真菌症	1 (<1)
傷害、中毒および処置合併症	3 (1)
アレルギー性輸血反応	1 (<1)
上腕骨骨折	1 (<1)
移植不全	1 (<1)
臨床検査	7 (3)
血中ビリルビン増加	2 (1)
血中クレアチニン増加	3 (1)
肝機能検査異常	2 (1)
トランスアミナーゼ上昇	1 (<1)
体重増加	1 (<1)

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表 2.7.6.2.22-22　重篤な有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
代謝および栄養障害	2 (1)
脱水	1 (<1)
代謝性アシドーシス	1 (<1)
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）	3 (1)
急性骨髄性白血病	1 (<1)
白血病	1 (<1)
真性多血症	1 (<1)
T 細胞性前リンパ性白血病	1 (<1)
神経系障害	2 (1)
頭蓋内圧上昇	1 (<1)
意識消失	1 (<1)
精神障害	1 (<1)
大うつ病	1 (<1)
自殺念慮	1 (<1)
腎および尿路障害	4 (2)
出血性膀胱炎	1 (<1)
腎不全	1 (<1)
急性腎不全	1 (<1)
慢性腎不全	1 (<1)
呼吸器、胸郭および縦隔障害	7 (3)
慢性閉塞性肺疾患	1 (<1)
肺水腫	1 (<1)
呼吸窮迫	3 (1)
呼吸不全	2 (1)
血管障害	1 (<1)
低血圧	1 (<1)

POS：ポサコナゾール
注：同意取得後に有害事象として報告された事象を集計した。
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

2.7.6.2.22.5.2.4　　投与中止に至った有害事象

ポサコナゾール新錠剤300 mg コホートで認められた投与中止に至った有害事象発現例数について、発現割合0%超の集計表を[表 2.7.6.2.22-23]に示す。

投与中止に至った有害事象の発現割合は18%（38/210例）であった。2例以上にみられた投与中止に至った有害事象は、悪心2%（4/210例）、真菌感染1%（3/210例）、肝機能検査異常1%（3/210例）、下痢1%（2/210例）、気管支肺アスペルギルス症1%（2/210例）、急性骨髄性白血病1%（2/210例）及び呼吸窮迫1%（2/210例）であった。

投与中止に至った副作用の発現割合は5%（11/210例）であった。2例以上にみられた投与中止に至った副作用は、肝機能検査異常1%（3/210例）及び悪心1%（2/210例）であった。投与中止に至った副作用のうち、肝機能検査異常2例、肝機能異常1例、移植片対宿主病1例、悪心1例及び高血

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圧1例が最終評価時点で未回復であったほかは、投与中止後に回復した。

なお、投与中止に至った有害事象の一覧は[資料5.3.7.6.1: P05615_discon]に示す。

表 2.7.6.2.22-23　投与中止に至った有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
Subjects Reporting Any Adverse Event	38 (18)
血液およびリンパ系障害	1 (<1)
微小血管症性溶血性貧血	1 (<1)
心臓障害	1 (<1)
洞性徐脈	1 (<1)
胃腸障害	10 (5)
腹痛	1 (<1)
大腸炎	1 (<1)
下痢	2 (1)
小腸炎	1 (<1)
腸炎	1 (<1)
麻痺性イレウス	1 (<1)
悪心	4 (2)
嘔吐	1 (<1)
肝胆道系障害	3 (1)
肝機能異常	1 (<1)
肝毒性	1 (<1)
黄疸	1 (<1)
免疫系障害	1 (<1)
移植片対宿主病	1 (<1)
感染症および寄生虫症	10 (5)
気管支肺アスペルギルス症	2 (1)
真菌感染	3 (1)
クレブシエラ感染	1 (<1)
食道カンジダ症	1 (<1)
肺炎	1 (<1)
全身性真菌症	1 (<1)
接合真菌症	1 (<1)
臨床検査	5 (2)
血中ビリルビン増加	1 (<1)
心電図 QT 延長	1 (<1)
肝機能検査異常	3 (1)
トランスアミナーゼ上昇	1 (<1)
代謝および栄養障害	1 (<1)
代謝性アシドーシス	1 (<1)
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）	2 (1)
急性骨髄性白血病	2 (1)

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表 2.7.6.2.22-23　投与中止に至った有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort n=210
精神障害	1 (<1)
自殺念慮	1 (<1)
呼吸器、胸郭および縦隔障害	5 (2)
慢性閉塞性肺疾患 　肺浸潤 　胸膜痛 　呼吸窮迫	1 (<1) 1 (<1) 1 (<1) 2 (1)
皮膚および皮下組織障害	1 (<1)
そう痒性皮疹	1 (<1)
血管障害	1 (<1)
高血圧	1 (<1)

POS：ポサコナゾール
注：同意取得後に有害事象として報告された事象を集計した。
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

2.7.6.2.22.5.2.5　臨床検査値

ポサコナゾール新錠剤300 mg コホートで臨床検査値の変動［Grade 0、1又は2（ベースライン時）から Grade 3又は4（治療期）への変動］が認められた臨床検査項目は、低カリウム血症12%（26/209例）、ALT 5%（11/208例）、高カリウム血症3%（6/209例）、低ナトリウム血症3%（6/209例）、総ビリルビン2%（5/208例）、AST 2%（4/208例）、ALP <1%（1/209例）及びクレアチニン<1%（1/209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2例であった。

2.7.6.2.22.5.2.6　バイタルサイン

ポサコナゾール新錠剤300 mg コホートでは、臨床的に懸念されるバイタルサインの変動は認められなかった。

2.7.6.2.22.5.2.7　心電図

ポサコナゾール新錠剤300 mg コホートでは、Fridericia 法で補正した QTc 間隔が500 msec を超えた被験者が1例認められたが、有害事象ではなく、治験薬の投与は継続された。

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2.7.6.2.22.6　　結論

侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症が確認又は予測される患者並びに同種 HSCT 後の GVHD の治療又は予防患者）を対象に、ポサコナゾール新錠剤200 mg 又は300 mg を予防投与した際の薬物動態及び安全性を評価した後期第 I 相／第Ⅲ相、2パート、非盲検、非対照、多施設共同試験において以下の結論が得られた。

【薬物動態】

- ポサコナゾール新錠剤300 mg を反復投与した際のポサコナゾールの定常状態の C_{avg} の算術平均は1580 ng/mL であり、90%（45/50例）の被験者が目標曝露量（定常状態の C_{avg} 500 ng/mL 以上）に到達した。
- ポサコナゾール新錠剤300 mg を反復投与した際のポサコナゾールの pC_{avg} は、ほとんどすべての被験者が目標曝露量（500 ng/mL 以上）に到達し、500 ng/mL 未満の被験者は1例のみであった。
- ポサコナゾール新錠剤300 mg を反復投与した際の HSCT 患者における血漿中ポサコナゾール濃度は、AML/MDS 患者に比べてやや高かった。

【有効性】

- ポサコナゾール新錠剤200 mg コホートの治験薬投与開始から最終投与7日後まで（Exposure Phase）の治療失敗率［侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例）の発症率］は10%（2/20例）であった［確定診断例2例］。
- ポサコナゾール新錠剤300 mg コホートの治験薬投与開始から最終投与7日後まで（Exposure Phase）の治療失敗率［侵襲性真菌症（治験担当医師判定による確定診断例／臨床診断例／疑い例）の発症率］は5%（10/210例）であった［確定診断例1例、疑い例9例］。
- 治験薬投与65日後の生存率は高かった。治験薬投与65日後の生存率は、ポサコナゾール新錠剤200 mg コホートで90%（18/20例）、ポサコナゾール新錠剤300 mg コホートで90%（190/210例）であった。

【安全性】

- ポサコナゾール新錠剤200 mg 又は300 mg を投与1日目は1日2回、2日目以降は1日1回経口投与した際の忍容性は良好であった。
- ポサコナゾール新錠剤300 mg を投与1日目は1日2回、2日目以降は1日1回経口投与した際に得られたポサコナゾール曝露量の範囲内での安全性プロファイルは、許容可能なものであった。
- ポサコナゾール新錠剤の安全性プロファイルは、過去に実施されたポサコナゾール経口懸濁液を投与した試験における安全性プロファイルと類似していた。

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2.7.6.2.22.7　　付録

付録 2.7.6.2.22-1　重篤な有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）（ポサコナゾール新錠剤 200 mg コホート）
（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 200 mg Cohort n=20
Subjects Reporting Any Adverse Event	6 (30)
血液およびリンパ系障害	2 (10)
貧血	1 (5)
発熱性好中球減少症	2 (10)
感染症および寄生虫症	4 (20)
感染性胆嚢炎	1 (5)
肺炎	1 (5)
真菌性肺炎	1 (5)
敗血症	1 (5)
敗血症性ショック	1 (5)
代謝および栄養障害	1 (5)
脱水	1 (5)
神経系障害	2 (10)
浮動性めまい	1 (5)
副鼻腔炎に伴う頭痛	1 (5)
腎および尿路障害	1 (5)
腎不全	1 (5)
血管障害	1 (5)
低血圧	1 (5)

POS：ポサコナゾール
注：同意取得後に有害事象として報告された事象を集計した。
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

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
Subjects Reporting Any Adverse Event	207 (99)	111 (53)
血液およびリンパ系障害	87 (41)	63 (30)
貧血	22 (10)	17 (8)
凝血異常	4 (2)	0
発熱性好中球減少症	42 (20)	30 (14)
白血球増加症	1 (<1)	0
白血球減少症	6 (3)	6 (3)
リンパ節症	4 (2)	0
リンパ球減少症	3 (1)	3 (1)
微小血管症性溶血性貧血	1 (<1)	1 (<1)
好中球減少症	15 (7)	6 (3)
汎血球減少症	3 (1)	0
脾臓出血	1 (<1)	1 (<1)
血小板減少症	29 (14)	22 (10)
血栓性血小板減少性紫斑病	1 (<1)	1 (<1)
心臓障害	26 (12)	8 (4)
徐脈	1 (<1)	0
心停止	1 (<1)	1 (<1)
心不全	3 (1)	1 (<1)
うっ血性心不全	3 (1)	0
心肺停止	1 (<1)	1 (<1)
心肺不全	1 (<1)	1 (<1)
心血管不全	1 (<1)	1 (<1)
左室不全	1 (<1)	1 (<1)
心筋虚血	1 (<1)	1 (<1)
心嚢液貯留	1 (<1)	0
心膜炎	1 (<1)	1 (<1)
洞性徐脈	3 (1)	0
洞性頻脈	1 (<1)	0
上室性期外収縮	1 (<1)	0
頻脈	13 (6)	2 (1)
先天性、家族性および遺伝性障害	3 (1)	0
形成不全	3 (1)	0
耳および迷路障害	9 (4)	0
耳介腫脹	2 (1)	0
耳垢栓塞	1 (<1)	0
耳痛	2 (1)	0
耳そう痒症	1 (<1)	0
聴力低下	1 (<1)	0
回転性めまい	5 (2)	0
内分泌障害	1 (<1)	0
副腎機能不全	1 (<1)	0
眼障害	21 (10)	0
眼精疲労	1 (<1)	0
眼瞼炎	1 (<1)	0
結膜出血	2 (1)	0

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
結膜炎	4 (2)	0
複視	1 (<1)	0
眼乾燥	7 (3)	0
眼出血	1 (<1)	0
眼刺激	1 (<1)	0
眼痛	1 (<1)	0
眼部腫脹	3 (1)	0
眼充血	1 (<1)	0
黄疸眼	2 (1)	0
眼窩周囲浮腫	1 (<1)	0
羞明	1 (<1)	0
強膜出血	1 (<1)	0
霧視	2 (1)	0
視力障害	1 (<1)	0
胃腸障害	148 (70)	18 (9)
腹部不快感	7 (3)	0
腹部膨満	9 (4)	0
腹痛	23 (11)	3 (1)
下腹部痛	1 (<1)	0
上腹部痛	14 (7)	1 (<1)
肛門出血	1 (<1)	0
肛門そう痒症	1 (<1)	0
肛門潰瘍	2 (1)	0
肛門直腸不快感	3 (1)	0
アフタ性口内炎	1 (<1)	0
腹水	1 (<1)	0
盲腸炎	3 (1)	1 (<1)
口唇のひび割れ	3 (1)	0
口唇炎	1 (<1)	0
大腸炎	5 (2)	1 (<1)
便秘	20 (10)	0
下痢	61 (29)	8 (4)
口内乾燥	10 (5)	0
消化不良	13 (6)	0
嚥下障害	4 (2)	0
小腸炎	2 (1)	1 (<1)
腸炎	1 (<1)	0
便失禁	3 (1)	0
変色便	1 (<1)	1 (<1)
硬便	1 (<1)	0
鼓腸	5 (2)	0
胃炎	4 (2)	0
消化管運動過剰	1 (<1)	0
消化管運動障害	1 (<1)	0
胃食道逆流性疾患	2 (1)	0
歯肉萎縮	1 (<1)	0
歯肉出血	7 (3)	0
歯肉肥厚	1 (<1)	0

付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
歯肉痛	3 (1)	0
歯肉腫脹	1 (<1)	0
歯肉潰瘍	1 (<1)	0
歯肉炎	2 (1)	0
吐血	1 (<1)	0
血便排泄	3 (1)	0
痔出血	1 (<1)	0
痔核	11 (5)	0
裂孔ヘルニア	2 (1)	0
麻痺性イレウス	1 (<1)	1 (<1)
口唇乾燥	1 (<1)	0
口唇出血	1 (<1)	0
メレナ	2 (1)	0
口腔内出血	8 (4)	0
口腔内潰瘍形成	3 (1)	0
悪心	56 (27)	3 (1)
好中球減少性大腸炎	3 (1)	1 (<1)
嚥下痛	3 (1)	0
口腔浮腫	1 (<1)	0
食道痙攣	1 (<1)	0
食道炎	1 (<1)	0
口腔内不快感	2 (1)	0
口腔障害	4 (2)	0
口腔粘膜紅斑	1 (<1)	0
口腔内痛	2 (1)	0
排便痛	1 (<1)	0
肛門周囲痛	5 (2)	0
直腸出血	1 (<1)	0
小腸閉塞	2 (1)	0
口内炎	6 (3)	0
顎下腺腫大	1 (<1)	0
舌苔	4 (2)	0
舌変色	1 (<1)	0
舌障害	1 (<1)	0
地図状舌	1 (<1)	0
舌潰瘍	1 (<1)	0
嘔吐	28 (13)	0
一般・全身障害および投与部位の状態	128 (61)	19 (9)
無力症	20 (10)	1 (<1)
腋窩痛	2 (1)	0
カテーテル留置部位出血	2 (1)	0
カテーテル留置部位分泌物	1 (<1)	0
カテーテル留置部位紅斑	20 (10)	0
カテーテル留置部位浮腫	1 (<1)	0
カテーテル留置部位疼痛	5 (2)	0
カテーテル留置部位発疹	1 (<1)	0
カテーテル留置部位腫脹	2 (1)	0
胸部不快感	3 (1)	0

付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
胸痛	8 (4)	0
悪寒	22 (10)	1 (<1)
医療機器閉塞	1 (<1)	0
不快感	1 (<1)	0
疾患進行	1 (<1)	1 (<1)
薬物相互作用	2 (1)	1 (<1)
顔面浮腫	1 (<1)	0
疲労	14 (7)	0
全身性浮腫	5 (2)	3 (1)
高熱	1 (<1)	0
硬結	1 (<1)	0
注入部位小水疱	2 (1)	0
注射部位出血	1 (<1)	0
局所腫脹	1 (<1)	0
倦怠感	1 (<1)	0
粘膜の炎症	29 (14)	5 (2)
多臓器不全	2 (1)	2 (1)
非心臓性胸痛	1 (<1)	0
浮腫	2 (1)	0
末梢性浮腫	33 (16)	1 (<1)
穿刺部位疼痛	1 (<1)	1 (<1)
発熱	59 (28)	6 (3)
医療機器関連の血栓症	4 (2)	0
肝胆道系障害	12 (6)	3 (1)
胆石症	1 (<1)	0
胆汁うっ滞	1 (<1)	0
肝細胞融解性肝炎	1 (<1)	1 (<1)
肝嚢胞	1 (<1)	0
肝不全	1 (<1)	0
肝機能異常	1 (<1)	1 (<1)
肝毒性	1 (<1)	0
高ビリルビン血症	3 (1)	0
黄疸	2 (1)	1 (<1)
免疫系障害	14 (7)	3 (1)
急性腸管移植片対宿主病	1 (<1)	0
薬物過敏症	2 (1)	1 (<1)
食物アレルギー	1 (<1)	0
移植片対宿主病	3 (1)	2 (1)
腸管移植片対宿主病	2 (1)	0
皮膚移植片対宿主病	3 (1)	0
低γグロブリン血症	3 (1)	0
季節性アレルギー	1 (<1)	0
感染症および寄生虫症	108 (51)	31 (15)
アシネトバクター感染	1 (<1)	0
肛門膿瘍	1 (<1)	1 (<1)
菌血症	6 (3)	1 (<1)
細菌感染	2 (1)	1 (<1)

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
BK ウイルス感染	1 (<1)	0
細気管支炎	3 (1)	0
気管支肺アスペルギルス症	2 (1)	0
カンジダ症	1 (<1)	0
カテーテル留置部位感染	1 (<1)	0
蜂巣炎	5 (2)	1 (<1)
クロストリジウム感染	6 (3)	1 (<1)
クロストリジウム・ディフィシレ大腸炎	5 (2)	0
膀胱炎	1 (<1)	0
サイトメガロウイルス感染	10 (5)	1 (<1)
サイトメガロウイルス血症	5 (2)	0
医療機器関連感染	4 (2)	1 (<1)
腸球菌感染	2 (1)	1 (<1)
腸球菌性敗血症	1 (<1)	0
エプスタイン・バーウイルス感染	1 (<1)	0
大腸菌性菌血症	1 (<1)	0
大腸菌感染	1 (<1)	0
毛包炎	4 (2)	0
真菌感染	3 (1)	1 (<1)
ノロウイルス性胃腸炎	1 (<1)	0
陰部ヘルペス	1 (<1)	0
ジアルジア症	1 (<1)	0
歯肉膿瘍	1 (<1)	0
単純ヘルペス	8 (4)	1 (<1)
麦粒腫	1 (<1)	0
ヒトヘルペスウイルス6感染	1 (<1)	0
感染	5 (2)	3 (1)
注入部位感染	1 (<1)	0
クレブシエラ感染	3 (1)	2 (1)
喉頭炎	1 (<1)	0
下気道感染	2 (1)	1 (<1)
真菌性下気道感染	1 (<1)	0
肺感染	1 (<1)	1 (<1)
メタニューモウイルス感染	1 (<1)	0
鼻咽頭炎	2 (1)	0
好中球減少性敗血症	1 (<1)	1 (<1)
食道カンジダ症	1 (<1)	0
口腔カンジダ症	2 (1)	0
口腔ヘルペス	5 (2)	0
口腔感染	1 (<1)	0
パラインフルエンザウイルス感染	2 (1)	1 (<1)
爪囲炎	1 (<1)	0
咽頭炎	2 (1)	0
ニューモシスティスジロヴェシ肺炎	1 (<1)	1 (<1)
肺炎	7 (3)	3 (1)
細菌性肺炎	2 (1)	0
RS ウイルス肺炎	1 (<1)	1 (<1)
シュードモナス性菌血症	3 (1)	2 (1)
シュードモナス性敗血症	2 (1)	1 (<1)

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
（器官別大分類及び基本語別、発現割合 0%超）
（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
シュードモナス感染	1 (<1)	1 (<1)
歯髄炎	1 (<1)	0
気道感染	1 (<1)	0
敗血症	5 (2)	5 (2)
敗血症性ショック	2 (1)	2 (1)
副鼻腔炎	2 (1)	1 (<1)
皮膚感染	1 (<1)	0
ブドウ球菌性菌血症	7 (3)	1 (<1)
ブドウ球菌感染	2 (1)	1 (<1)
ブドウ球菌性敗血症	1 (<1)	1 (<1)
レンサ球菌性菌血症	1 (<1)	0
レンサ球菌性敗血症	1 (<1)	1 (<1)
皮下組織膿瘍	1 (<1)	0
重複感染	1 (<1)	0
全身性真菌症	1 (<1)	1 (<1)
歯膿瘍	1 (<1)	0
上気道感染	1 (<1)	0
尿路感染	2 (1)	0
腸球菌性尿路感染	1 (<1)	0
腟膿瘍	1 (<1)	1 (<1)
ウイルス感染	1 (<1)	0
接合真菌症	1 (<1)	0
傷害、中毒および処置合併症	28 (13)	4 (2)
アレルギー性輸血反応	2 (1)	0
咬刺傷	1 (<1)	0
挫傷	3 (1)	0
擦過傷	3 (1)	0
上腕骨骨折	1 (<1)	1 (<1)
眼窩周囲血腫	1 (<1)	0
処置による疼痛	5 (2)	0
引っかき傷	1 (<1)	0
サンバーン	1 (<1)	0
各種物質毒性	1 (<1)	0
輸血反応	9 (4)	2 (1)
移植不全	1 (<1)	1 (<1)
血管確保合併症	1 (<1)	0
創部分泌	1 (<1)	0
臨床検査	75 (36)	13 (6)
アシネトバクター検査陽性	1 (<1)	0
活性化部分トロンボプラスチン時間延長	3 (1)	0
アラニンアミノトランスフェラーゼ増加	15 (7)	2 (1)
アスパラギン酸アミノトランスフェラーゼ増加	12 (6)	1 (<1)
細菌検査陽性	7 (3)	0
芽球細胞陽性	1 (<1)	1 (<1)
血中アルブミン減少	4 (2)	0
血中アルカリホスファターゼ増加	6 (3)	0
血中ビリルビン増加	8 (4)	5 (2)
血中クレアチニン増加	6 (3)	2 (1)

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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
血液培養陽性	2 (1)	0
血中ブドウ糖増加	1 (<1)	0
血中免疫グロブリン G 減少	1 (<1)	0
血中乳酸脱水素酵素増加	1 (<1)	0
血中マグネシウム減少	1 (<1)	0
血中リン減少	1 (<1)	0
血中カリウム減少	8 (4)	1 (<1)
血中尿素増加	1 (<1)	0
呼吸音異常	6 (3)	0
クロストリジウム検査陽性	1 (<1)	0
心電図 QT 延長	2 (1)	1 (<1)
心電図異常 T 波	1 (<1)	0
心電図 T 波振幅減少	1 (<1)	0
心電図2相性 T 波	1 (<1)	0
心電図 T 波逆転	1 (<1)	0
エンテロバクター検査陽性	1 (<1)	0
ヘモグロビン減少	3 (1)	1 (<1)
ヘモフィルス検査陽性	1 (<1)	0
心拍数不整	1 (<1)	0
肝酵素上昇	4 (2)	1 (<1)
INR 増加	5 (2)	0
肝機能検査異常	5 (2)	1 (<1)
酸素飽和度低下	3 (1)	0
血小板数減少	2 (1)	0
総蛋白減少	1 (<1)	0
総蛋白増加	1 (<1)	0
プロトロンビン時間延長	1 (<1)	0
QRS 軸異常	1 (<1)	0
ラオウルテラ検査陽性	1 (<1)	0
トランスアミナーゼ上昇	1 (<1)	1 (<1)
尿量減少	2 (1)	0
尿量増加	1 (<1)	0
ウイルス負荷増加	1 (<1)	0
体重減少	3 (1)	0
体重増加	6 (3)	1 (<1)
白血球数減少	2 (1)	1 (<1)
代謝および栄養障害	89 (42)	17 (8)
食欲減退	17 (8)	0
脱水	5 (2)	0
水分過負荷	3 (1)	0
体液貯留	6 (3)	0
痛風	1 (<1)	0
高血糖	4 (2)	0
高カリウム血症	1 (<1)	0
高リン酸塩血症	3 (1)	0
高尿酸血症	1 (<1)	0
低アルブミン血症	8 (4)	2 (1)
低カルシウム血症	13 (6)	1 (<1)

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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
低血糖症	2 (1)	0
低カリウム血症	46 (22)	7 (3)
低マグネシウム血症	20 (10)	1 (<1)
低ナトリウム血症	4 (2)	2 (1)
過小食	1 (<1)	0
低リン酸血症	17 (8)	6 (3)
低蛋白血症	1 (<1)	0
血液量減少症	2 (1)	0
代謝性アシドーシス	2 (1)	1 (<1)
腫瘍崩壊症候群	1 (<1)	0
ビタミン K 欠乏	1 (<1)	0
筋骨格系および結合組織障害	45 (21)	2 (1)
関節痛	4 (2)	0
関節炎	1 (<1)	0
背部痛	13 (6)	0
骨痛	2 (1)	0
胂径部痛	3 (1)	0
関節硬直	1 (<1)	0
関節腫脹	1 (<1)	0
中足骨痛	1 (<1)	0
筋痙縮	3 (1)	0
筋力低下	3 (1)	0
筋骨格系胸痛	4 (2)	0
筋骨格痛	2 (1)	0
筋肉痛	3 (1)	1 (<1)
頚部痛	1 (<1)	0
四肢痛	10 (5)	1 (<1)
腱痛	1 (<1)	0
腱鞘炎	1 (<1)	0
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）	6 (3)	5 (2)
急性骨髄性白血病	3 (1)	2 (1)
再発急性骨髄性白血病	1 (<1)	1 (<1)
白血病	1 (<1)	1 (<1)
肺新生物	1 (<1)	0
真性多血症	1 (<1)	1 (<1)
T 細胞性前リンパ性白血病	1 (<1)	1 (<1)
神経系障害	57 (27)	3 (1)
味覚消失	1 (<1)	0
失語症	2 (1)	0
灼熱感	1 (<1)	0
認知障害	1 (<1)	0
意識レベルの低下	1 (<1)	0
注意力障害	2 (1)	0
浮動性めまい	13 (6)	0
味覚異常	1 (<1)	0
ジスキネジー	1 (<1)	0
頭部不快感	1 (<1)	0

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
頭痛	30 (14)	2 (1)
筋緊張亢進	1 (<1)	0
頭蓋内圧上昇	1 (<1)	0
嗜眠	1 (<1)	0
意識消失	1 (<1)	1 (<1)
錯感覚	1 (<1)	0
失神寸前の状態	3 (1)	0
下肢静止不能症候群	1 (<1)	0
坐骨神経痛	1 (<1)	0
感覚障害	1 (<1)	0
副鼻腔炎に伴う頭痛	1 (<1)	0
傾眠	1 (<1)	0
失神	3 (1)	0
咬舌	1 (<1)	0
振戦	2 (1)	0
第6脳神経障害	1 (<1)	0
精神障害	39 (19)	1 (<1)
異常な夢	1 (<1)	0
激越	3 (1)	0
不安	14 (7)	0
錯乱状態	2 (1)	0
抑うつ気分	1 (<1)	0
うつ病	3 (1)	0
幻覚	2 (1)	0
幻聴	1 (<1)	0
不眠症	15 (7)	0
大うつ病	1 (<1)	1 (<1)
神経過敏	1 (<1)	0
睡眠障害	5 (2)	0
自殺念慮	1 (<1)	1 (<1)
腎および尿路障害	32 (15)	4 (2)
膀胱痙縮	2 (1)	0
出血性膀胱炎	2 (1)	0
排尿困難	11 (5)	0
糖尿	1 (<1)	0
血尿	5 (2)	0
ヘモグロビン尿	1 (<1)	0
失禁	1 (<1)	0
尿意切迫	2 (1)	0
頻尿	3 (1)	0
多尿	1 (<1)	0
蛋白尿	1 (<1)	0
腎不全	5 (2)	1 (<1)
急性腎不全	3 (1)	2 (1)
慢性腎不全	1 (<1)	1 (<1)
腎機能障害	2 (1)	0
尿失禁	2 (1)	0
尿閉	1 (<1)	0

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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
生殖系および乳房障害	9 (4)	0
乳汁漏出症	1 (<1)	0
陰茎出血	1 (<1)	0
陰嚢障害	1 (<1)	0
陰嚢浮腫	1 (<1)	0
陰嚢痛	1 (<1)	0
陰嚢潰瘍	1 (<1)	0
精巣障害	1 (<1)	0
膣出血	2 (1)	0
膣潰瘍	1 (<1)	0
呼吸器、胸郭および縦隔障害	94 (45)	12 (6)
急性呼吸不全	1 (<1)	1 (<1)
アレルギー性咳嗽	1 (<1)	0
無気肺	1 (<1)	0
気管支痙攣	3 (1)	1 (<1)
慢性閉塞性肺疾患	1 (<1)	1 (<1)
咳嗽	35 (17)	0
発声障害	1 (<1)	0
呼吸困難	17 (8)	1 (<1)
労作性呼吸困難	3 (1)	0
鼻出血	30 (14)	0
喀血	6 (3)	0
しゃっくり	2 (1)	1 (<1)
低酸素症	6 (3)	0
間質性肺疾患	1 (<1)	1 (<1)
肺硬化	1 (<1)	0
肺浸潤	4 (2)	0
鼻閉	6 (3)	0
鼻部不快感	1 (<1)	0
鼻乾燥	1 (<1)	0
口腔咽頭不快感	1 (<1)	0
口腔咽頭痛	12 (6)	0
咽頭紅斑	3 (1)	0
胸水	3 (1)	0
胸膜痛	3 (1)	2 (1)
湿性咳嗽	3 (1)	0
肺水腫	2 (1)	2 (1)
ラ音	4 (2)	0
呼吸異常	1 (<1)	0
呼吸窮迫	2 (1)	2 (1)
呼吸不全	3 (1)	2 (1)
鼻漏	7 (3)	0
くしゃみ	1 (<1)	0
頻呼吸	1 (<1)	1 (<1)
咽喉刺激感	1 (<1)	0
扁桃障害	1 (<1)	0
上気道咳症候群	1 (<1)	0
喘鳴	1 (<1)	0

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付録 2.7.6.2.22-2　すべての有害事象及び重度／生命を脅かす有害事象発現例数（%）
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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
皮膚および皮下組織障害	103 (49)	5 (2)
ざ瘡	1 (<1)	0
脱毛症	4 (2)	0
水疱	1 (<1)	0
血性水疱	2 (1)	0
皮膚乾燥	8 (4)	0
斑状出血	1 (<1)	0
湿疹	1 (<1)	0
紅斑	12 (6)	0
過剰肉芽組織	1 (<1)	0
皮下出血	1 (<1)	0
多汗症	3 (1)	0
嵌入爪	2 (1)	0
機械性蕁麻疹	2 (1)	0
寝汗	3 (1)	0
手掌紅斑	2 (1)	0
手掌・足底発赤知覚不全症候群	1 (<1)	0
ポードレンジ	1 (<1)	0
点状出血	19 (9)	1 (<1)
そう痒症	16 (8)	0
紫斑	3 (1)	0
発疹	34 (16)	1 (<1)
紅斑性皮疹	1 (<1)	0
全身性皮疹	2 (1)	0
斑状皮疹	2 (1)	0
斑状丘疹状皮疹	3 (1)	1 (<1)
丘疹性皮疹	1 (<1)	0
そう痒性皮疹	5 (2)	1 (<1)
レッドマン症候群	1 (<1)	0
皮膚変色	2 (1)	0
皮膚剥脱	1 (<1)	0
皮膚病変	6 (3)	0
皮膚腫瘤	1 (<1)	0
皮膚反応	1 (<1)	0
顔面腫脹	3 (1)	0
中毒性皮疹	1 (<1)	0
蕁麻疹	6 (3)	1 (<1)
外科および内科処置	6 (3)	0
収れん薬療法	3 (1)	0
中心静脈カテーテル除去	1 (<1)	0
腫瘤切除	1 (<1)	0
抜歯	1 (<1)	0
血管障害	44 (21)	3 (1)
潮紅	1 (<1)	0
血腫	5 (2)	0
出血	2 (1)	0
ほてり	1 (<1)	0
高血圧	23 (11)	2 (1)

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（ポサコナゾール新錠剤 300 mg コホート）（All Treated Subjects）（P05615 試験）（続き）

	Number of Subjects (%) All Treated Subjects POS 300 mg Cohort	
	All	Severe/Life-Threatening
高血圧クリーゼ	1 (<1)	0
低血圧	13 (6)	1 (<1)
起立性低血圧	1 (<1)	0
血栓性静脈炎	2 (1)	0
表在性血栓性静脈炎	1 (<1)	0
血管炎	1 (<1)	0
静脈血栓症	1 (<1)	0
四肢静脈血栓症	1 (<1)	0

POS：ポサコナゾール
注：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有害事象を集計した。
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

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付録 2.7.6.2.22-3　死亡に至った重篤な副作用及びその他の重篤な副作用の叙述（P05615 試験）

P05615試験の重篤な副作用の叙述には、治験データベース及び Global Pharmacovigilance（GPV）データベースからの情報を記載した。

1)　割付番号[redacted] ポサコナゾール新錠剤200 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：腎不全

(1)　患者背景

既往歴：粘膜炎、下痢、悪心、嘔吐
合併症：急性骨髄性白血病（AML）、貧血（Grade 2）、好中球減少症（Grade 4）、血小板減少症（Grade 4）、腹痛
併用薬：トレチノイン

(2)　有害事象の経過

被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤200 mg の1日2回経口投与を受けた。同日、軽度の胸膜痛が発現した。治験薬投与2日目、ポサコナゾール新錠剤200 mg の1日1回経口投与を開始した。治験薬投与3日目、軽度のそう痒性皮疹が脚に発現した。治験薬投与6日目、生命を脅かす程度の好中球減少症（検査値未報告）が発現し、治療としてフィルグラスチムを投与した。治験薬投与7日目、中等度の発熱が発現し、治療としてバンコマイシンを投与した。治験薬投与8日目、生命を脅かす程度の血小板減少症が発現し、治療として血小板輸血を実施した。治験薬投与13日目、中等度の発熱は回復した。被験者の腎機能検査値は、試験開始前は基準範囲内であった。治験薬投与14日目、クレアチニンが344 µmol/L まで増加し、生命を脅かす程度の腎不全が発現した。同日、治験薬の投与を中止した。軽度の胸膜痛及び生命を脅かす程度の血小板減少症は回復したが、軽度の嘔吐が発現し、治療としてメトクロプラミド及びオンダンセトロンを投与した。血圧及び脈拍の測定値は以下のとおりであった。

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Day	Pulse (bpm)	Blood Pressure (mmHg)
治験薬投与開始5日前	92	121/76
治験薬投与1日目	80	105/59
治験薬投与2日目	70	115/71
治験薬投与3日目	104	118/75
治験薬投与8日目	92	134/83
治験薬投与終了後1日目	64	115/66
治験薬投与終了後2日目	72	135/90
治験薬投与終了後9日目	85	137/94

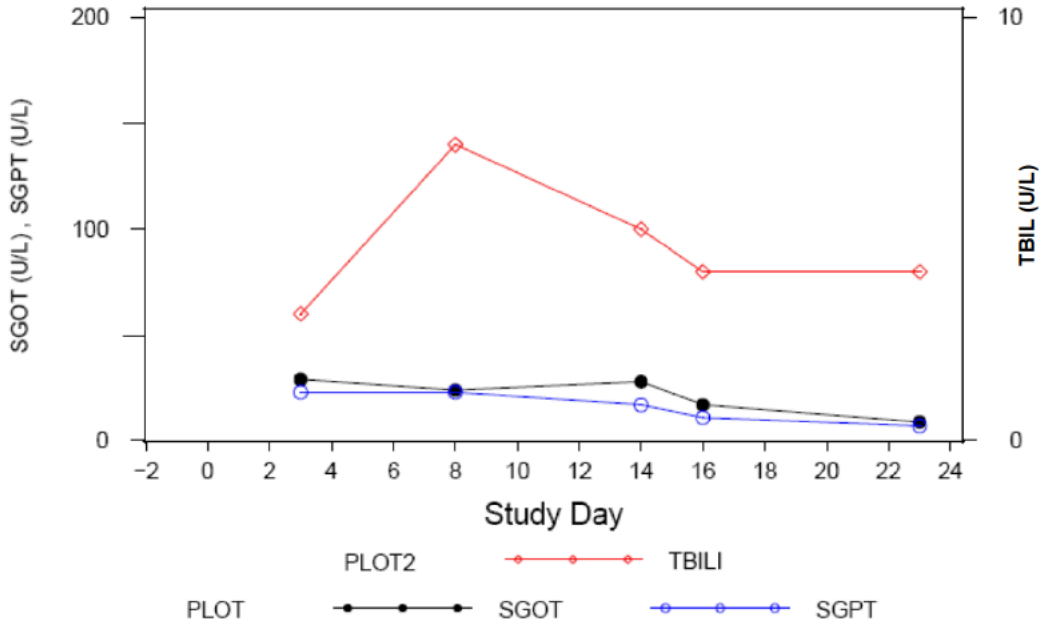
治験薬投与終了後1日目に実施した胸部・胸郭の X 線で異常が認められたが、臨床的に意味はないと判定された。同日、生命を脅かす程度の好中球減少症（検査値未報告）は回復した。治験薬投与終了後6日目、中等度の貧血（検査値未報告）が発現し、治療として赤血球製剤を投与した。同日、軽度の嘔吐は回復した。治験薬投与終了後8日目、中等度の貧血（検査値未報告）は回復した。治験薬投与終了後14日目、フロセミドの投与により腎不全は回復した。

治験担当医師は、腎不全は重篤な有害事象で程度は生命を脅かすものであり、バンコマイシンとの因果関係をたぶんありと判定し、治験薬との因果関係をどちらともいえないと判定した。

Day	Platelets (10^9/L)	NEUT (10^9/L)	BUN (mmol/L)	血清クレアチニン (μmol/L)
治験薬投与開始5日前	627	3.20	2.5	70
治験薬投与開始2日前	-	-	-	61
治験薬投与1日目	-	-	-	63
治験薬投与3日目	210	1.02	5.2	58
治験薬投与6日目	-	-	-	65
治験薬投与7日目	-	-	-	72
治験薬投与8日目	47	0.02	3.7	64
治験薬投与10日目	-	-	-	70
治験薬投与13日目	-	-	-	63
治験薬投与14日目	73	0.43	6.8	344
治験薬投与終了後1日目	-	-	-	495
治験薬投与終了後2日目	93	1.91	9.7	677
治験薬投与終了後3日目	-	-	-	725
治験薬投与終了後6日目	-	-	-	539
治験薬投与終了後8日目	-	-	-	345
治験薬投与終了後9日目	439	1.73	8.3	279
治験薬投与終了後10日目	-	-	-	230
治験薬投与終了後13日目	-	-	-	168
治験薬投与終了後15日目	-	-	-	141
治験薬投与終了後20日目	-	-	-	115

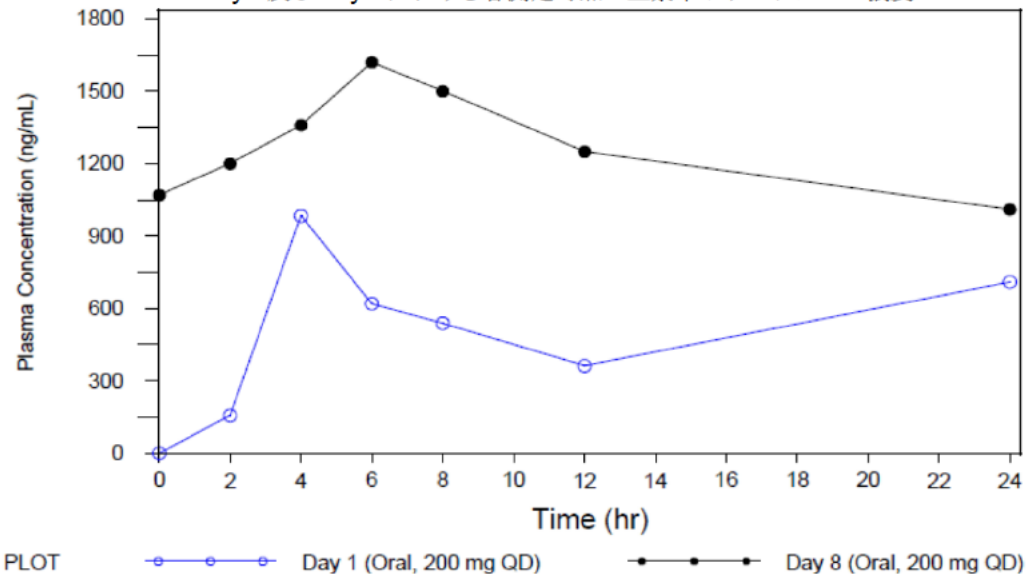
P05615 試験　　割付番号[redacted]

肝機能検査値の推移

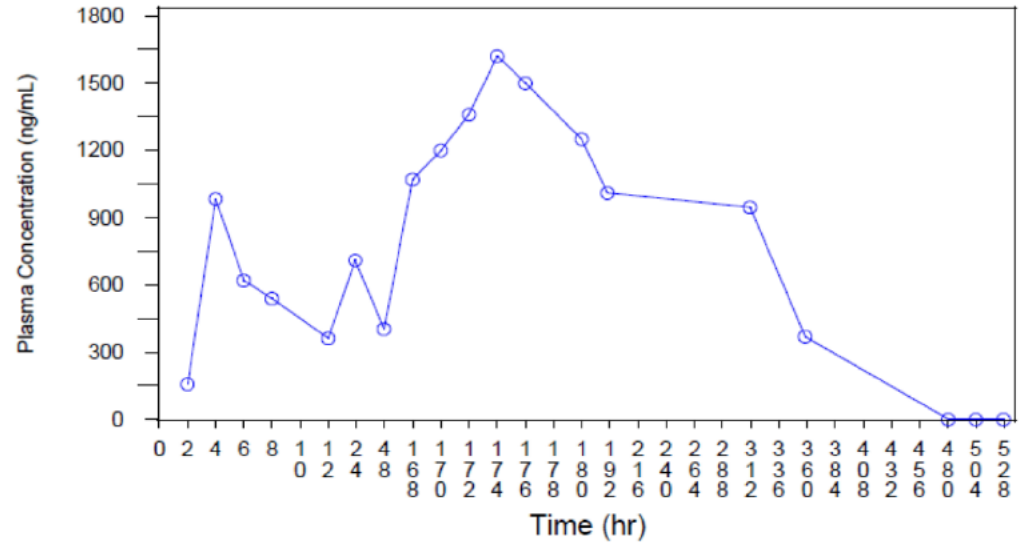


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P05615 試験　　割付番号[redacted]
Day 1 及び Day 8 における各測定時点の血漿中ポサコナゾール濃度



P05615 試験　　割付番号[redacted]
各測定時点の血漿中ポサコナゾール濃度
200 mg 1 日 1 回経口投与



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2)　割付番号[redacted]（ポサコナゾール新錠剤300 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：肝機能検査異常

(1)　患者背景

既往歴：同種骨髄移植、クロストリジウム感染

合併症：AML、腹痛、貧血、肛門潰瘍、菌血症、眼瞼炎（左眼）、労作性呼吸困難、疲労、発熱性好中球減少症（間欠性）、腫脹（せつによる、左大腿）、単純ヘルペス、間欠性の低マグネシウム血症、低ナトリウム血症（間欠性）、炎症（粘膜）、末梢性浮腫、汎血球減少症、皮膚潰瘍（殿溝）、皮膚潰瘍（左胸壁側面）、睡眠時無呼吸症候群、メチシリン耐性ブドウ球菌感染、頻脈

併用薬：シクロスポリン、ジフェンヒドラミン、ピペラシリン／タゾバクタム、アシクロビル、ヒドロモルフォン、バシトラシン、フロセミド、バンコマイシン

(2)　有害事象の経過

被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤300 mg の1日2回経口投与を受け、治験薬投与2日目にポサコナゾール新錠剤300 mg の1日1回経口投与を開始した。治験薬投与9日目、中等度の悪心が発現し、治療としてオンダンセトロン及びジフェンヒドラミンを投与した。治験薬投与12日目、軽度の左肺硬化が発現した。治験薬投与13日目、軽度の間欠性の下痢が発現し、体液バランス維持のためフロセミドを投与した。治験薬投与14日目、カリウム値の維持のためカリウムの投与を開始した。治験薬投与15日目、マグネシウム値の維持のためマグネシウムを投与した。治験薬投与16日目、カリウムの投与を終了した。治験薬投与20日目、中等度の肝機能検査値上昇により静脈内輸液が必要となり、被験者は入院した。同日、被験者は治験薬を服用しなかった。治験薬投与22日目、下痢が回復した。治験薬投与23日目、肝機能検査異常（検査値未報告）の有害事象により治験薬の投与を中止した。肝機能は改善したものの、回復日は報告されなかった。治験薬投与終了後5日目、血栓性血小板減少性紫斑病（TTP）により、被験者は入院した。同日に血漿製剤（1単位）を投与した。中等度の悪心、軽度の左肺硬化及び TTP の回復日は報告されなかった。

治験担当医師は、肝機能検査異常及び TTP は重篤な有害事象であり、肝機能検査異常と治験薬との因果関係はどちらともいえないと判定した。また、TTP の程度は生命を脅かすものであったが、治験薬との因果関係は考えにくいと判定した。

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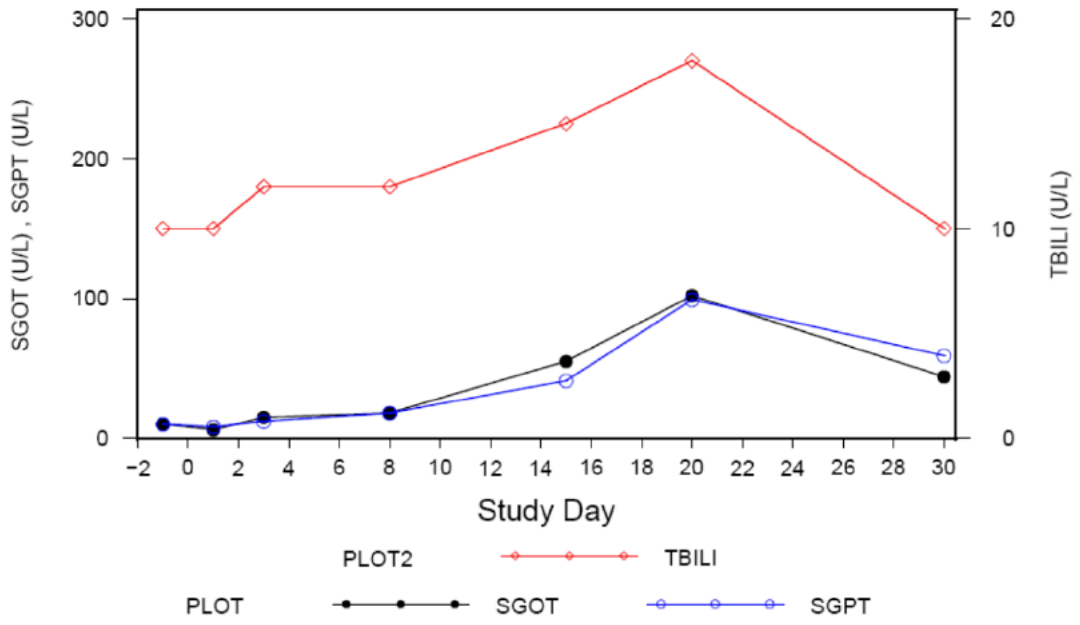
Day	血清クレアチニン (μmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	T. Bili (μmol/L)
治験薬投与開始1日前	106	10 (Low)	10	84	10
治験薬投与1日目	97	6 (Low)	8	90	10
治験薬投与3日目	115 (High)	15	12	112	12
治験薬投与8日目	141 (High)	18	18	140 (High)	12
治験薬投与15日目	115 (High)	55 (High)	41	141 (High)	15
治験薬投与20日目	-	102 (High)	99 (High)	194 (High)	18
治験薬投与終了後1日目	166 (High)	68 (High)	90	155 (High)	19 (High)
治験薬投与終了後1日目	177 (High)	-	-	149 (High)	-
治験薬投与終了後7日目	141 (High)	44 (High)	59 (High)	68	10
治験薬投与終了後13日目	119 (High)	19	28	74	5

Day	Platelets (10^9/L)	WBC (10^9/L)	NUET (10^9/L)
治験薬投与開始1日前	20 (Low)	0.2 (Low)	0.06 (Low)
治験薬投与開始1日前	-	0.1 (Low)	0.10 (Low)
治験薬投与1日目	22 (Low)	0.1 (Low)	0.05 (Low)
治験薬投与3日目	13 (Low)	0.1 (Low)	0.02 (Low)
治験薬投与8日目	27 (Low)	0.4 (Low)	0.22 (Low)
治験薬投与15日目	38 (Low)	3.7 (Low)	1.40 (Low)
治験薬投与終了後7日目	33 (Low)	13.9 (High)	11.11 (High)

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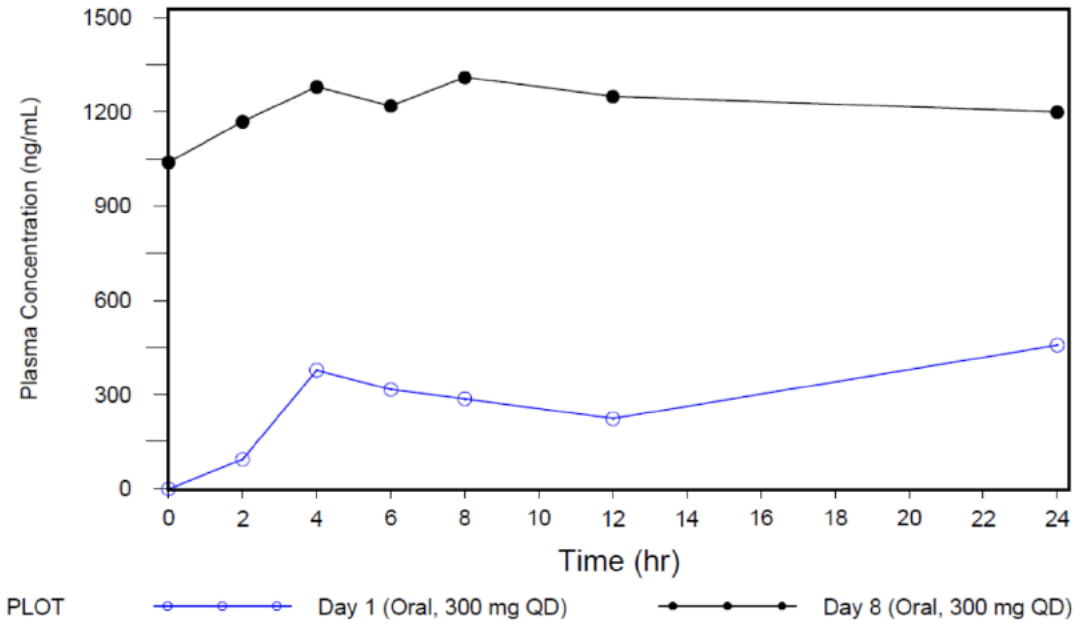
P05615 試験　　割付番号[redacted]

肝機能検査値の推移



P05615 試験　　割付番号[redacted]

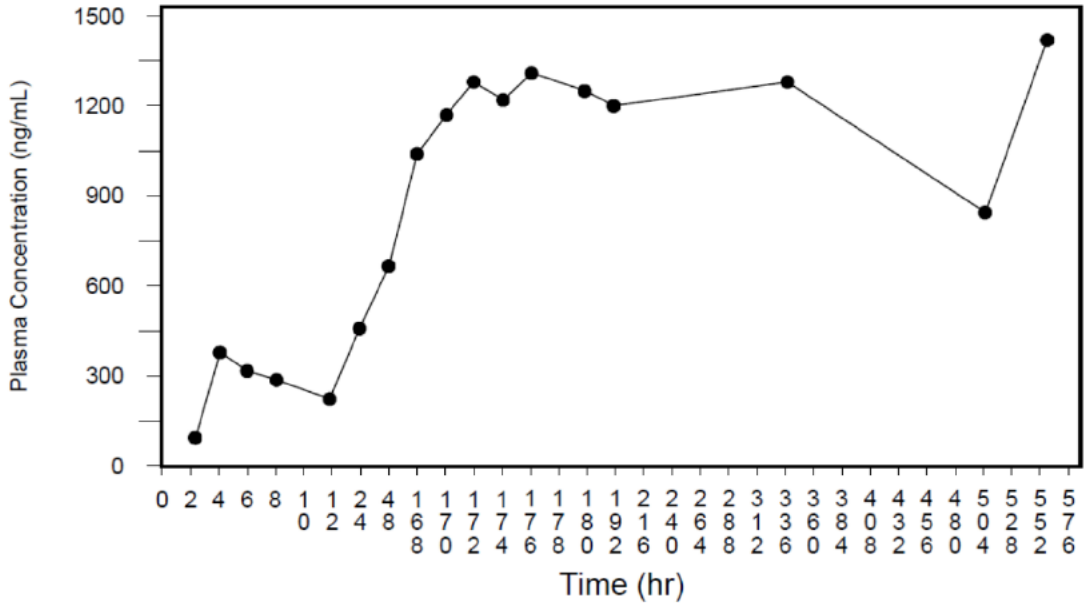
Day 1 及び Day 8 における各測定時点の血漿中ポサコナゾール濃度



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P05615 試験　　割付番号[redacted]

各測定時点の血漿中ポサコナゾール濃度
300 mg 1 日 1 回経口投与



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3)　割付番号[redacted]（ポサコナゾール新錠剤300 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：肝機能検査異常

(1)　患者背景

既往歴：下肢骨折、ヘルニア、顔面痛

合併症：AML、腎結石症、肥満、膀胱機能障害、貧血、血中カルシウム減少、呼吸音異常、悪寒（間欠性）、下痢、呼吸困難（間欠性）、疲労（間欠性）、発熱性好中球減少症（間欠性）、胃食道逆流性疾患、口腔単純ヘルペス、多汗症、低カリウム血症（間欠性）、低ナトリウム血症（間欠性）、悪心（間欠性）、口腔内痛、汎血球減少症、湿性咳嗽、発疹、頻脈、発熱性好中球減少症

併用薬：赤血球製剤、水酸化アルミニウム、パントプラゾール、ジフェンヒドラミン、血小板製剤、シプロフロキサシン、バンコマイシン

(2)　有害事象の経過

被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤300 mg の1日2回経口投与を受けた。治験薬投与2日目、ポサコナゾール新錠剤300 mg の1日1回経口投与を開始した。治験薬投与6日目、肝機能検査値が上昇し始め、同日の治験薬投与後に、肝機能検査異常の有害事象のため治験薬の投与を中断した。治験薬の投与中断中も肝機能検査値は上昇を続け、基準範囲上限（ULN）の10倍を超えたため、治験薬投与8日目にバンコマイシン及びバラシクロビルの投与を中止した。治験薬投与9日目、肝機能検査異常が悪化したため、治験薬の投与を中止した。治験薬投与終了後16日目、肝機能検査悪化（検査値未報告）は回復した。治験薬投与終了後52日目、生命を脅かす程度の発熱性好中球減少症（検査値未報告）が発現し、被験者は入院した。治験薬投与終了後55日目、重度の呼吸窮迫が発現し、被験者は集中治療室に搬送され、挿管された。治験薬投与終了後58日目、発熱性好中球減少症（検査値未報告）は回復した。治験薬投与終了後68日目、挿管を要した呼吸窮迫は回復した。

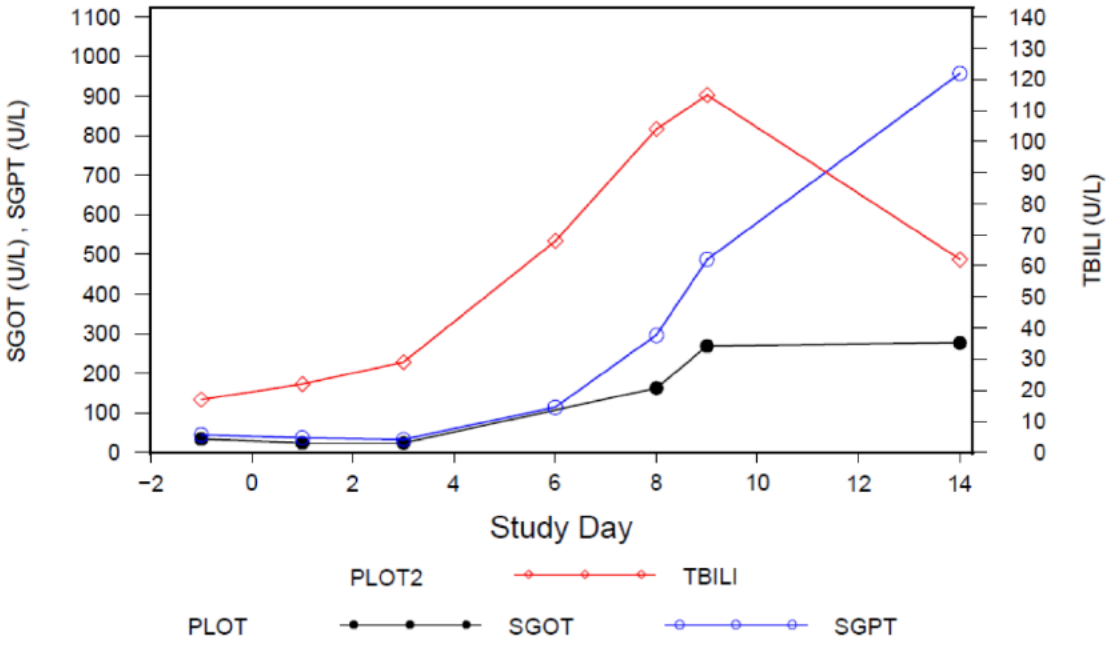
治験担当医師は、肝機能検査異常、発熱性好中球減少症及び呼吸窮迫は重篤な有害事象であり、肝機能検査異常及び発熱性好中球減少症の程度は生命を脅かすもので、肝機能検査異常と治験薬との因果関係はどちらともいえないと判定し、発熱性好中球減少症と治験薬との因果関係は考えにくいと判定した。また、呼吸窮迫は医学的に重要な事象で、本事象と治験薬との因果関係は考えにくいと判定した。

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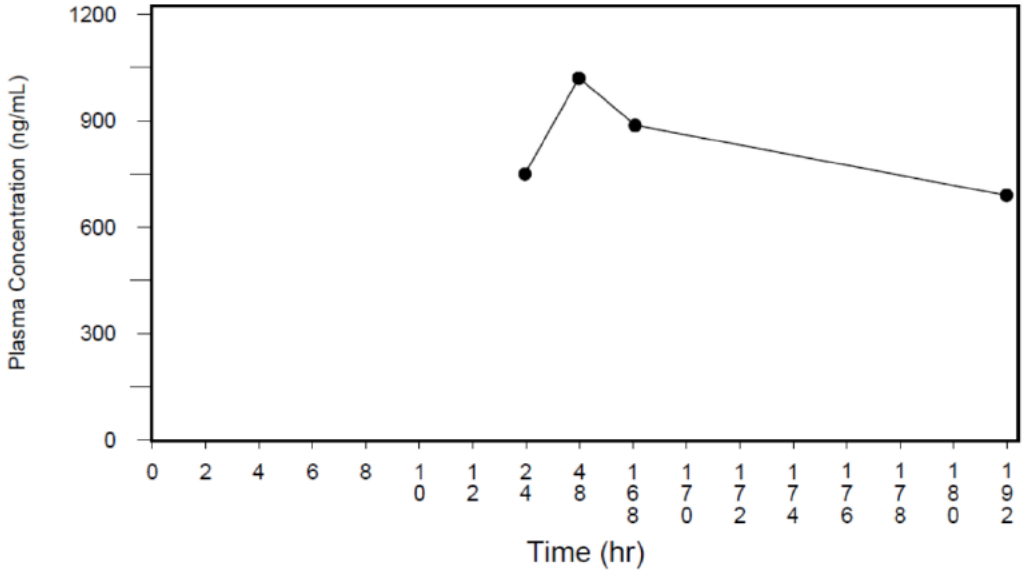
Day	AST (U/L)	ALT (U/L)	ALP (U/L)	T. Bili (μmol/L)
治験薬投与開始1日前	34	45 (High)	50	17
治験薬投与1日目	24	37 (High)	45	22 (High)
治験薬投与3日目	24	33	68	29 (High)
治験薬投与6日目	-	114 (High)	-	-
治験薬投与8日目	163 (High)	296 (High)	91	104 (High)
治験薬投与9日目	269 (High)	488 (High)	84	115 (High)
治験薬投与9日目	316 (High)	594 (High)	92	137 (High)
治験薬投与終了後5日目	277 (High)	958 (High)	123	62 (High)

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P05615 試験　　割付番号[redacted]
肝機能検査値の推移



P05615 試験　　割付番号[redacted]
各測定時点の血漿中ポサコナゾール濃度
300 mg 1 日 1 回経口投与



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4)　割付番号[redacted]　ポサコナゾール新錠剤300 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：血中クレアチニン増加、薬物相互作用

(1)　患者背景

既往歴：同種骨髄移植、AML、乳房嚢胞、心房細動、消化不良、頭痛、高リン酸塩血症、高血圧、高尿酸血症、低カルシウム血症、低カリウム血症、低マグネシウム血症、発熱、皮膚線条、口内炎（Grade 2）、悪心、嘔吐

合併症：裂孔ヘルニア

併用薬：フィトナジオン、シクロスポリン、パラセタモール、ニトレンジピン、カルシウム、カリウム、マグネシウム、デクストロプロポキシフェン、ピペラシリン／タゾバクタム、バンコマイシン、メトクロプラミド、オンダンセトロン、オメプラゾール

(2)　有害事象の経過

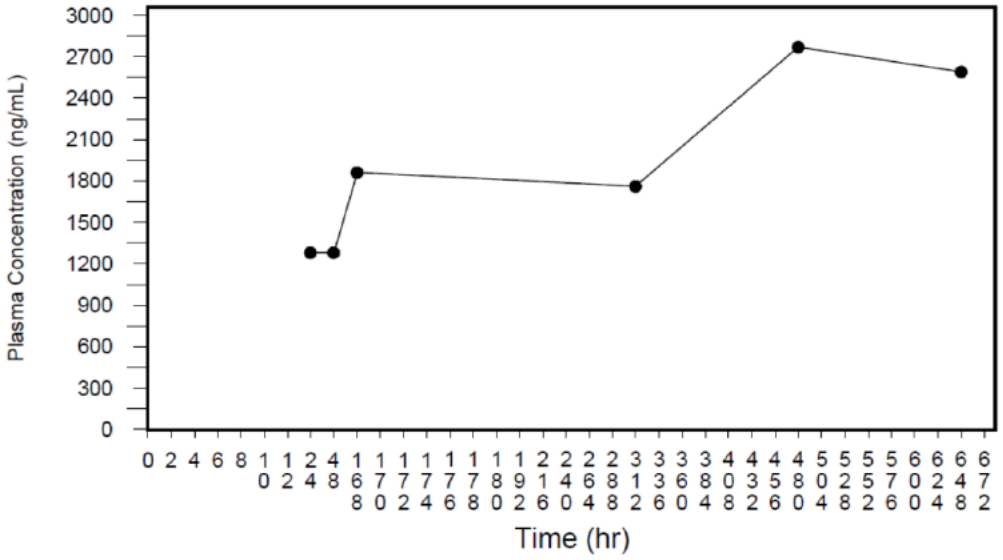
被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤300 mg の1日2回経口投与を受けた。同日、軽度の胃痛（有害事象名：上腹部痛）及び軽度の悪心が発現し、胃痛の治療として水酸化マグネシウム及びパラセタモールを投与した。治験薬投与開始時点で、被験者のクレアチニン値は基準範囲内であった。治験薬投与2日目、ポサコナゾール新錠剤300 mg の1日1回経口投与を開始した。治験薬投与3日目、中等度のサイトメガロウイルス（CMV）が再活性化し、治療としてガンシクロビルを静脈内投与した。治験薬投与6日目、胃痛は回復した。治験薬投与10日目、CMV 再活性化は回復した。治験薬投与13日目、トキソプラスマ及びニューモシスチスの予防のため、スルファメトキサゾール／トリメトプリムの投与を開始した。治験薬投与14日目、軽度の悪心は回復した。治験薬投与28日目、規定どおり治験薬の投与を終了した。治験薬投与終了後2日目、中等度の血中クレアチニン増加（2.3 mg/dL）が発現し、被験者は入院した。入院後、水分補給を実施、シクロスポリンの用量を減量し、スルファメトキサゾール／トリメトプリムの投与を中止した。シクロスポリンについては、減量以外の措置は取らなかった。同日、スルファメトキサゾール／トリメトプリムの投与を終了した。治験薬投与終了後6日目、クレアチニン値が1.6 mg/dL となり、被験者は退院した。治験薬投与終了後38日目、血中クレアチニン増加（2.3 mg/dL）は回復した。

治験担当医師は、シクロスポリン、スルファメトキサゾール及びトリメトプリムは、併用被疑薬と判定し、血中クレアチニン増加がシクロスポリンとの薬物相互作用によるものである可能性は除外できないとした。治験担当医師は、上腹部痛、悪心及び CMV 感染は非重篤な事象で、上腹部痛及び悪心と治験薬との因果関係はどちらともいえないと判定し、CMV 感染と治験薬との因果関係は考えにくいと判定した。また、血中クレアチニン増加及びシクロスポリンとの薬物相互作用はいずれも重篤な有害事象であり、治験薬との因果関係についてはどちらともいえないと判定した。

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Day	血清クレアチニン (μmol/L)	AST (U/L)	ALT (U/L)	LDH (U/L)	T. Bili (μmol/L)
治験薬投与開始7日前	95	16	22	160	8
治験薬投与1日目	97	-	-	323 (High)	-
治験薬投与3日目	116 (High)	18	8	288 (High)	9
治験薬投与8日目	93	-	-	380 (High)	-
治験薬投与14日目	136 (High)	23	11	345 (High)	11
治験薬投与21日目	146 (High)	24	15	295 (High)	12
治験薬投与28日目	240 (High)	33	17	417 (High)	10
治験薬投与終了後8日目	136 (High)	27	16	257 (High)	9
治験薬投与終了後38日目	124	-	-	-	-

P05615 試験　　割付番号[redacted]
各測定時点の血漿中ポサコナゾール濃度
300 mg 1 日 1 回経口投与



5)　割付番号[redacted]　ポサコナゾール新錠剤300 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：薬物相互作用、血中クレアチニン増加

(1)　患者背景

既往歴：同種骨髄移植、腹痛、背部痛、腰痛、下痢（化学療法後の胃腸毒性）、鼻出血（血小板減少症が原因）、大腸菌性菌血症、発熱性好中球減少症（胸部 X 線検査正常）、高尿酸血症、低マグネシウム血症、直腸膿瘍、皮膚病変（右大腿）（緑膿菌、アシネトバクター・バウマンニイ及びエンテロコッカス・フェカリスを分離）、口内炎（化学療法後の胃腸毒性）

合併症：CMV 感染、不眠症、移植片対宿主病

併用薬：アロプリノール、マグネシウム、シクロスポリン、ブロマゼパム、メチルプレドニゾロン

(2)　有害事象の経過

被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤300 mg の1日2回経口投与を受けた。治験薬投与2日目、ポサコナゾール新錠剤300 mg の1日1回経口投与を開始した。同日、中等度の血中クレアチニン増加が発現し、治療として塩化ナトリウム9%を投与、また軽度の低アルブミン血症（検査値未報告）が発現し、治療としてアルブミンを投与した。シクロスポリンとの薬物相互作用のため、被験者は入院した。治験薬投与3日目、軽度の低カリウム血症（カリウム3.5 mmol/L）が発現した。治験薬投与4日目、軽度の低 γ グロブリン血症が発現し、低 γ グロブリン血症の治療として免疫グロブリンを投与した。治験薬投与5日目、中等度のヘモグロビン尿及び中等度の血中ビリルビン増加（検査値未報告）が認められ、血中ビリルビン増加の治療としてブデソニド及びウルソデオキシコール酸を投与した。治験薬投与7日目、軽度の低アルブミン血症（検査値未報告）及び軽度の低カリウム血症（検査値未報告）は回復した。治験薬投与8日目の治験薬投与後に、シクロスポリンとの薬物相互作用による血中クレアチニン増加（256 µmol/L）が悪化して重度と判定され、このためポサコナゾールの投与を中断し、入院を延長した。同日、中等度の血小板減少症（血小板数33,700/MMC）及び軽度の高リン酸塩血症が発現した。治験薬投与12日目、被験者は退院し、ポサコナゾール新錠剤300 mg の1日1回経口投与を再開した。治験薬投与13日目、血小板減少症（血小板数6,000 mm^2）及び血中クレアチニン増加（2.7 mg/dL）のため被験者は再入院した。移植後のシクロスポリン（被疑薬）に関連した血栓性微小血管症性貧血（有害事象名：微小血管症性溶血性貧血）（有害事象の一覧[資料5.3.7.3.1: P05615_ae]では治験薬投与2日目に重篤な有害事象として報告された）及び鼻出血（有害事象名：血小板減少症）が発現し、総ビリルビン増加（2.96 mg/dL）、血中乳酸脱水素酵素（LDH）増加（783 U/L）及び“hemospheicuria”が認められた（GPV データベースからの情報）。治験薬投与14日目、血小板減少症の治療として免疫グロブリンの投与を再開した。治験薬投与15日目、軽度の体重減少が認められた。治験薬投与16日目、微小血管症性溶血性貧血のた

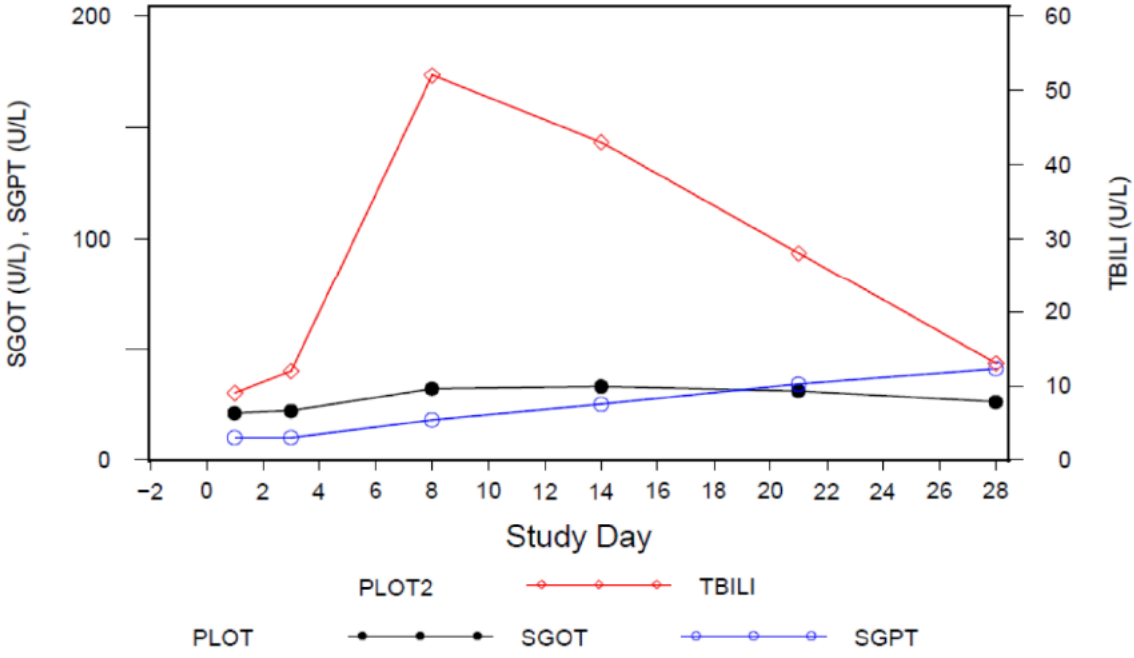
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め治験薬の投与を中止した。同日、高リン酸塩血症が回復した。治験薬投与終了後2日目、メロペネムの投与を開始した。治験薬投与終了後3日目、鼻出血及び血小板減少症（検査値未報告）は回復し、被験者は退院した。同日、血小板減少症の治療としての免疫グロブリン投与を終了した。治験薬投与終了後8日目、中等度の血中ビリルビン増加（検査値未報告）が回復した。治験薬投与終了後12日目、薬物相互作用及び血中クレアチニン増加（122 µmol/L）が回復した。非重篤な有害事象については、治験薬投与終了後64日目にヘモグロビン尿が回復し、治験薬投与終了後85日目に低γグロブリン血症が回復し、治験薬投与終了後169日目に血小板減少症（検査値未報告）が回復した。軽度の体重減少の回復日は報告されなかった。

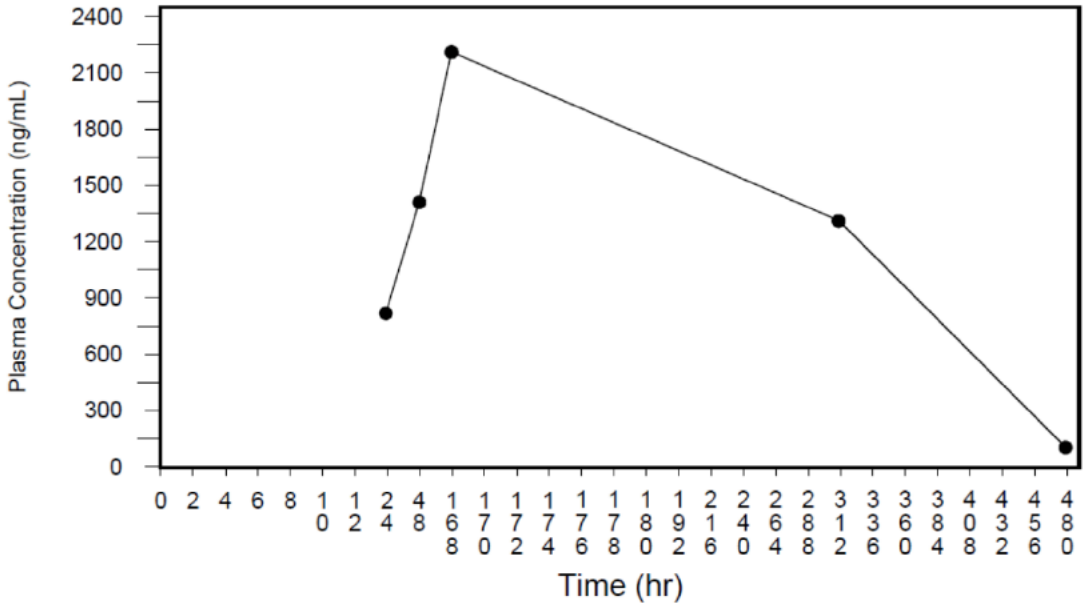
治験担当医師は、薬物相互作用、血中クレアチニン増加、微小血管症性溶血性貧血及び血小板減少症（2回発現：治験薬投与8日目及び治験薬投与13日目）は重篤な有害事象であり、薬物相互作用及び血中クレアチニン増加と治験薬との因果関係はどちらともいえないと判定した。また、微小血管症性溶血性貧血及び血小板減少症と治験薬との因果関係は考えにくいと判定した。

Day	Platelets (10^9/L)	血清クレアチニン (mg/dL)	AST (U/L)	ALT (U/L)	T. Bili (µmol/L)
治験薬投与開始6日前	-	1.3	-	-	-
治験薬投与開始5日前	103 (Low)	1.3	27	8	9
治験薬投与開始4日前	-	1.2	-	-	-
治験薬投与開始3日前	-	1.4	-	-	-
治験薬投与開始2日前	-	1.4	-	-	-
治験薬投与開始1日前	-	1.4	-	-	-
治験薬投与1日目	54 (Low)	1.5	21	10	9
治験薬投与2日目	-	1.7	-	-	-
治験薬投与3日目	64 (Low)	2.1	22	10	12
治験薬投与8日目	32 (Low)	-	32	18	52 (High)
治験薬投与13日目	-	2.7	-	-	-
治験薬投与14日目	14 (Low)	-	33	25	43 (High)
治験薬投与終了後5日目	24 (Low)	-	31	34	28 (High)
治験薬投与終了後12日目	38 (Low)	-	26	41	13

P05615 試験　　割付番号[redacted]
肝機能検査値の推移



P05615 試験　　割付番号[redacted]
各測定時点の血漿中ポサコナゾール濃度
300 mg 1 日 1 回経口投与



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6)　割付番号[redacted]　ポサコナゾール新錠剤300 mg を食事条件を規定せず1日1回経口投与）
その他の重篤な副作用名：慢性腎不全

(1)　患者背景

既往歴：同種骨髄移植、虫垂炎、虫垂切除歴、発熱性好中球減少症

合併症：骨髄異形成症候群、AML、高血圧、CMV 感染、慢性腎不全（部分的回復を伴う）、振戦（手、タクロリムスとの因果関係が疑われる）、腸炎、低アルブミン血症、胆石症、腎嚢胞、水腫性胆嚢炎

併用薬：タクロリムス、メトロニダゾール、メトクロプラミド、イミペネム、リネゾリド

(2)　有害事象の経過

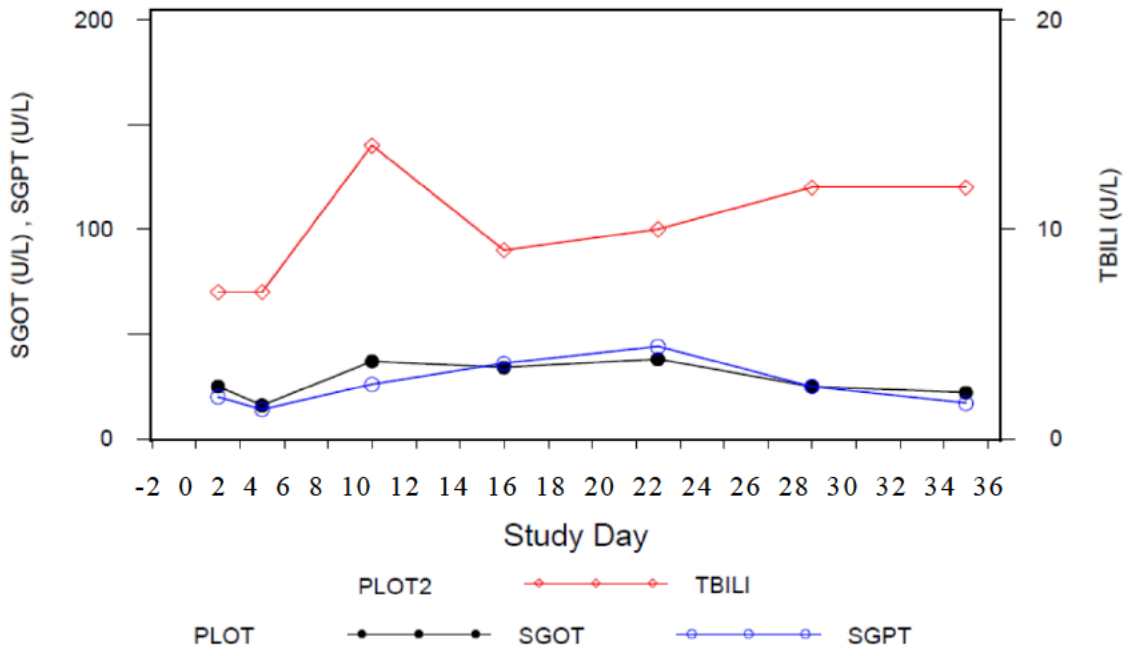
被験者（[redacted]歳、[redacted]性）は、治験薬投与1日目にポサコナゾール新錠剤300 mg の1日2回経口投与を受けた。同日、合併症の水腫性胆嚢炎が回復した。治験薬投与2日目、ポサコナゾール新錠剤300 mg の1日1回経口投与を開始した。治験薬投与4日目に合併症の腸炎は回復したが、治験薬投与6日目までイミペネム及びリネゾリドを投与し、治験薬投与7日目に被験者は退院した。非重篤な有害事象として、治験薬投与8日目に中等度の慢性腎不全が認められた。治験薬投与15日目、中等度の下痢が発現した。治験薬投与16日目、軽度の食欲減退が発現し、中等度の下痢は回復した。治験薬投与20日目、中等度の慢性腎不全は回復した。治験薬投与21日目、中等度の腹痛及び中等度の胃炎が発現した。治験薬投与23日目、中等度の下痢が再発したが、同日中に回復した。治験薬投与25日目、中等度の胃炎は回復した。治験薬投与28日目、規定どおり治験薬の投与を終了した。臨床検査の結果、血清尿素増加（94 mg/dL、基準範囲10～50 mg/dL）、血清クレアチニン増加（4.61 mg/dL、基準範囲0.7～1.2 mg/dL）、尿酸増加（9.3 mg/dL、基準範囲3.4～7.0 mg/dL）が認められ、クレアチニンクリアランス（CCr）（計算値）は14であり、被験者は Grade 4の慢性腎不全と診断された。浮腫は認められず、カリウム値は基準範囲内であった。また、被験者は Grade 1の食欲不振（有害事象名：食欲減退）と診断されていた。治験薬投与終了後2日目、バルガンシクロビル（被疑薬）の投与を中断した後、血液生化学検査値は緩やかに改善し、血清クレアチニン及び血中尿素は減少し、治験担当医師により、CCr（計算値）は部分的に回復したと判定された。治験薬投与終了後2日目、慢性腎不全は改善して Grade 3と判定され、更に治験薬投与終了後7日目に Grade 2まで回復した。軽度の食欲減退及び慢性腎不全の回復日は報告されなかった。

治験担当医師は、慢性腎不全及び腸炎は重篤な有害事象であり、慢性腎不全は医学的に重要であるとし、治験薬との因果関係はどちらともいえないと判定した。また、腸炎と治験薬との因果関係は考えにくいと判定した。

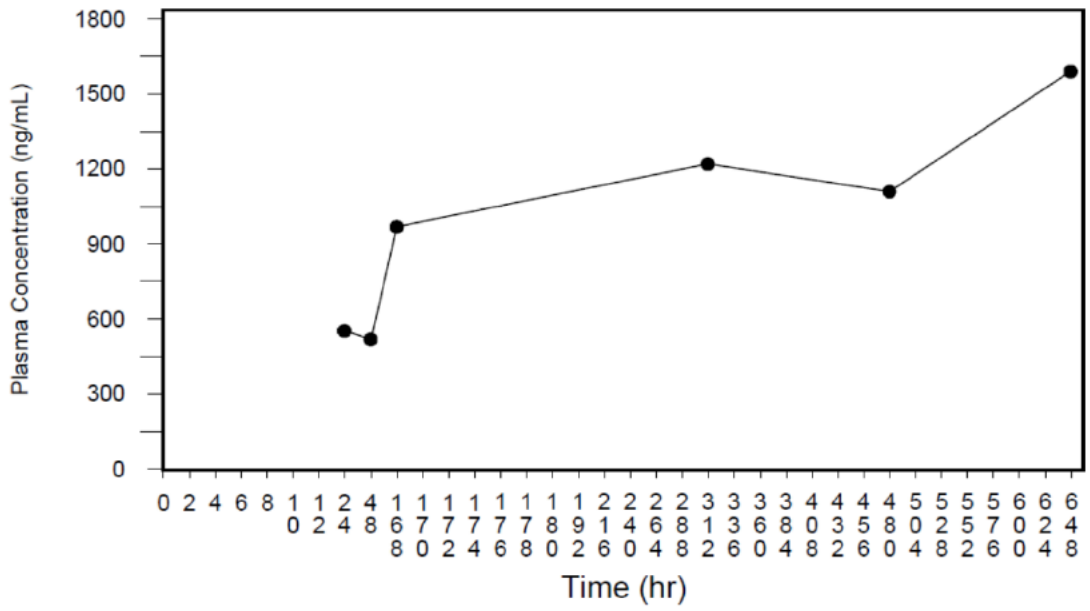
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Day	WBC (10^9/L)	NEUT (10^9/L)	血清クレアチニン (μmol/L)	AST (U/L)	ALT (U/L)	Temp. (°C)
治験薬投与開始7日前	0.8 (Low)	0.23 (Low)	106	28	39	38.5
治験薬投与1日目	6.0	5.17	97	25	20	37.2
治験薬投与2日目	-	-	-	-	-	36.6
治験薬投与3日目	1.9 (Low)	1.16 (Low)	115	16	14	36.6
治験薬投与8日目	3.0 (Low)	2.06	159 (High)	37 (High)	26	36.5
治験薬投与14日目	2.1 (Low)	1.51 (Low)	186 (High)	34	36	36.9
治験薬投与21日目	3.7 (Low)	3.21	256 (High)	38 (High)	44 (High)	37
治験薬投与28日目	1.4 (Low)	0.76 (Low)	407 (High)	25	25	36.8
治験薬投与終了後7日目	1.5 (Low)	0.89 (Low)	221 (High)	22	17	36.7

P05615 試験　　割付番号[redacted]
肝機能検査値の推移



P05615 試験　　割付番号[redacted]
各測定時点の血漿中ポサコナゾール濃度
300 mg 1 日 1 回経口投与



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