

アクテムラ皮下注162 mg シリンジ・AI
(トシリズマブ (遺伝子組換え))
[大型血管炎]

第2部 (モジュール2) : CTD の概要 (サマリー)

2.7 臨床概要

2.7.1 生物薬剤学試験及び関連する分析法

中外製薬株式会社

略語一覧

略語	英名	和名
■	■	■
ELISA	enzyme-linked immunosorbent assay	酵素免疫測定法
IL-6	interleukin 6	インターロイキン6
IL-6R	interleukin 6 receptor	インターロイキン6レセプター
SC法	screening Method	スクリーニング法

目次

	<u>頁</u>
2.7 臨床概要.....	4
2.7.1 生物薬剤学試験及び関連する分析法.....	4
2.7.1.1 背景及び概観.....	4
2.7.1.1.1 分析法.....	4
2.7.1.2 個々の試験結果の要約.....	5
2.7.1.3 全試験を通しての結果の比較と解析.....	5
2.7.1.4 付録.....	5

2.7 臨床概要

2.7.1 生物薬剤学試験及び関連する分析法

2.7.1.1 背景及び概観

トシリズマブは、ヒト IL-6レセプター（以降、IL-6R）に結合し、IL-6R と IL-6の結合を競合的に阻害することで IL-6シグナル伝達を阻害するヒト化抗ヒト IL-6R モノクローナル抗体である。トシリズマブの点滴静注用製剤は2005年4月に製造販売承認を取得し、皮下注製剤は2013年3月に製造販売承認を取得している。

本邦において高安動脈炎患者を対象とした第 III 相試験（以降、MRA632JP 試験）及び海外において巨細胞性動脈炎患者を対象とした第 III 相試験（以降、WA28119試験）の2試験を実施し、有効性及び安全性が示されたことから、「大型血管炎（高安動脈炎，巨細胞性動脈炎）」（1週間隔での皮下投与）の効能・効果，及び用法・用量の追加を目的とした承認事項一部変更承認申請を行うこととした。なお，MRA632JP 試験と WA28119試験では同じ皮下注製剤が使用された。

2.7.1.1.1 分析法

MRA632JP 試験において用いられた血清中トシリズマブ濃度測定法及び血清中抗トシリズマブ抗体（SC 法）測定法は，アクテムラ皮下注162 mg シリンジ・オートインジェクター承認時資料5.3.1.4-1項及び5.3.1.4-2項に記載した内容と同じである。抗トシリズマブ-Fab 抗体測定法及び抗トシリズマブ IgE 型抗体測定法は点滴静注用製剤の初回承認時資料へ項の「1.被験物質及びその定量法」に記載した内容と同じである。

WA28119試験において用いられた血清中トシリズマブ濃度測定法及び血清中抗トシリズマブ抗体（SC 法）測定法は，MRA632JP 試験において用いられた測定法を []（以降 []）に技術移管したものである。血清中抗トシリズマブ中和抗体測定法は [] にて確立された。抗トシリズマブ IgE 型抗体測定法は MRA632JP 試験において用いられた測定法と同じであり，株式会社 []（以降， []）で確立された。

各測定の実験施設を表 2.7.1.1.1-1 に示した。

表 2.7.1.1.1-1 各試験の測定施設

測定項目	MRA632JP 試験	WA28119試験
血清中トシリズマブ濃度測定	[]	[]
血清中抗トシリズマブ抗体（SC 法）測定	[]	[]
抗トシリズマブ-Fab 抗体測定	[]	—
血清中抗トシリズマブ中和抗体測定	—	[]
抗トシリズマブ IgE 型抗体測定	[]	[]

以下に， [] にて実施された各測定法のバリデーション試験の結果を示す。

(1) 血清中トシリズマブ濃度測定法

本測定法は， [] を固相化したプレートに [] 標識 [] を結合し，トシリズマブを含む試料を添加後， [] 標識 [] 及び [] 標識 [] でトシリズマブを検出する ELISA 法である。本測定の定量範囲は100～3200 ng/mL であった。測定内及び測定間再現性を検討した結果，いずれもその真度は100 ± 20% 以内，精度は20%以下（健康成人の血清に3200 ng/mL となるようトシリズマブを添加した試料の測定間再現性の精度が21.6%であった点を除く）であった。本測定法と MRA632JP 試

験に用いた血清中トシリズマブ濃度測定法とのクロスバリデーションを実施した結果は採用基準を満たした(5.3.1.4-1)。

(2) 血清中抗トシリズマブ抗体(SC法)測定法

本測定法は、XXXXXXXXXX標識トシリズマブ及びXXXX標識トシリズマブを用いたブリッジング ELISA 法である。XXXXXXXXXXを固相化したプレートにXXXXXXXXXX標識トシリズマブを結合させる。別途、抗トシリズマブ抗体を含む試料にXXXX標識トシリズマブを添加し、抗トシリズマブ抗体とXXXX標識トシリズマブの免疫複合体を形成させる。この免疫複合体をXXXXXXXXXX標識トシリズマブと反応させ、XXXXXXXXXX標識XXXXXXXXXXで検出する。測定ごとにカットポイントを設定することにより、陽性/陰性を判定した。陽性と判断された試料については、非特異的結合の影響を確認するため、トシリズマブを添加することにより吸収試験を実施した。吸収試験により陽性と判断された試料については、ウサギ抗トシリズマブ抗体を用いて作成した検量線より血清中抗トシリズマブ抗体濃度を算出した。検量線の定量範囲は0.781 ng-equivalents/mL~100 ng-equivalents/mL(血清中濃度に換算して7.81 ng-equivalents/mL~1000 ng-equivalents/mL)であった。測定内及び測定間再現性を検討した結果、いずれもその真度は $100 \pm 20\%$ 以内、精度は20%以下であった(5.3.1.4-2)。

(3) 血清中抗トシリズマブ中和抗体測定法

本測定法は、XXXXXXXXXX標識 IL-6R 及びXXXX標識トシリズマブを用いた ELISA 法である。XXXXXXXXXXを固相化したプレートにXXXXXXXXXX標識 IL-6R を結合させる。別途、抗トシリズマブ中和抗体を含む試料にXXXX標識トシリズマブを添加し、抗トシリズマブ中和抗体とXXXX標識トシリズマブの免疫複合体を形成させる。この免疫複合体を含む試料溶液を固相のXXXXXXXXXX標識 IL-6R と反応させる。抗トシリズマブ中和抗体とXXXX標識トシリズマブの免疫複合体はXXXXXXXXXX標識 IL-6R と結合できず、洗浄により除かれるが、抗トシリズマブ中和抗体が結合していないXXXX標識トシリズマブはXXXXXXXXXX標識 IL-6R と結合する。XXXXXXXXXX標識 IL-6R と結合したXXXX標識トシリズマブをXXXXXXXXXX標識XXXXXXXXXXで検出する。ウサギ抗トシリズマブ抗体を用いて作成した検量線より血清中抗トシリズマブ中和抗体濃度を算出した。定量範囲は211 ng-equivalents/mL~2400 ng-equivalents/mL(血清中濃度)であった。定量範囲内の濃度に設定した試料の測定内及び測定間再現性を検討した結果、いずれもその真度は $100 \pm 20\%$ 以内、精度は20%以下(濃度250 ng-equivalents/mLの試料の測定内再現性の精度が27.1%であった点を除く)であった(5.3.1.4-3)。

2.7.1.2 個々の試験結果の要約

本項目に該当する試験は実施されていない。

2.7.1.3 全試験を通しての結果の比較と解析

本項目に該当する試験は実施されていない。

2.7.1.4 付録

該当なし。

アクテムラ皮下注162 mg シリンジ・AI (トシリズマブ (遺伝子組換え))

[大型血管炎]

第2部 (モジュール2) : CTD の概要 (サマリー)

2.7.2 臨床薬理試験

中外製薬株式会社

略語一覧

略語	英名	和名
BLQ	below the limit of quantification	定量下限未満
CRP	C reactive protein	C 反応性蛋白
IL-6	interleukin 6	インターロイキン6
IL-6R	interleukin 6 receptor	インターロイキン6レセプター
MRA	—	トシリズマブの治験略号
MRA-SC	—	トシリズマブの皮下注製剤
PK/PD	Pharmacokinetics/Pharmacodynamics	薬物動態/薬力学
QW	every week	週に1回
Q2W	every 2 week	2週に1回
sIL-6R	soluble interleukin 6 receptor	可溶性インターロイキン6レセプター
TCZ	Tocilizumab	トシリズマブ

目次

	頁
2.7.2 臨床薬理試験.....	4
2.7.2.1 背景及び概観.....	4
2.7.2.2 個々の試験結果の要約.....	4
2.7.2.2.1 高安動脈炎（MRA632JP 試験）.....	4
2.7.2.2.1.1 試験デザイン.....	4
2.7.2.2.1.2 血清中トシリズマブトラフ濃度推移.....	5
2.7.2.2.1.3 血清中トシリズマブトラフ濃度と CRP 値の関係.....	8
2.7.2.2.1.4 血清中トシリズマブトラフ濃度と血中 IL-6 濃度との関係.....	11
2.7.2.2.1.5 血清中トシリズマブトラフ濃度と血中 sIL-6R 濃度との関係.....	13
2.7.2.2.1.6 血清中トシリズマブトラフ濃度と体重の関係.....	15
2.7.2.2.2 巨細胞性動脈炎（WA28119 試験）.....	17
2.7.2.2.2.1 試験デザイン.....	17
2.7.2.2.2.2 血清中トシリズマブ濃度推移.....	17
2.7.2.2.2.3 MRA-SC 162 mg/週及び 162 mg/2 週投与による CRP 値の経時的推移.....	21
2.7.2.2.2.4 MRA-SC 162 mg/週及び 162 mg/2 週投与による血中 IL-6 濃度の経時的推移.....	25
2.7.2.2.2.5 MRA-SC 162 mg/週及び 162 mg/2 週投与による血中 sIL-6R 濃度の経時的推移.....	25
2.7.2.3 全試験を通しての結果の比較と解析.....	26
2.7.2.3.1 MRA-SC 162 mg/週投与における MRA632JP 試験と WA28119 試験の薬物動態の比較.....	26
2.7.2.3.1.1 血清中トシリズマブトラフ濃度の経時的推移の比較.....	26
2.7.2.3.1.2 CRP 値の経時的推移の比較.....	28
2.7.2.3.1.3 血中 IL-6 濃度の経時的推移の比較.....	28
2.7.2.3.1.4 血中 sIL-6R 濃度の経時的推移の比較.....	28
2.7.2.3.2 WA28119 試験の MRA-SC 162 mg/週投与と 162 mg/2 週投与の比較.....	28

2.7.2 臨床薬理試験

2.7.2.1 背景及び概観

トシリズマブ皮下注製剤（以降、本剤又は MRA-SC）は、可溶性及び膜結合性インターロイキン6レセプター（以降、IL-6R）に対するヒト化モノクローナル抗体であるトシリズマブ（遺伝子組換え）（以降、トシリズマブ）を有効成分とし、IL-6のシグナルを阻害することにより、IL-6が関与する疾患に対する治療薬として開発が進められている。

本邦において高安動脈炎患者を対象とした第 III 相試験（以下、MRA632JP 試験）及び海外において巨細胞性動脈炎患者を対象とした第 III 相試験（以下、WA28119試験）の2試験を実施し、MRA-SC 投与時の血清中トシリズマブ薬物濃度推移に関する情報が得られている。試験の概要を表 2.7.2.1-1に示す。各試験で MRA-SC の薬物動態及び PK/PD を検討した。

表 2.7.2.1-1 MRA-SC の薬物動態評価に用いた試験の概要

国内／海外	相	試験番号	デザイン	投与量 (mg)	投与群・投与例数	採血時点
国内	III	MRA632JP	多施設共同 【二重盲検期間】 ランダム化二重盲検 【非盲検期間】 非盲検	【二重盲検期間】 プラセボ/週 162 mg/週 【非盲検期間】 162 mg/週	【二重盲検期間】 プラセボ群：18例 MRA-SC 群：18例 【非盲検期間】 162 mg/週：36例	【二重盲検期間】 初回投与前，初回投与後 1，2，4週，その後4週ごとの MRA-SC 投与前，再発の徴候発現時及び二重盲検期間最終観察時又は中止時 【非盲検期間】 初回投与前，初回投与後 1，2，4週，その後4週ごとの MRA-SC 投与前，再発の徴候発現時及び非盲検期間最終観察時又は中止時
海外	III	WA28119	多施設共同 【二重盲検期間】 ランダム化二重盲検	【二重盲検期間】 プラセボ/週 162 mg/週 162 mg/2週	【二重盲検期間】* プラセボ+26週群：50例 プラセボ+52週群：51例 MRA-SC QW 群：100例 MRA-SC Q2W 群：49例	【二重盲検期間】 初回投与前，初回投与後 1，2，3，8，16，24， 36，48，52週の MRA-SC 投与前，最終投与8週後 又は中止時

* プラセボ+26週群：プラセボ/週投与と26週間の副腎皮質ステロイド漸減投与
 プラセボ+52週群：プラセボ/週投与と52週間の副腎皮質ステロイド漸減投与
 MRA-SC QW 群：162 mg/週投与と26週間の副腎皮質ステロイド漸減投与
 MRA-SC Q2W 群：162 mg/2週投与と26週間の副腎皮質ステロイド漸減投与

2.7.2.2 個々の試験結果の要約

2.7.2.2.1 高安動脈炎（MRA632JP 試験）

2.7.2.2.1.1 試験デザイン

高安動脈炎患者を対象に0.1 mg/kg/日までの経口副腎皮質ステロイドの規定された減量を継続しながら、MRA-SC のプラセボ（18例，以下、プラセボ群）又は、MRA-SC（18例，以下、MRA-SC 群）を1週間隔で皮下投与する二重盲検並行群間比較試験を実施した。二重盲検期間で高安動脈炎の再発が認められた被験者は、再発が認められた日から原則として4週間以内に非盲検期間に移行し、副腎皮質ステロイドを増量し、MRA-SC の投与を受けた。高安動脈炎患者におけるトシリズマブの薬物動態の検討を行うために、二重盲検期間の初回投与前，初回投与後1，2，4週，その後4週ごとの MRA-SC 投与前，再発の徴候発現時（徴候発現7日以内）及び二重盲検期間最終観察時又は中止時に採血を実施した。非盲検期間は二重盲検期間と同様

のスケジュールで採血を実施した。ただし、二重盲検期間最終観察時と非盲検期間の初回投与が同日の場合、別途採血は実施しなかった。

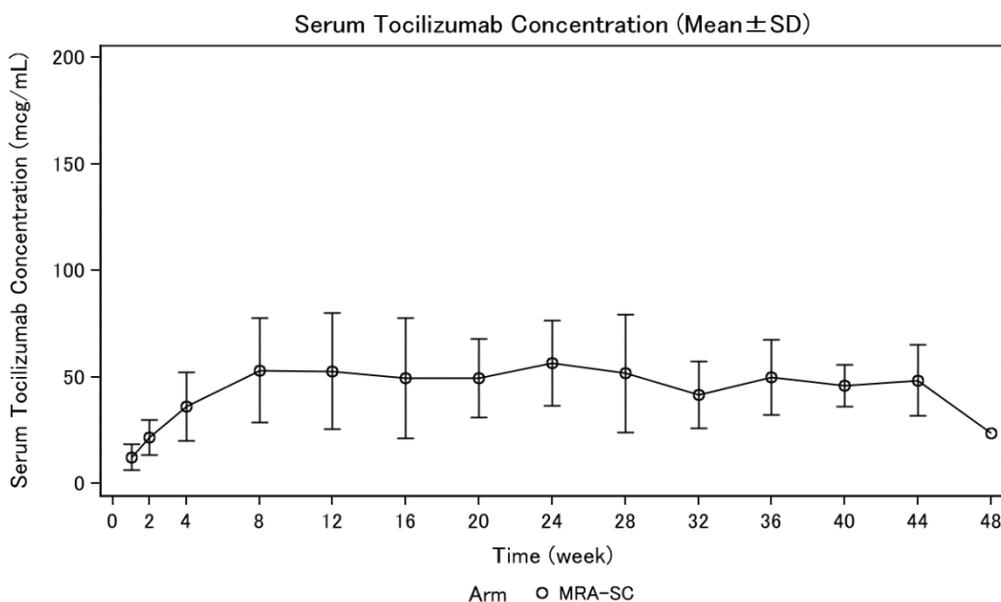
2.7.2.2.1.2 血清中トシリズマブトラフ濃度推移

MRA632JP 試験で得られた二重盲検期間と非盲検期間の血清中トシリズマブトラフ濃度推移を図 2.7.2.2.1.2-1及び図 2.7.2.2.1.2-2に、血清中トシリズマブトラフ濃度の要約統計量一覧を表 2.7.2.2.1.2-1～表 2.7.2.2.1.2-3に示す。なお、中止例を除く全被験者が非盲検期間でトシリズマブを少なくとも52週間投与終了した2016年11月10日時点でカットオフしたデータを用いている。なお、本章では、二重盲検期間中に認められた高安動脈炎の再発が非盲検期間移行後まで継続していた場合、非盲検期間における再発時のデータに含めて解析を行った。

(1) 二重盲検期間

MRA-SC 162 mg/週の反復皮下投与した被験者の平均血清中トシリズマブトラフ濃度は、初回投与後8週までに、また、二重盲検下の被験者14例の血清中トシリズマブトラフ濃度は初回投与後12週までにほぼ定常状態に達した。例数が1例であった初回投与後48週を除き、初回投与後12週以降の平均血清中トシリズマブトラフ濃度は、41.8～56.6 µg/mL で推移した。初回投与後8週前に再発した症例はなく、再発した8例の計14時点における血清中トシリズマブ濃度の平均値（最小値～最大値）は69.3 µg/mL（45.6～114 µg/mL）であり、定常状態の血清中トシリズマブ濃度と比較して著しく異なるものではなく、再発の有無と血清中トシリズマブ濃度との間に明確な関連は認められなかった。

図 2.7.2.2.1.2-1 二重盲検期間における MRA-SC 162 mg/週の反復投与時の血清中トシリズマブトラフ濃度推移 (Mean ± SD)



Program : GRAPH_CONC_SMR_V2_mod.sas
Output : MEAN_TOCILIZUMAB_CONC.rtf

Datetime: January 15, 2016 18:32:00

[5.3.5.1-1 図 11.4.2.1-1を再掲]

表 2.7.2.2.1.2-1 二重盲検期間における MRA-SC 162 mg/週の反復投与時の血清中トシリズマブトラフ濃度の要約統計量

Analyte : Serum Tocilizumab
Dose Group : MRA-SC

Week	N	NBLQ	Mean	SD	CV (%)	Min	Median	Max	Geometric mean
0	18	18	N. C.	N. C.	N. C.	N. C.	N. C.	N. C.	N. C.
1	18	0	12.4	6.06	48.8	2.69	13.8	25.3	10.7
2	18	0	21.7	8.20	37.8	8.28	21.6	41.0	20.2
4	17	0	36.1	16.0	44.3	13.7	39.0	64.1	32.6
8	15	0	53.2	24.4	45.9	12.1	54.0	101	46.9
12	14	0	52.8	27.3	51.7	21.9	50.3	131	47.6
16	10	0	49.5	28.1	56.7	23.8	45.5	118	44.0
20	8	0	49.4	18.5	37.4	18.5	50.4	81.9	45.9
24	7	0	56.6	20.1	35.5	28.9	57.0	85.0	53.2
28	5	0	51.7	27.8	53.7	24.7	48.2	95.4	46.2
32	4	0	41.8	15.7	37.5	27.2	42.2	55.4	39.5
36	3	0	49.9	17.7	35.4	29.6	58.4	61.7	47.4
40	3	0	45.9	9.68	21.1	35.8	46.8	55.1	45.2
44	3	0	48.5	16.8	34.7	31.6	48.6	65.2	46.4
48	1	0	23.8	N. C.	N. C.	23.8	23.8	23.8	23.8

Unit : mcg/mL ; NC : Not Calculated

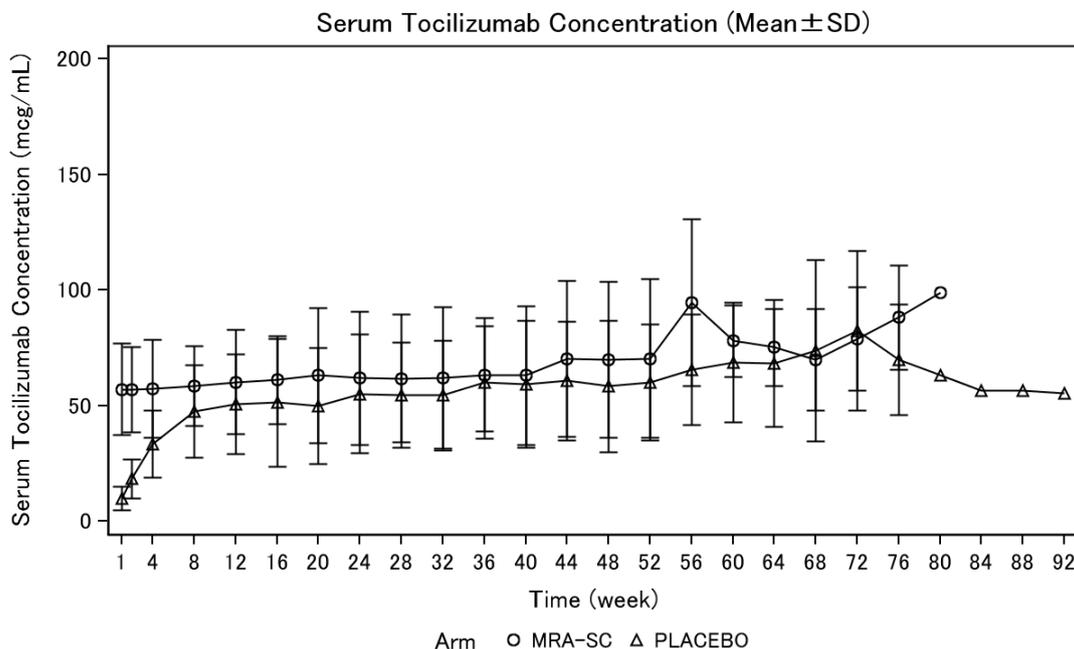
PROGRAM : REP_CONC_SMR_V2_mod.sas
OUTPUT : TABLE_MEAN_TOCILIZUMAB_CONC_MRA-SC.txt
DATETIME : January 8, 2016 11:49:00

[5.3.5.1-1 表 15.4-1を再掲]

(2) 非盲検期間

非盲検期間では、全36例に MRA-SC 162 mg/週の反復皮下投与を実施した。二重盲検期間に MRA-SC 群であった集団の非盲検期間における投与1週後、プラセボ群の初回投与後12週に平均血清中トシリズマブトラフ濃度はほぼ定常状態に達し、2例以上の時点において49.8～94.5 µg/mL で推移した。非盲検期間の定常状態に達した血清中トシリズマブトラフ濃度は二重盲検期間の41.8～56.6 µg/mL と大きな差異は認められなかった。MRA-SC 群及びプラセボ群の再発時における血清中トシリズマブトラフ濃度はそれぞれ、70.8～116 µg/mL 及び18.0～83.9 µg/mL の範囲にあった。

図 2.7.2.2.1.2-2 非盲検期間における MRA-SC 162 mg/週の反復投与時の血清中トシリズマブトラフ濃度推移 (Mean ± SD)



Program : GRAPH_CONC_SMR_V2_mod.sas
Output : MEAN_TOCILIZUMAB_CONC.rtf

Datetime: January 18, 2017 15:59:00

[5.3.5.1-7 図 8.1-1を再掲]

表 2.7.2.2.1.2-2 非盲検期間における MRA-SC 群の血清中トシリズマブトラフ濃度の要約統計量一覧

Analyte : Serum Tocilizumab
Dose Group : MRA-SC

Week	N	NBLQ	Mean	SD	CV (%)	Min	Median	Max	Geometric mean
1	18	0	57.1	19.6	34.4	27.7	55.5	99.2	54.0
2	18	0	57.1	18.4	32.3	29.7	57.9	104	54.3
4	18	0	57.2	21.2	37.0	29.7	55.3	116	53.8
8	17	0	58.5	17.3	29.5	26.3	59.7	91.6	55.8
12	17	0	60.1	22.5	37.4	24.2	59.8	113	56.1
16	17	0	61.0	19.1	31.3	18.2	60.9	87.6	57.4
20	17	0	63.1	29.1	46.2	21.4	64.2	146	57.1
24	17	0	61.9	28.8	46.6	19.2	58.8	137	55.4
28	17	0	61.8	27.7	44.8	24.8	56.4	146	57.0
32	17	0	62.1	30.5	49.1	24.3	53.9	140	56.1
36	17	0	63.3	24.5	38.7	28.7	61.0	129	59.4
40	17	0	63.1	29.9	47.4	28.8	60.4	153	57.8
44	16	0	70.3	33.8	48.1	34.4	56.6	164	64.3
48	16	0	69.8	33.8	48.4	31.0	61.7	164	63.4
52	16	0	70.4	34.3	48.7	29.1	64.2	169	63.9
56	7	0	94.5	36.2	38.3	66.4	86.8	163	89.5
60	5	0	78.0	15.4	19.8	64.8	70.4	95.8	76.8
64	3	0	75.2	16.6	22.0	63.1	68.5	94.1	74.1
68	3	0	69.8	21.9	31.3	54.8	59.8	94.9	67.8
72	3	0	78.9	22.4	28.4	57.2	77.4	102	76.7
76	2	0	88.1	22.5	25.5	72.2	88.1	104	86.7
80	1	0	99.0	N. C.	N. C.	99.0	99.0	99.0	99.0

Unit : mcg/mL ; NC : Not Calculated

PROGRAM : REP_CONC_SMR_V2_mod.sas
OUTPUT : TABLE_MEAN_TOCILIZUMAB_CONC_MRA-SC.txt
DATETIME : January 18, 2017 15:59:00

[5.3.5.1-7 表 8.1-1を再掲]

表 2.7.2.2.1.2-3 非盲検期間におけるプラセボ群の血清中トシリズマブトラフ濃度の要約統計量一覧

Analyte : Serum Tocilizumab
Dose Group : PLACEBO

Week	N	NBLQ	Mean	SD	CV (%)	Min	Median	Max	Geometric mean
1	17	0	9.92	4.93	49.6	0.346	8.99	21.3	8.02
2	17	0	18.4	8.29	45.1	1.61	18.0	35.0	15.6
4	18	0	33.5	14.6	43.5	9.42	33.2	65.2	30.2
8	17	0	47.6	20.0	42.1	7.21	54.4	75.3	42.1
12	17	0	50.6	21.5	42.5	6.01	58.2	86.5	44.2
16	16	0	51.3	27.7	53.9	5.71	47.3	88.2	40.9
20	15	0	49.8	25.2	50.6	1.94	48.1	89.0	37.7
24	15	0	55.1	25.7	46.7	7.31	61.5	91.9	46.8
28	15	0	54.5	22.8	41.8	7.94	47.7	88.1	48.1
32	15	0	54.4	23.7	43.5	10.7	44.9	92.9	48.5
36	15	0	60.2	24.4	40.5	15.8	59.6	113	55.0
40	15	0	59.3	27.5	46.3	16.4	48.5	107	53.3
44	14	0	60.8	25.8	42.4	14.2	56.2	105	54.8
48	14	0	58.4	28.3	48.5	14.0	49.3	108	51.6
52	13	0	60.1	25.2	41.9	16.0	53.8	101	54.5
56	6	0	65.6	23.9	36.4	42.2	59.4	104	62.2
60	6	0	68.8	25.8	37.6	43.5	61.5	107	64.9
64	6	0	68.4	27.4	40.0	40.2	59.4	109	64.1
68	5	0	73.8	39.4	53.4	42.6	53.5	134	66.4
72	3	0	82.3	34.4	41.8	61.2	63.7	122	78.1
76	3	0	69.7	23.9	34.3	48.3	65.4	95.5	67.1
80	1	0	63.3	N. C.	N. C.	63.3	63.3	63.3	63.3
84	1	0	56.4	N. C.	N. C.	56.4	56.4	56.4	56.4
88	1	0	56.5	N. C.	N. C.	56.5	56.5	56.5	56.5
92	1	0	55.4	N. C.	N. C.	55.4	55.4	55.4	55.4

Unit : mcg/mL ; NC : Not Calculated

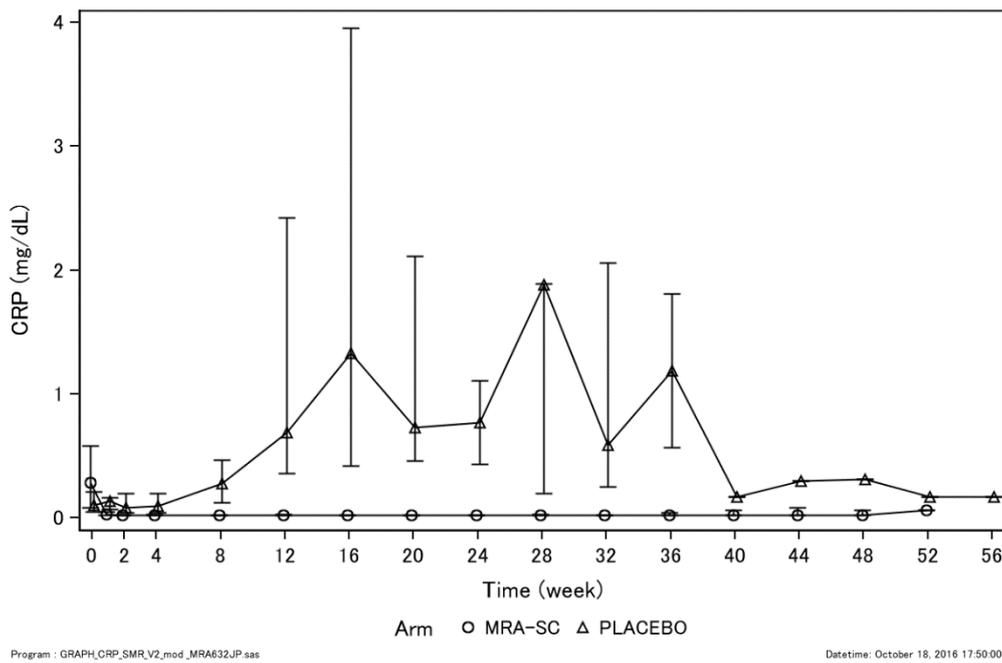
PROGRAM : REP_CONC_SMR_V2_mod.sas
OUTPUT : TABLE_MEAN_TOCILIZUMAB_CONC_PLACEBO.txt
DATETIME : January 18, 2017 15:59:00

[5.3.5.1-7 表 8.1-2を再掲]

2.7.2.2.1.3 血清中トシリズマブトラフ濃度と CRP 値の関係

二重盲検期間における CRP 値の中央値の経時的推移を [図 2.7.2.2.1.3-1](#) に示す。また、MRA-SC 初回投与前の CRP 値を含む全期間の血清中トシリズマブトラフ濃度と CRP 値の関係を [図 2.7.2.2.1.3-2](#) に、二重盲検期間及び非盲検期間の再発時の血清中トシリズマブトラフ濃度と CRP 値の関係を [図 2.7.2.2.1.3-3](#) と [図 2.7.2.2.1.3-4](#) に示す。二重盲検期間におけるプラセボ群及び MRA-SC 群の投与前 CRP 値は 0.264 ± 0.432 mg/dL (平均値 \pm 標準偏差, 以降同様, 18例), 0.462 ± 0.518 mg/dL (18例) であった。二重盲検期間におけるプラセボ群の CRP 値は初回投与後12週以降, 個体間の変動が大きく, CRP 値の平均値は1 mg/dL 以上を示した。([図 2.7.2.2.1.3-1](#))。二重盲検期間及び非盲検期間で MRA-SC 162 mg 初回投与後, CRP 値は1例の1時点を除き, 血清中トシリズマブ濃度に関わらず, 低値を示した([図 2.7.2.2.1.3-2](#))。二重盲検期間のプラセボ群では, 再発した11例中8例で, 1 mg/dL 以上の CRP 値が認められたが, MRA-SC 群では, 再発した8例の計14時点における血清中トシリズマブ濃度は45.6~114 μ g/mL と定常状態の血清中トシリズマブトラフ濃度と比較して著しく異なるものではなく, CRP 値の上昇は認められなかった([図 2.7.2.2.1.2-1](#), [図 2.7.2.2.1.3-3](#))。非盲検期間においては, 11週間本剤の投与がなかった被験者1例を除き, MRA-SC 162 mg/週の反復投与により, 再発時の CRP 値の上昇は認められなかった([図 2.7.2.2.1.3-4](#), [5.3.5.1-7 表 11.4-2](#))。MRA-SC 162 mg/週の反復投与により, CRP 値は陰性化を維持できるものと考えられた。

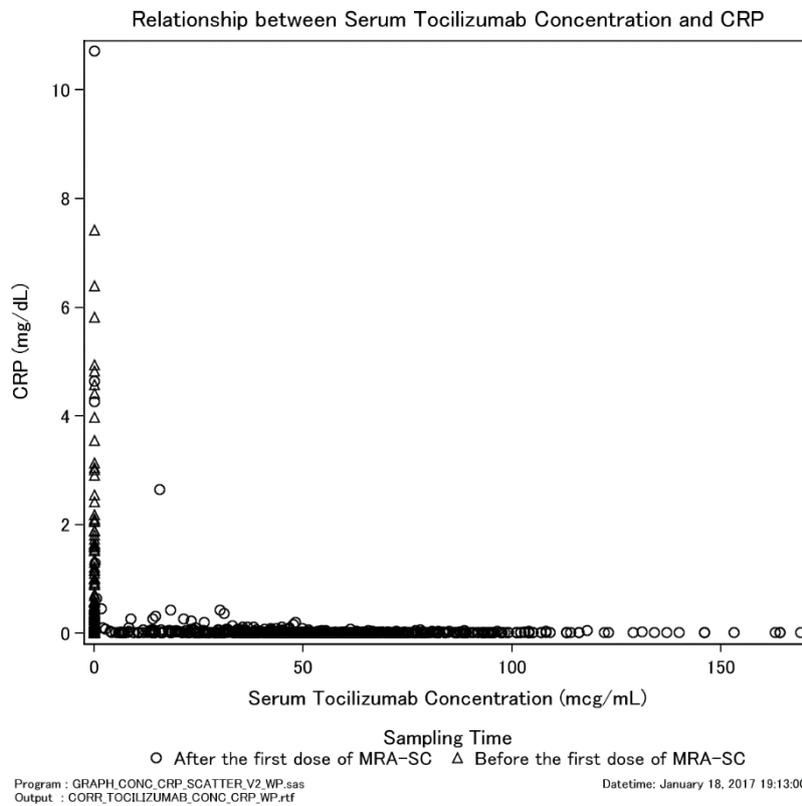
図 2.7.2.2.1.3-1 二重盲検期間における CRP 値の中央値の経時的推移



プロット：中央値，バー：第1四分位～第3四分位

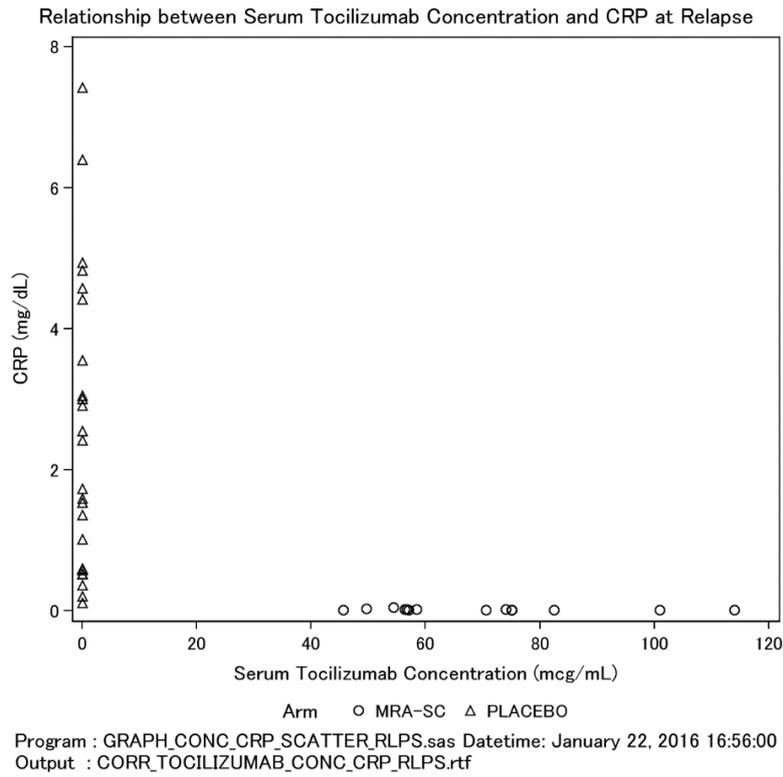
[5.3.5.3-2 図 10-1を再掲]

図 2.7.2.2.1.3-2 全期間における血清中トシリズマブ濃度と CRP 値の関係



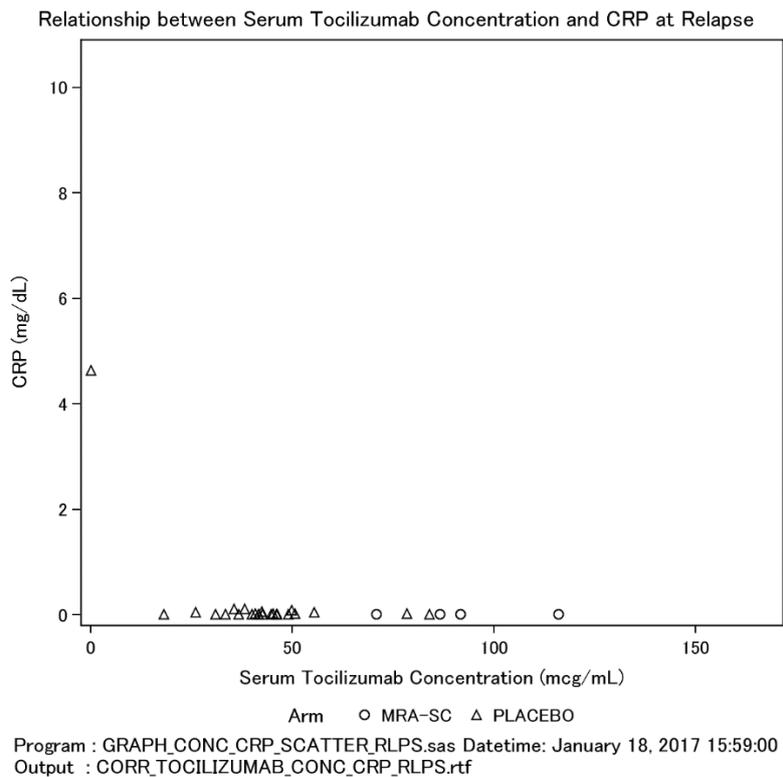
[5.3.5.1-7 図 8.2-1を再掲]

図 2.7.2.2.1.3-3 二重盲検期間の再発時の血清中トシリズマブトラフ濃度と CRP 値の関係



[5.3.5.1-1 図 15.4-11を再掲]

図 2.7.2.2.1.3-4 非盲検期間の再発時の血清中トシリズマブトラフ濃度と CRP 値の関係

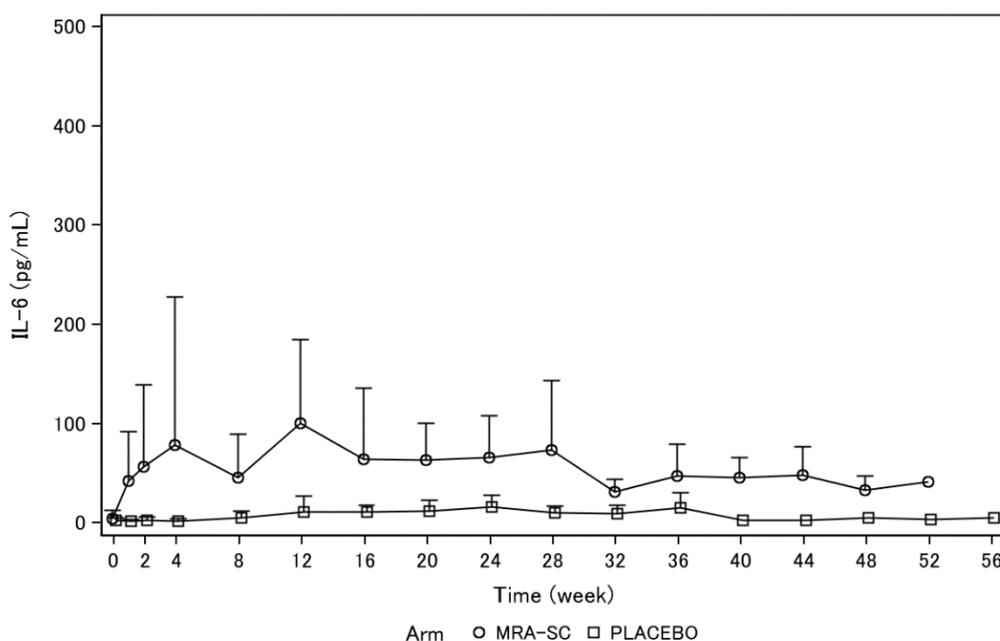


[5.3.5.1-7 図 11.6-1を再掲]

2.7.2.2.1.4 血清中トシリズマブトラフ濃度と血中 IL-6濃度の関係

二重盲検期間の血中 IL-6濃度の平均値の経時的推移を [図 2.7.2.2.1.4-1](#) に、全期間の血清中トシリズマブトラフ濃度と血中 IL-6濃度の関係を [図 2.7.2.2.1.4-2](#) に、二重盲検期間及び非盲検期間の再発時の血清中トシリズマブトラフ濃度と血中 IL-6濃度の関係を [図 2.7.2.2.1.4-3](#) と [図 2.7.2.2.1.4-4](#) に示す。二重盲検期間における血中 IL-6濃度は、MRA-SC 群では初回投与後1週までに急激に増加した。プラセボ群では MRA-SC 群で認められた血中 IL-6濃度の大きな変動は認められず、血中 IL-6濃度は MRA-SC を投与した被験者と比較して低値を示した ([図 2.7.2.2.1.4-1](#))。全期間において、本剤投与開始に伴い、血中 IL-6濃度は増加した。 ([図 2.7.2.2.1.4-1](#), 5.3.5.1-7 表 11.2-8) これは IL-6の消失経路の一つである IL-6R との結合が抗 IL-6R 抗体であるトシリズマブにより阻害され、血中に滞留したためと考えられるが、血清中トシリズマブトラフ濃度と血中 IL-6濃度の間に明確な関連は認められなかった ([図 2.7.2.2.1.4-2](#))。また、二重盲検期間に再発した8例中3例及び二重盲検期間中から再発が継続して認められた症例を含む非盲検期間に再発した12例中4例は血中 IL-6濃度500 pg/mL 以上を示したが、他の二重盲検期間及び非盲検期間に再発した5例、8例は無再発症例と同程度の血中 IL-6濃度の上昇であり、再発の有無と血中 IL-6濃度との間に明確な関連は認められなかった ([図 2.7.2.2.1.4-3](#), [図 2.7.2.2.1.4-4](#))。

図 2.7.2.2.1.4-1 二重盲検期間における血中 IL-6濃度の経時的推移



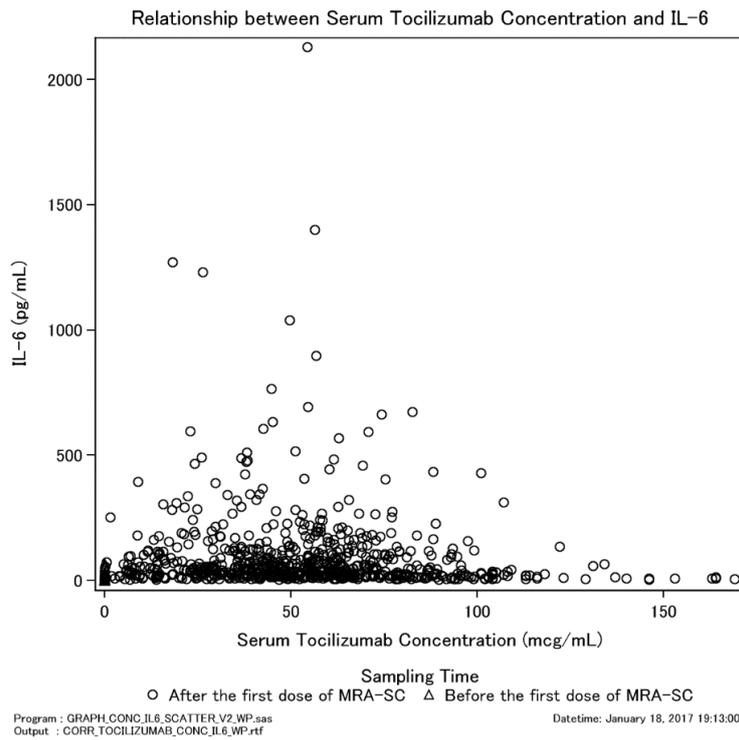
Program : GRAPH_IL6_SMR_V2_mod_MRA632JP.sas

Datetime: October 18, 2016 17:50:00

プロット：平均値，バー：標準偏差

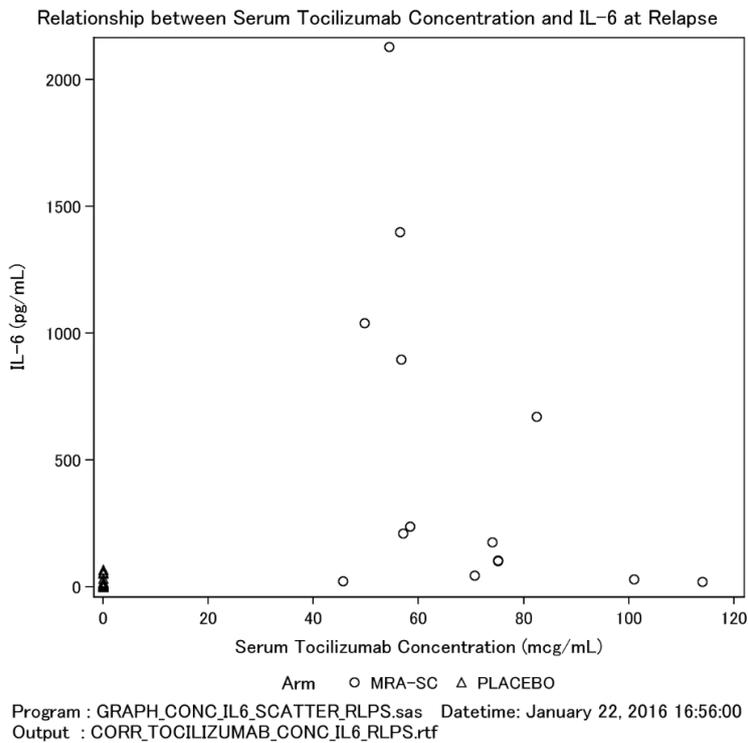
[5.3.5.3-2 図 10-3を再掲]

図 2.7.2.2.1.4-2 全期間における血清トシリズマブトラフ濃度と血中 IL-6濃度の関係



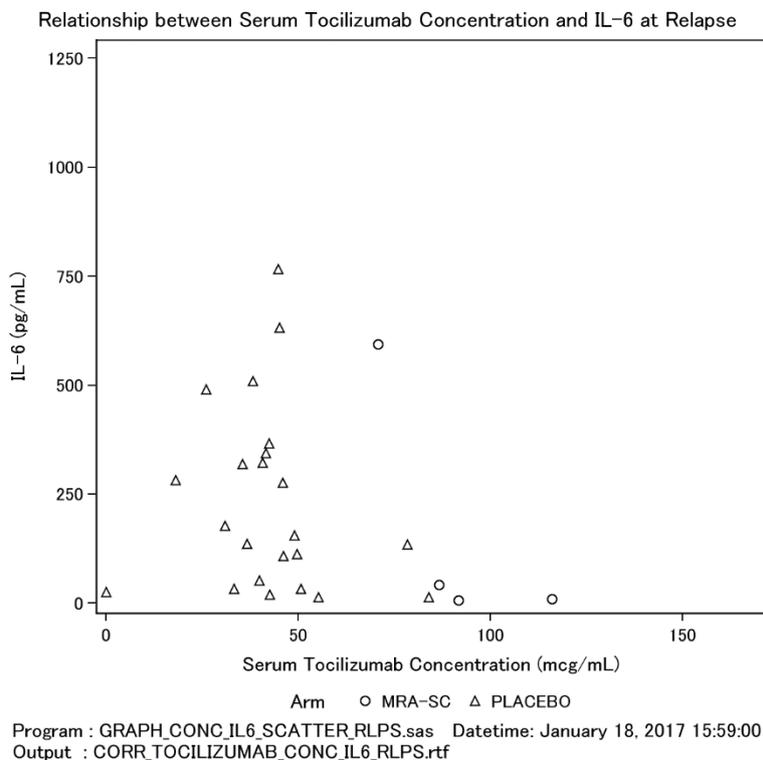
[5.3.5.1-7 図 8.3-1を再掲]

図 2.7.2.2.1.4-3 二重盲検期間の再発時における血清トシリズマブトラフ濃度と血中 IL-6濃度の関係



[5.3.5.1-1 図 15.4-12を再掲]

図 2.7.2.2.1.4-4 非盲検期間の再発時における血清トシリズマブトラフ濃度と血中 IL-6 濃度の関係

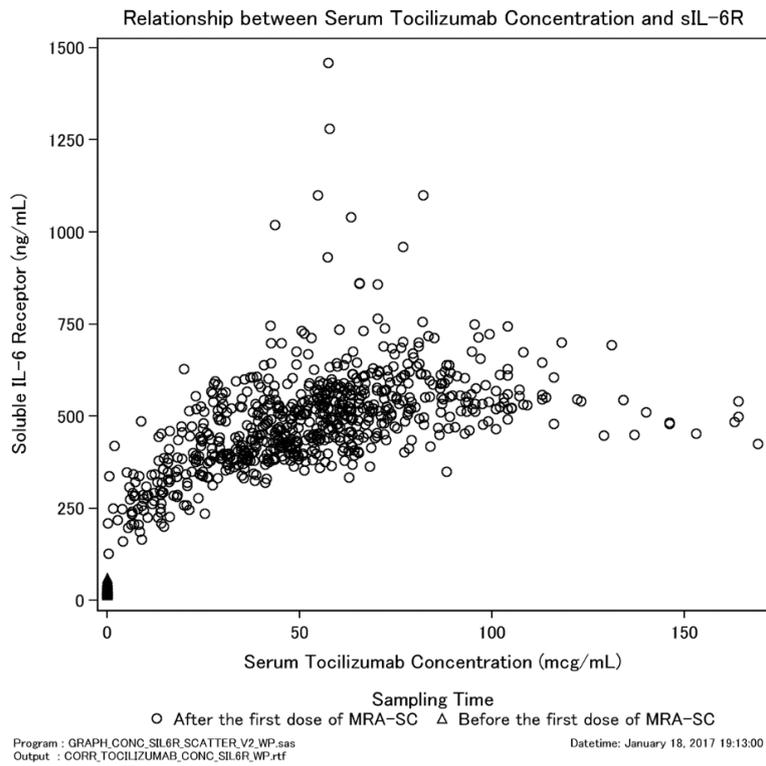


[5.3.5.1-7 図 11.6-2を再掲]

2.7.2.2.1.5 血清中トシリズマブトラフ濃度と血中 sIL-6R 濃度の関係

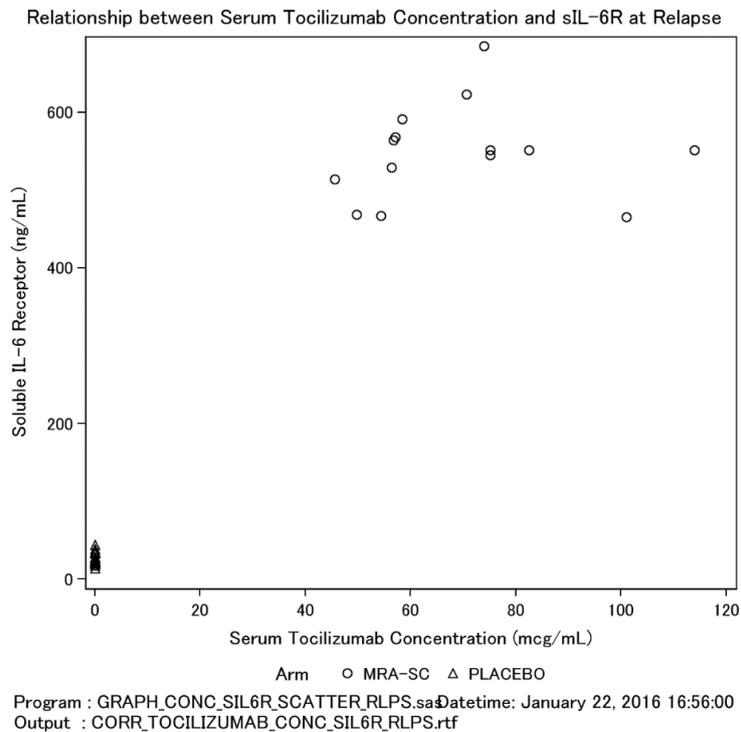
全期間の血清中トシリズマブトラフ濃度と血中可溶性 IL-6R (sIL-6R) 濃度の関係を [図 2.7.2.2.1.5-1](#) に、二重盲検期間及び非盲検期間の再発時の血清中トシリズマブトラフ濃度と血中 sIL-6R 濃度の関係を [図 2.7.2.2.1.5-2](#) と [図 2.7.2.2.1.5-3](#) に示す。MRA-SC 162 mg/週投与により、血中 sIL-6R 濃度は血清中トシリズマブ濃度約 25~50 µg/mL まで濃度依存的に上昇し、それ以上の血清中トシリズマブ濃度では血中 sIL-6R 濃度 500~600 ng/mL 付近で一定となる傾向が認められた ([図 2.7.2.2.1.5-1](#))。また、二重盲検下の被験者 14 例が定常状態に達した初回投与後 12 週時及び全期間において初回投与後 12 週時までの本剤投与中止例を除く 35 例の被験者での初回投与 12 週時の平均血中 sIL-6R 濃度は、それぞれ 527.29 ± 111.41 ng/mL, 502.17 ± 95.88 ng/mL (平均値 ± 標準偏差) であった (5.3.5.1-1 表 15.2.1-30, 5.3.5.1-7 表 11.2-8)。二重盲検期間及び非盲検期間の再発時の血中 sIL-6R 濃度は、再発が認められなかった被験者の血中 sIL-6R 濃度と大きな差異は認められなかった ([図 2.7.2.2.1.5-1](#), [図 2.7.2.2.1.5-2](#) 及び [図 2.7.2.2.1.5-3](#))。トシリズマブは濃度依存的に血中 sIL-6R と免疫複合体を形成することで、sIL-6R/IL-6 複合体から IL-6 を遊離させ、IL-6R を介する IL-6 シグナルを阻害する。血清中トシリズマブトラフ濃度 25~50 µg/mL 以上で、血中 sIL-6R 濃度が一定となっていることから、IL-6R を介する IL-6 シグナルは十分阻害されていると推測でき、2 例以上の時点における二重盲検期間の定常状態の平均トラフ濃度が 41.8~56.6 µg/mL であった MRA-SC 162 mg/週の用法・用量は妥当であると考えられた。

図 2.7.2.2.1.5-1 全期間における血清トシリズマブトラフ濃度と血中 sIL-6R 濃度の関係



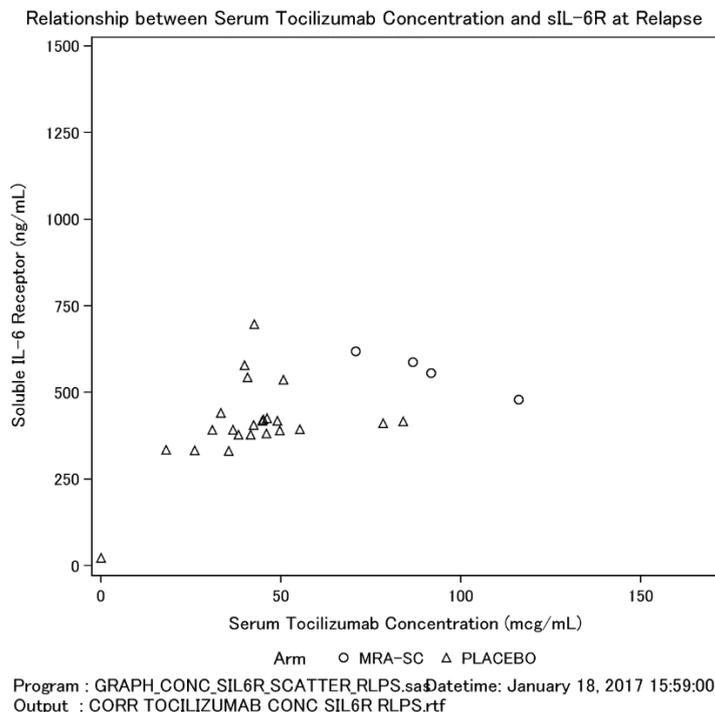
[5.3.5.1-7 図 8.4-1を再掲]

図 2.7.2.2.1.5-2 二重盲検期間の再発時における血清トシリズマブトラフ濃度と血中 sIL-6R 濃度の関係



[5.3.5.1-1 図 15.4-13を再掲]

図 2.7.2.2.1.5-3 非盲検期間の再発時における血清トシリズマブトラフ濃度と血中 sIL-6R 濃度の関係

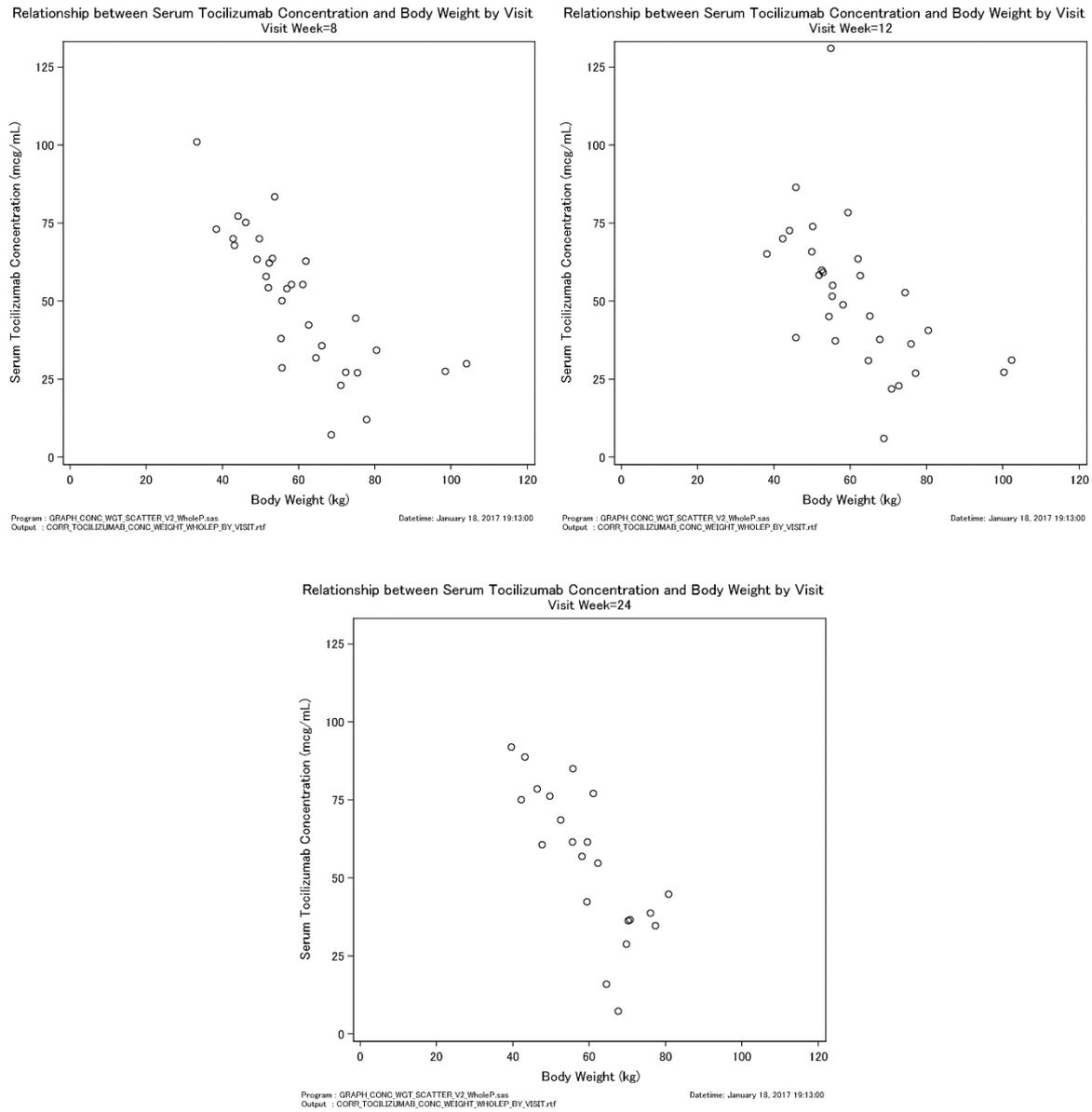


[5.3.5.1-7 図 11.6-2を再掲]

2.7.2.2.1.6 血清中トシリズマブトラフ濃度と体重の関係

MRA-SC は、1回投与量を固定した製剤であることから分布容積、クリアランスへの影響を与える可能性がある内因性要因の体重について検討した。全期間における MRA-SC 初回投与後8, 12, 24週時の体重と血清中トシリズマブトラフ濃度の関係を図 2.7.2.2.1.6-1に示した。視察的評価の結果、いずれの採血時点でも負の相関がある可能性が考えられた。2.7.2.2.1.2及び2.7.2.2.1.3項に示した結果、MRA-SC 162 mg/週投与は、CRP 値を陰性化させるには十分な投与量であったが、再発の有無と血清中トシリズマブトラフ濃度との間に明確な関連は認められなかった。以上のことから本用量においては、被験者体重範囲内では血清中トシリズマブ濃度は十分であったと考え、本疾患での体重を考慮した投与量調整は必要ないと判断した。

図 2.7.2.1.6-1 全期間における MRA-SC 初回投与後8, 12, 24週時の血清トシリズマブトラフ濃度と体重の関係



[5.3.5.1-7 図 8.6-1を再掲]

2.7.2.2.2 巨細胞性動脈炎 (WA28119試験)

2.7.2.2.2.1 試験デザイン

海外の巨細胞性動脈炎患者を対象に、以下の4群に2:1:1:1の比で割り付け、規定された副腎皮質ステロイドの減量を行いながら、MRA-SC 162 mg を1週若しくは2週間隔、又はプラセボを1週間隔で皮下投与するプラセボ対照二重盲検並行群間比較試験を実施した。巨細胞性動脈炎患者におけるトシリズマブの薬物動態の検討を行うために、二重盲検期間の初回投与前、初回投与後1, 2, 3, 8, 16, 24, 36, 48, 52週の MRA-SC 投与前及び最終投与8週後又は中止時に採血を実施した。非盲検期間は二重盲検期間と同様のスケジュールで採血を実施した。ランダム化後12週以内に巨細胞性動脈炎の症状の寛解を達成し、52週時まで再発を認めなかった被験者をレスポンドーとし、52週時までの再発又は中止例、ランダム化後12週以内に巨細胞性動脈炎の症状が寛解に至らなかった被験者、副腎皮質ステロイドの減量不可例を、ノンレスポンドーとして取り扱うこととした。

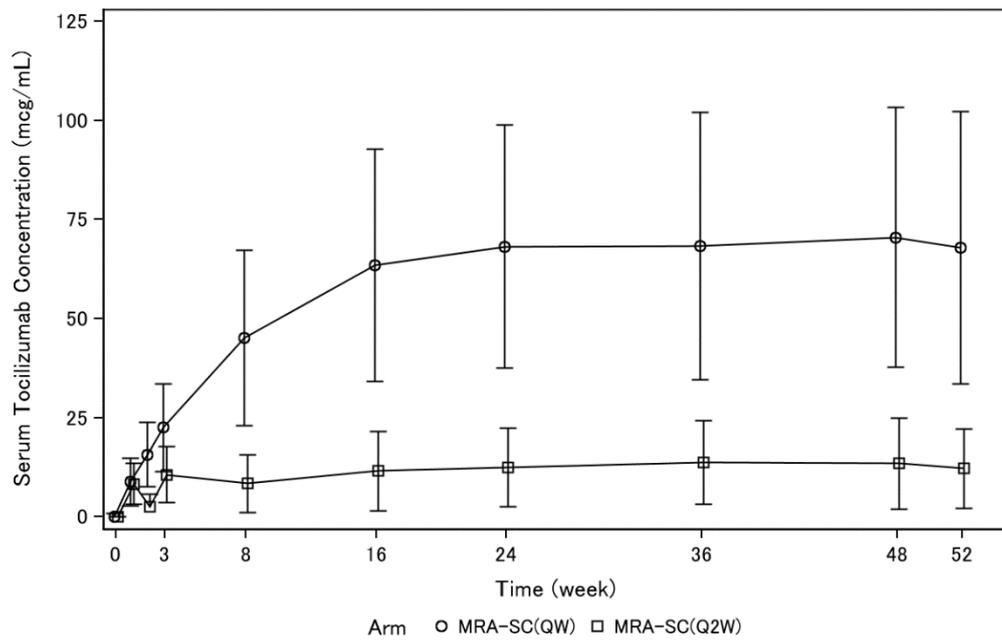
- MRA-SC 162 mg/週と26週間の副腎皮質ステロイド漸減投与 (以下, MRA-SC QW 群)
- MRA-SC 162 mg/2週と26週間の副腎皮質ステロイド漸減投与 (以下, MRA-SC Q2W 群)
- プラセボ/週と26週間の副腎皮質ステロイド漸減投与 (以下, プラセボ+26週群)
- プラセボ/週と52週間の副腎皮質ステロイド漸減投与 (以下, プラセボ+52週群)

2.7.2.2.2.2 血清中トシリズマブ濃度推移

二重盲検期間の血清中トシリズマブ濃度推移を [図 2.7.2.2.2.2-1](#) に、二重盲検期間における MRA-SC QW 群及び MRA-SC Q2W 群の血清中トシリズマブ濃度の要約統計量一覧を [表 2.7.2.2.2.2-1](#) に示す。また、レスポンドーとノンレスポンドーの血清中トシリズマブ濃度推移を [図 2.7.2.2.2.2-2](#) と [図 2.7.2.2.2.2-3](#) に示す。

MRA-SC QW 群において、MRA-SC 162 mg/週の反復皮下投与後、血清中トシリズマブトラフ濃度は、初回投与後16週以降ほぼ定常状態に達し、初回投与後16週以降の平均トラフ濃度は、63.49～70.46 µg/mL で推移した。また、MRA-SC Q2W 群では、MRA-SC 162 mg/2週の反復皮下投与後、血清中トシリズマブ濃度がほぼ定常状態に達した初回投与後16週以降の平均トラフ濃度は、11.57～13.77 µg/mL で推移した。24週時における MRA-SC QW 群の血清中トシリズマブ濃度は、MRA-SC Q2W 群と比較して、5.47倍と高い結果が得られた。MRA-SC QW 群及び MRA-SC Q2W 群において、レスポンドーの初回投与後52週後の平均血清中トシリズマブ濃度は、69.18 ± 35.00 µg/mL 及び13.26 ± 10.43 µg/mL であった。一方、MRA-SC QW 群及び MRA-SC Q2W 群のノンレスポンドーにおいては、64.89 ± 33.51 µg/mL 及び8.95 ± 8.38 µg/mL であった。いずれの MRA-SC 投与群においてもレスポンドーとノンレスポンドーの平均血清中トシリズマブ濃度に大きな差異は認められなかった。

図 2.7.2.2.2.2-1 二重盲検期間における MRA-SC QW 群及び MRA-SC Q2W 群の血清中トシリズマブ濃度推移 (Mean ± SD)



Program : GRAPH_CONC_SMR_V2_mod_GiACTA_2.sas

Datetime: October 18, 2016 17:50:00

[5.3.5.3-2 図 10-7を再掲]

表 2.7.2.2.2-1 二重盲検期間における MRA-SC QW 群及び MRA-SC Q2W 群の
血清中トシリズマブ濃度の要約統計量一覧

Summary of Mean TCZ (mcg/mL) concentration by Visit, PK Population
Protocol: WA28119

Visit	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Baseline		
n	99	48
Mean (SD)	0.07 (0.72)	0.00 (0.02)
Median	0.00	0.00
Min - Max	0.0 - 7.2	0.0 - 0.1
Week 1		
n	98	43
Mean (SD)	8.84 (5.99)	8.34 (5.15)
Median	7.64	7.98
Min - Max	0.2 - 30.7	0.1 - 21.8
Week 2		
n	96	39
Mean (SD)	15.71 (8.09)	2.48 (3.27)
Median	15.30	0.89
Min - Max	0.1 - 42.2	0.1 - 15.1
Week 3		
n	94	44
Mean (SD)	22.51 (11.07)	10.68 (6.99)
Median	22.50	10.03
Min - Max	0.7 - 56.2	0.1 - 39.0
Week 8		
n	92	45
Mean (SD)	45.23 (22.12)	8.37 (7.28)
Median	43.25	6.48
Min - Max	3.3 - 114.0	0.1 - 33.2
Week 16		
n	89	45
Mean (SD)	63.49 (29.31)	11.57 (10.04)
Median	61.70	10.00
Min - Max	16.4 - 155.0	0.1 - 40.2
Week 24		
n	87	41
Mean (SD)	68.18 (30.71)	12.46 (9.83)
Median	64.70	11.40
Min - Max	16.6 - 146.0	0.1 - 34.2

Pre-dose BLQ records at Baseline are set to 0; all other BLQ records are set to missing.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pk_mean.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pk_mean_PK_TCZ_PRE.out
11JUL2016 23:03

Summary of Mean TCZ (mcg/mL) concentration by Visit, PK Population
 Protocol: WA28119

Visit	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Week 36		
n	81	39
Mean (SD)	68.39 (33.71)	13.77 (10.46)
Median	60.40	12.50
Min - Max	3.9 - 152.0	0.3 - 39.8
Week 48		
n	81	40
Mean (SD)	70.46 (32.75)	13.49 (11.45)
Median	69.10	10.70
Min - Max	2.0 - 150.0	0.3 - 50.6
Week 52		
n	72	33
Mean (SD)	67.93 (34.40)	12.22 (10.02)
Median	62.80	10.70
Min - Max	0.3 - 194.0	0.3 - 40.5

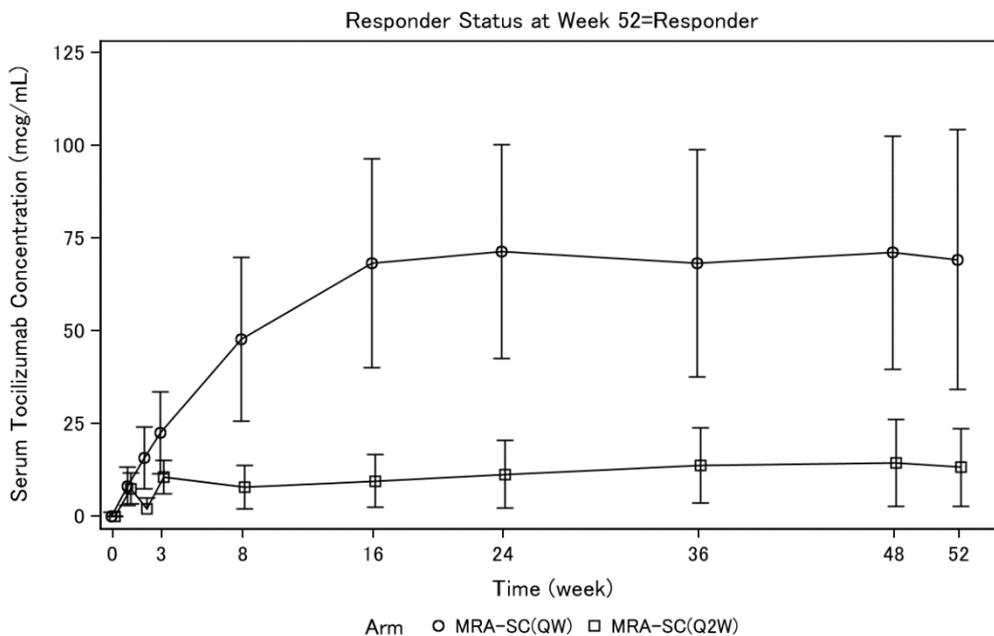
Pre-dose BLQ records at Baseline are set to 0; all other BLQ records are set to missing.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pk_mean.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pk_mean_PK_TCZ_PRE.out
 11JUL2016 23:03

Page 2 of 2

[5.3.5.1-3 t_pk_mean_PK_TCZ_PRE を再掲]

図 2.7.2.2.2-2 レスポンダーにおける MRA-SC QW 群及び MRA-SC Q2W 群の血清中トシリズマブ濃度推移 (Mean ± SD)

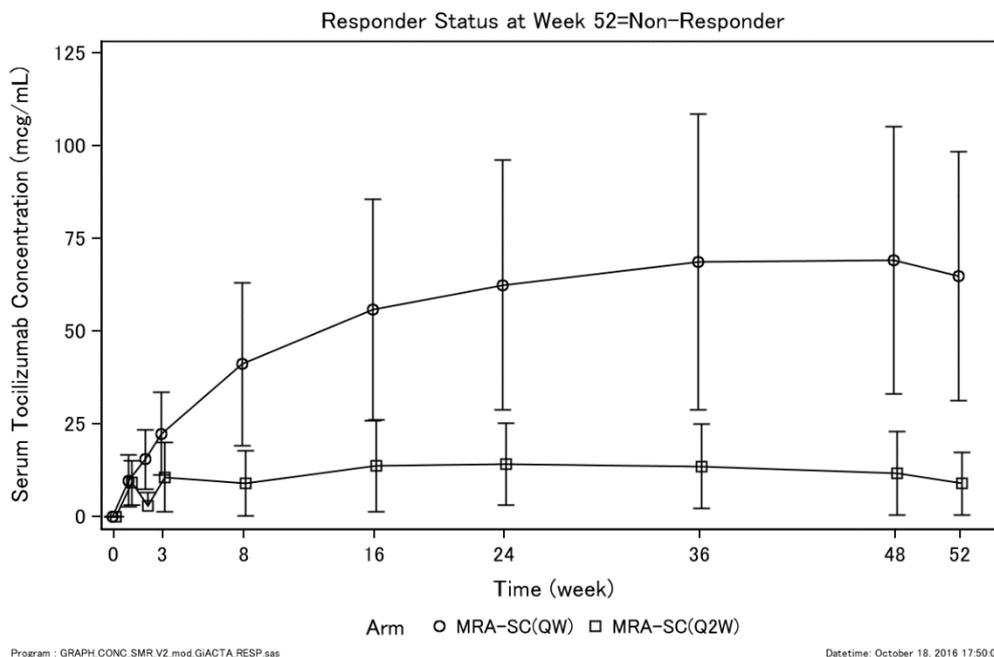


Program : GRAPH_CONC_SMR_V2_mod_GIACTA_RESP.sas

Datetime: October 18, 2016 17:50:00

[5.3.5.3-2 図 10-8を再掲]

図 2.7.2.2.2-3 ノンレスポonderにおけるMRA-SC QW群及びMRA-SC Q2W群の血清中トシリズマブ濃度推移 (Mean ± SD)

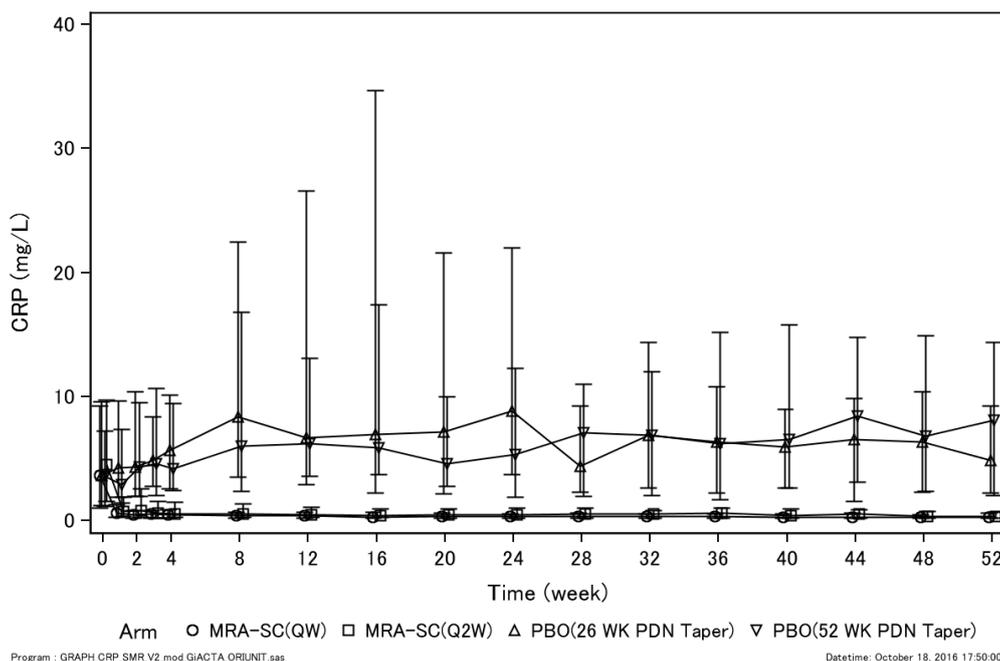


[5.3.5.3-2 図 10-9を再掲]

2.7.2.2.2.3 MRA-SC 162 mg/週及び162 mg/2週投与によるCRP値の経時的推移

各群のCRP値の中央値の経時的推移を図2.7.2.2.2.3-1に、投与前及び採血時点におけるCRP値の要約統計量一覧を表2.7.2.2.2.3-1に示す。投与前CRP値の中央値は、MRA-SC QW群で、3.67 mg/L (平均値 ± 標準偏差: 6.78 ± 8.70 mg/L, 100例)、MRA-SC Q2W群で、4.52 mg/L (11.36 ± 25.38 mg/L, 49例)、プラセボ+26週群で、3.64 mg/L (7.69 ± 10.32 mg/L, 50例)、プラセボ+52週群で、3.56 mg/L (8.17 ± 21.00 mg/L, 51例)であり、各群で大きな偏りは見受けられなかった。プラセボ群+26週群及びプラセボ+52週群では、プラセボの初回投与後、CRP値の中央値は4.28~8.84 mg/L、2.93~8.43 mg/Lの範囲で変動した。一方、MRA-SCを投与したMRA-SC QW群及びMRA-SC Q2W群のCRP値の中央値は、0.27~0.63 mg/L、0.33~0.83 mg/Lとプラセボ群+26週群及びプラセボ+52週群と比較して、MRA-SCの初回投与後に速やかに低下した。MRA-SC QW群では、投与1週後全98例が10.3 mg/L (1.03 mg/dL)以下に、また、被験者の75%以上が2週から52週まで陰性化していると考えられる1 mg/L (0.1 mg/dL)以下へと顕著に低下した。MRA-SC Q2W群では、初回投与後、被験者の50%以上が、1週から52週まで1 mg/L (0.1 mg/dL)以下に低下した。MRA-SC QW群とMRA-SC Q2W群の両群でCRP値の陰性化が認められたが、MRA-SC QW群のいずれの時点においてもCRP値の中央値、第3四分位点はMRA-SC Q2W群より低値を示した。MRA-SC 162 mg/2週よりも162 mg/週の用法・用量でのCRP値を陰性化する効果は高いことが示された。

図 2.7.2.2.3-1 CRP 値の中央値の経時的推移



プロット：中央値，バー：第1四分位～第3四分位

[5.3.5.3-2 図 10-10を再掲]

表 2.7.2.2.3-1 投与前及び採血時点における CRP 値の要約統計量一覧

Summary of Median and IQR CRP (mg/L) values by Visit, Safety Population
 Protocol: WA28119

Visit	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Baseline				
n	50	51	100	49
Mean (SD)	7.69 (10.32)	8.17 (21.00)	6.78 (8.70)	11.36 (25.38)
Median	3.64	3.56	3.67	4.52
Interquartile Range	1.20 - 9.59	1.17 - 7.24	1.02 - 9.26	1.55 - 9.75
Min - Max	0.2 - 47.1	0.2 - 149.0	0.2 - 45.5	0.2 - 154.0
Week 1				
n	49	51	98	49
Mean (SD)	10.23 (22.47)	5.45 (6.81)	1.28 (1.89)	1.97 (3.51)
Median	4.28	2.93	0.63	0.79
Interquartile Range	1.89 - 9.69	1.40 - 7.35	0.29 - 1.29	0.36 - 1.91
Min - Max	0.4 - 153.0	0.2 - 34.4	0.2 - 10.3	0.2 - 19.8
Week 2				
n	50	48	98	48
Mean (SD)	10.27 (16.62)	7.29 (8.16)	0.92 (1.52)	4.04 (9.41)
Median	4.34	4.36	0.48	0.83
Interquartile Range	1.99 - 10.40	1.99 - 9.55	0.23 - 0.82	0.28 - 2.60
Min - Max	0.3 - 85.1	0.2 - 36.7	0.2 - 10.3	0.2 - 46.0
Week 3				
n	49	51	93	48
Mean (SD)	8.85 (12.42)	6.87 (6.61)	0.90 (1.34)	1.05 (1.08)
Median	4.87	4.61	0.54	0.59
Interquartile Range	2.75 - 8.40	2.02 - 10.70	0.25 - 0.85	0.20 - 1.54
Min - Max	0.2 - 69.3	0.2 - 33.3	0.2 - 9.5	0.2 - 4.7

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_mediqr.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_mediqr_SE_CRP.out
 11JUL2016 23:00

Summary of Median and IQR CRP (mg/L) values by Visit, Safety Population
Protocol: WA28119

Visit	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Week 4				
n	49	50	97	49
Mean (SD)	9.90 (11.29)	7.59 (8.77)	0.99 (2.10)	1.37 (2.03)
Median	5.68	4.21	0.48	0.56
Interquartile Range	2.58 - 10.10	2.41 - 9.46	0.22 - 0.90	0.27 - 1.48
Min - Max	0.6 - 49.7	0.2 - 42.8	0.2 - 17.8	0.2 - 10.5
Week 8				
n	49	50	91	48
Mean (SD)	15.59 (17.52)	16.32 (27.17)	0.73 (1.01)	1.68 (3.17)
Median	8.40	6.01	0.40	0.55
Interquartile Range	3.54 - 22.50	2.36 - 16.80	0.20 - 0.71	0.27 - 1.33
Min - Max	0.2 - 86.5	0.2 - 125.0	0.2 - 7.7	0.2 - 18.8
Week 12				
n	49	49	93	48
Mean (SD)	16.70 (22.40)	14.67 (24.98)	0.64 (0.72)	2.19 (8.05)
Median	6.71	6.23	0.41	0.52
Interquartile Range	2.89 - 26.60	3.59 - 13.10	0.20 - 0.72	0.28 - 1.09
Min - Max	0.2 - 116.0	0.2 - 128.0	0.2 - 4.7	0.2 - 56.0

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_mediqr.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_mediqr_SE_CRP.out
11JUL2016 23:00

Summary of Median and IQR CRP (mg/L) values by Visit, Safety Population
Protocol: WA28119

Visit	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Week 16				
n	48	48	91	48
Mean (SD)	22.27 (34.77)	11.50 (12.55)	1.02 (5.04)	1.56 (4.53)
Median	6.93	5.91	0.29	0.44
Interquartile Range	2.24 - 34.65	3.69 - 17.40	0.20 - 0.66	0.26 - 0.99
Min - Max	0.2 - 206.0	0.2 - 66.5	0.2 - 48.4	0.2 - 31.3
Week 20				
n	46	47	91	48
Mean (SD)	16.81 (22.40)	10.34 (14.55)	0.93 (3.76)	1.76 (6.15)
Median	7.15	4.63	0.33	0.46
Interquartile Range	2.20 - 21.60	2.78 - 9.98	0.20 - 0.64	0.20 - 0.93
Min - Max	0.2 - 85.0	0.6 - 81.3	0.2 - 36.1	0.2 - 42.7
Week 24				
n	47	47	88	47
Mean (SD)	16.30 (21.85)	11.64 (21.38)	0.47 (0.47)	3.56 (13.09)
Median	8.84	5.32	0.32	0.46
Interquartile Range	3.69 - 22.00	1.91 - 12.30	0.20 - 0.58	0.22 - 1.02
Min - Max	0.2 - 119.0	0.7 - 135.0	0.2 - 3.8	0.2 - 88.0
Week 28				
n	47	46	88	43
Mean (SD)	8.81 (10.98)	10.31 (15.16)	0.50 (0.53)	1.32 (2.46)
Median	4.42	7.08	0.34	0.55
Interquartile Range	2.33 - 9.28	1.97 - 11.00	0.20 - 0.61	0.21 - 1.04
Min - Max	0.5 - 51.5	0.7 - 95.9	0.2 - 3.5	0.2 - 13.4

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_mediqr.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_mediqr_SE_CRP.out
11JUL2016 23:00

Summary of Median and IQR CRP (mg/L) values by Visit, Safety Population
Protocol: WA28119

Visit	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Week 32				
n	45	46	88	43
Mean (SD)	11.68 (16.53)	10.48 (14.81)	1.78 (11.80)	1.39 (4.60)
Median	6.86	6.90	0.33	0.54
Interquartile Range	2.63 - 14.40	2.07 - 12.00	0.20 - 0.57	0.20 - 0.82
Min - Max	0.3 - 91.5	0.7 - 89.8	0.2 - 111.0	0.2 - 30.5
Week 36				
n	46	47	85	42
Mean (SD)	11.27 (18.27)	11.61 (15.11)	1.04 (4.91)	1.93 (6.66)
Median	6.37	6.20	0.32	0.60
Interquartile Range	2.25 - 10.80	1.68 - 15.20	0.20 - 0.54	0.25 - 1.04
Min - Max	0.2 - 94.5	0.5 - 78.7	0.2 - 45.4	0.2 - 43.4
Week 40				
n	45	46	86	41
Mean (SD)	8.89 (10.56)	11.15 (11.12)	0.85 (2.54)	1.25 (2.64)
Median	5.94	6.54	0.29	0.39
Interquartile Range	2.65 - 8.97	2.66 - 15.80	0.20 - 0.58	0.20 - 0.98
Min - Max	0.3 - 44.4	0.7 - 48.4	0.2 - 17.5	0.2 - 15.6

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_mediqr.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_mediqr_SE_CRP.out
11JUL2016 23:00

Page 4 of 5

Summary of Median and IQR CRP (mg/L) values by Visit, Safety Population
Protocol: WA28119

Visit	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Week 44				
n	44	46	86	41
Mean (SD)	8.68 (10.05)	12.38 (14.94)	0.90 (2.93)	2.20 (5.59)
Median	6.54	8.43	0.30	0.56
Interquartile Range	1.57 - 9.84	3.09 - 14.80	0.20 - 0.59	0.20 - 0.89
Min - Max	0.2 - 48.7	0.2 - 74.9	0.2 - 25.4	0.2 - 28.0
Week 48				
n	44	45	84	40
Mean (SD)	8.91 (9.78)	12.41 (15.92)	1.71 (10.25)	0.71 (0.95)
Median	6.36	6.82	0.27	0.35
Interquartile Range	2.33 - 10.40	2.36 - 14.90	0.20 - 0.52	0.20 - 0.74
Min - Max	0.3 - 44.1	0.6 - 81.7	0.2 - 93.2	0.2 - 5.0
Week 52				
n	35	33	76	35
Mean (SD)	8.10 (10.40)	10.00 (10.06)	1.42 (4.30)	0.83 (1.60)
Median	4.90	8.12	0.30	0.33
Interquartile Range	2.25 - 9.25	2.02 - 14.40	0.20 - 0.59	0.20 - 0.72
Min - Max	0.3 - 47.0	0.6 - 38.7	0.2 - 29.6	0.2 - 9.4

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_mediqr.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_mediqr_SE_CRP.out
11JUL2016 23:00

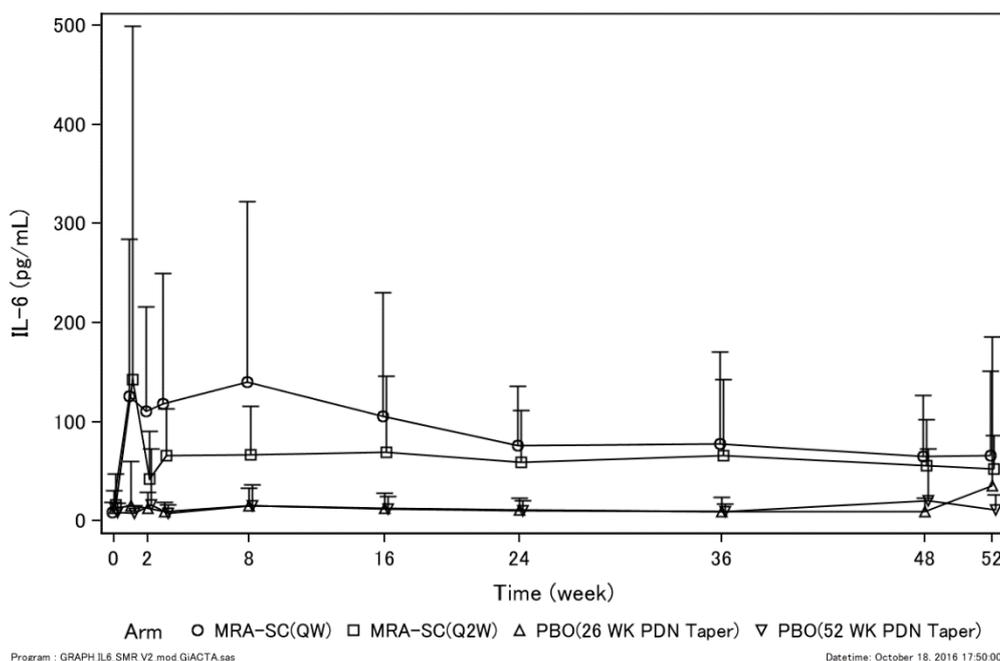
Page 5 of 5

[5.3.5.1-3 t_lb_mediqr_SE_CRP を再掲]

2.7.2.2.2.4 MRA-SC 162 mg/週及び162 mg/2週投与による血中 IL-6濃度の経時的推移

血中 IL-6濃度の平均値の経時的推移を図 2.7.2.2.2.4-1に示す。血中 IL-6濃度は、MRA-SC 162 mg/週及び162 mg/2週の初回投与前から投与後1週にかけて増加した。プラセボの2群ではMRA-SC QW 群やMRA-SC Q2W 群で認められた血中 IL-6濃度の大きな変動は認められなかった。MRA-SC QW 群の平均血中 IL-6濃度は、初回投与後2週以降、MRA-SC Q2W 群と比較し、高値であることが示され、52週後においては、 65.99 ± 84.92 pg/mL（平均値 ± 標準偏差）であり、MRA-SC Q2W 群では 52.70 ± 33.10 pg/mL であった。

図 2.7.2.2.2.4-1 血中 IL-6濃度の平均値の経時的推移

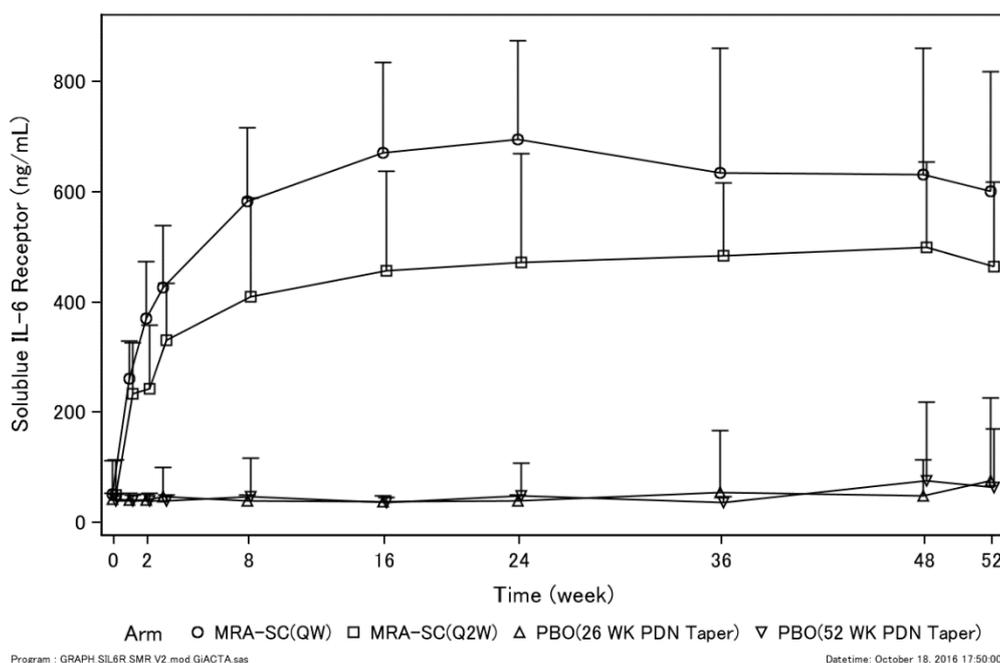


[5.3.5.3-2 図 10-11を再掲]

2.7.2.2.2.5 MRA-SC 162 mg/週及び162 mg/2週投与による血中 sIL-6R 濃度の経時的推移

血中 sIL-6R 濃度の平均値の経時的推移を図 2.7.2.2.2.5-1に示す。血中 sIL-6R 濃度は、いずれの MRA-SC 投与群においても16週まで増加し、その後定常に達することが認められた。52週時のMRA-SC QW 群及びMRA-SC Q2W 群の血中 sIL-6R 濃度は 600.53 ± 217.52 ng/mL（平均値 ± 標準偏差）、 464.30 ± 153.64 ng/mL と、MRA-SC QW 群の血中 sIL-6R 濃度が29%高かった。定常状態に達する時点が16週時と血清トシリズマブトラフ濃度と同様の推移を示していることから、血中トシリズマブ濃度と sIL-6R 濃度は関連していると考えられる。MRA-SC Q2W 群では、MRA-SC QW 群より血中 sIL-6R 濃度は低値を示した。トシリズマブは濃度依存的に血中 sIL-6R と免疫複合体を形成することで sIL-6R の消失半減期が延長し、血中 sIL-6R 濃度が上昇すると考えられている。2週間隔の投与では1週間隔の投与より血中 sIL-6R 濃度が低値を示したことから、トシリズマブの血中濃度が足りず、トシリズマブと sIL-6R との結合が飽和していない可能性が示された。

図 2.7.2.2.2.5-1 血中 sIL-6R 濃度の平均値の経時的推移



[5.3.5.3-2 図 10-12を再掲]

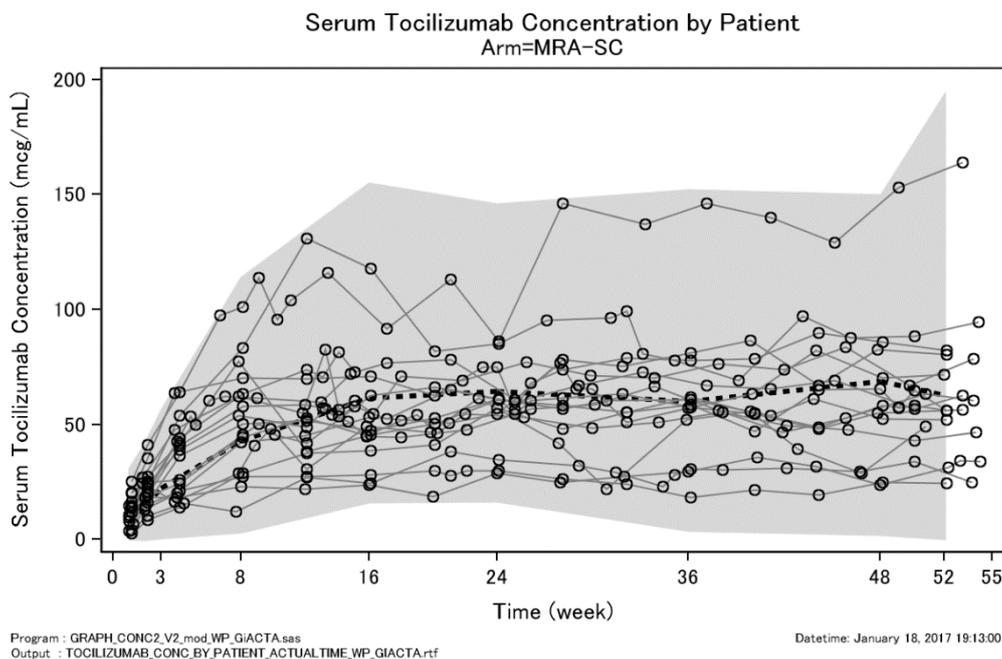
2.7.2.3 全試験を通しての結果の比較と解析

2.7.2.3.1 MRA-SC 162 mg/週投与における MRA632JP 試験と WA28119試験の薬物動態の比較

2.7.2.3.1.1 血清中トシリズマブトラフ濃度の経時的推移の比較

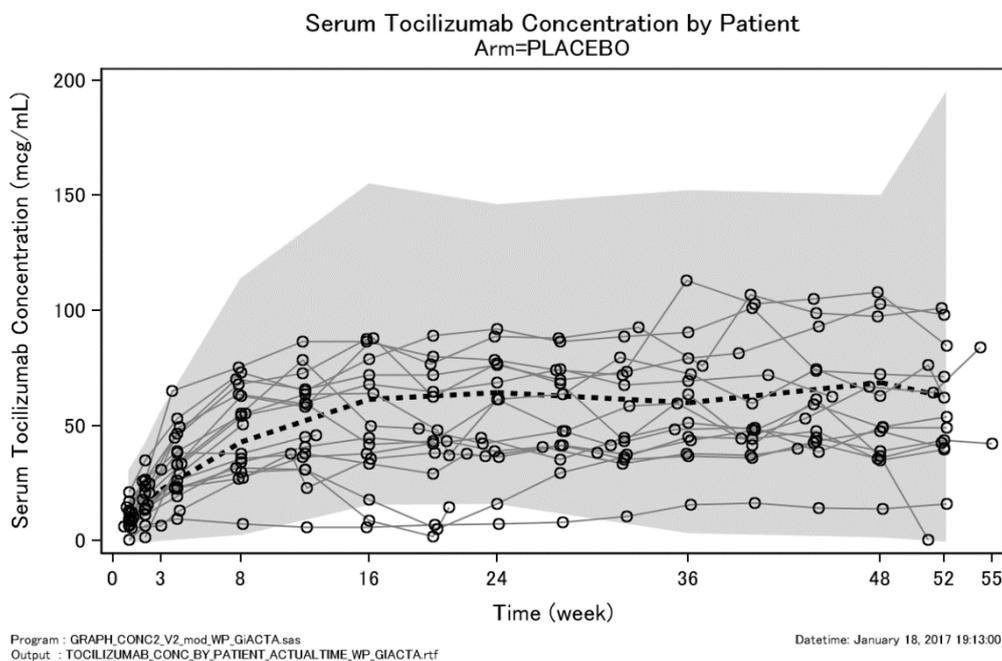
高安動脈炎対象の国内第 III 相試験である MRA632JP 試験と巨細胞性動脈炎対象の海外第 III 相試験である WA28119試験から得られた MRA-SC 162 mg/週の反復皮下投与時の血清中トシリズマブトラフ濃度推移を比較した結果、MRA632JP 試験の初回投与後12週以降の2例以上の時点における平均血清中トシリズマブトラフ濃度は、41.8~94.5 $\mu\text{g/mL}$ であり、WA28119試験の初回投与後16週以降の平均血清中トシリズマブトラフ濃度は、63.49~70.46 $\mu\text{g/mL}$ であった。両試験の初回投与後16週以降において、定常状態に達した血清中トシリズマブトラフ濃度に大きな違いは認められなかった (図 2.7.2.2.1.2-1, 図 2.7.2.2.1.2-2及び図 2.7.2.2.2.2-1)。また、MRA632JP 試験で得られた全期間の MRA-SC 群における個別血清中トシリズマブトラフ濃度推移あるいは、非盲検期間のプラセボ群における MRA-SC 投与後の個別血清中トシリズマブトラフ濃度推移と WA28119試験における血清トシリズマブトラフ濃度の最小値、最大値を網掛けで示した図を図 2.7.2.3.1.1-1及び図 2.7.2.3.1.1-2に示す。全期間の MRA-SC 群及び非盲検期間のプラセボ群における MRA632JP 試験の個別血清中トシリズマブトラフ濃度はほぼ、WA28119試験における血清トシリズマブトラフ濃度の最小値-最大値の範囲に入ることが明らかとなった。以上の結果より、大型血管炎 (高安動脈炎, 巨細胞性動脈炎) 患者において、MRA-SC 162 mg/週投与時の薬物動態の疾患による差及び人種間差は認められなかったと判断できる。

図 2.7.2.3.1.1-1 全期間のMRA-SC群におけるMRA632JP試験とWA28119試験の血清中トシリズマブトラフ濃度の比較



MRA632JP試験の全期間におけるMRA-SC群の個別血清中トシリズマブトラフ濃度推移とWA28119試験の二重盲検期間における血清トシリズマブトラフ濃度の最小値、最大値を網掛けで示し、破線はWA28119試験の血清トシリズマブトラフ濃度の中央値の推移を示している。 [5.3.5.3-3 図 10-5を再掲]

図 2.7.2.3.1.1-2 非盲検期間のプラセボ群におけるMRA632JP試験とWA28119試験の血清中トシリズマブトラフ濃度の比較



MRA632JP試験の非盲検期間のプラセボ群におけるMRA-SC投与後の個別血清中トシリズマブトラフ濃度推移とWA28119試験の二重盲検期間における血清トシリズマブトラフ濃度の最小値、最大値を網掛けで示し、破線はWA28119試験の血清トシリズマブトラフ濃度の中央値の推移を示している。 [5.3.5.3-3 図 10-6を再掲]

2.7.2.3.1.2 CRP 値の経時的推移の比較

MRA632JP 試験では、1例の1時点を除き、MRA-SC 162 mg 初回投与後、CRP 値は血清中トシリズマブ濃度に関わらず、低値を示した。WA28119試験の MRA-SC 162 mg/週投与の MRA-SC QW 群では、投与1週後1.03 mg/dL 以下に、また、被験者の75%が2週から52週まで0.1 mg/dL 以下に低下することが認められた。以上の両試験より、大型血管炎（高安動脈炎、巨細胞性動脈炎）患者においては、MRA-SC 162 mg/週投与により CRP 値は陰性化し、反復投与により維持できるものと考えられた。

2.7.2.3.1.3 血中 IL-6濃度の経時的推移の比較

MRA632JP 試験及び WA28119試験の両試験において、MRA-SC 162 mg/週投与により、血中 IL-6濃度は初回投与後1週にかけて急激な上昇が認められたが、血清中トシリズマブトラフ濃度と血中 IL-6濃度の間に明確な関連は認められなかった。またプラセボ群の血中 IL-6濃度は MRA-SC を投与した被験者と比較して、大きな変動は認められず、低値を示した。大型血管炎（高安動脈炎、巨細胞性動脈炎）患者において、MRA-SC 投与後の血中 IL-6濃度が上昇した理由は、IL-6の消失経路の一つである IL-6R との結合が抗 IL-6R 抗体であるトシリズマブにより阻害され、血中に滞留したためと考えられる。

2.7.2.3.1.4 血中 sIL-6R 濃度の経時的推移の比較

MRA632JP 試験の MRA-SC 162 mg/週投与により、血中 sIL-6R 濃度は血清中トシリズマブトラフ濃度約25~50 µg/mL まで濃度依存的に上昇し、それ以上の血清中トシリズマブトラフ濃度では血中 sIL-6R 濃度500~600 ng/mL 付近で一定となる傾向が認められた。また、二重盲検下の被験者14例が定常状態に達した初回投与後12週時及び全期間において初回投与後12週時までの本剤投与中止例を除く35例の被験者での初回投与12週時の平均血中 sIL-6R 濃度は、それぞれ 527.29 ± 111.41 ng/mL, 502.17 ± 95.88 ng/mL（平均値 ± 標準偏差）であった（5.3.5.1-1 表 15.2.1-30, 5.3.5.1-7 表 11.2-8）。WA28119試験の MRA-SC QW 群では、血中 sIL-6R 濃度は16週まで増加し、その後定常に達し、52週時の MRA-SC QW 群の血中 sIL-6R 濃度は 600.53 ± 217.52 ng/mL であった。定常状態に達する時点が16週時と血清トシリズマブトラフ濃度と同様の推移を示した。以上のことから、血中トシリズマブ濃度と sIL-6R 濃度は関連していると考えられる。

2.7.2.3.2 WA28119試験の MRA-SC 162 mg/週投与と162 mg/2週投与の比較

WA28119試験の MRA-SC 162 mg/週及び162 mg/2週皮下注の初回投与後24週の血清中トシリズマブトラフ濃度は、 68.18 ± 30.71 µg/mL（平均値 ± 標準偏差, 162 mg/週, 87例）及び 12.46 ± 9.83 µg/mL（162 mg/2週, 41例）であり、24週時における MRA-SC QW 群の血清中トシリズマブトラフ濃度は、MRA-SC Q2W 群と比較して、5.47倍と高い結果が得られた。また、MRA-SC 投与後の CRP 値の中央値及び第3四分位点は、MRA-SC QW 群のいずれの時点においても MRA-SC Q2W 群より低値を示し、MRA-SC 162 mg/2週よりも162 mg/週の用法・用量での CRP 値を陰性化する効果は高いことが予想された。血中 IL-6濃度に関しては、IL-6の消失経路の一つである IL-6R との結合がトシリズマブにより阻害され、血中に滞留することが予想された。実際、MRA-SC QW 群の平均血中 IL-6濃度は初回投与後2週以降 MRA-SC Q2W 群と比べ、高値であり、52週後においては25%高値であることが示された。トシリズマブは濃度依存的に血中 sIL-6R と免疫複合体を形成することで、sIL-6R の消失半減期が延長し、血中 sIL-6R 濃度が上昇すると考えられている。WA28119試験の52週時の MRA-SC QW 群及び MRA-SC Q2W 群の血中 sIL-6R 濃度は 600.53 ± 217.52 ng/mL（平均値 ± 標準偏差）、 464.30 ± 153.64 ng/mL と、MRA-SC QW 群の血中 sIL-6R 濃度が29%高かった。また、MRA632JP 試験の血清中トシリズマブトラフ濃度25~50 µg/mL 以上において、血中 sIL-6R 濃度500~600 ng/mL 付近で一定とな

った結果も合わせると、2週間隔の投与では、トシリズマブの血中濃度が足りず、トシリズマブと IL-6R との結合が飽和していない可能性が示された。以上より、MRA-SC 162 mg/2週よりも162 mg/週の用法・用量の方が適切であると考えられる。

アクテムラ皮下注162 mg シリンジ・AI
（トシリズマブ（遺伝子組換え））
[大型血管炎]

第2部 （モジュール2）：CTD の概要（サマリー）

2.7.3 臨床的有効性

中外製薬株式会社

略語一覧

略語	英名	和名
AI	auto injector	オートインジェクター
CI	confidence interval	信頼区間
CMH	Cochran-Mantel-Haenszel	—
CRP	C reactive protein	C 反応性蛋白
CT	computed tomography	コンピュータ断層撮影
CTCAE	common toxicity criteria for adverse event	有害事象共通用語規準
DMARD (s)	disease modifying anti-rheumatic drug (s)	疾患修飾抗リウマチ薬
DSA	digital subtraction angiography	—
ESR	erythrocyte sedimentation rate	赤血球沈降速度
HLA	human leukocyte antigen	ヒト白血球抗原
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for human use	医薬品規制調和国際会議
IL-6	interleukin 6	インターロイキン6
IL-6R	interleukin 6 receptor	インターロイキン6レセプター
ITT	intent to treat	—
MRA	—	トシリズマブの治験略号
MRA	magnetic resonance angiography	磁気共鳴血管造影法
MRA-SC	—	トシリズマブの皮下注製剤
MTX	methotrexate	メトトレキサート
PET/CT	positron emission/computerized tomography	—
PMR	polymyalgia rheumatica	リウマチ性多発筋痛症
QW	every week	週に1回
Q2W	every 2 week	2週に1回
RA	rheumatoid arthritis	関節リウマチ
SC	subcutaneous injection	皮下注射
SAA	serum amyloid A	血清アミロイド A
sIL-6R	soluble interleukin 6 receptor	可溶性インターロイキン6レセプター
TNF	tumor necrosis factor	腫瘍壊死因子
100 PYs	100 patient years	100人・年

目次

	頁
2.7.3 臨床的有効性.....	5
2.7.3.1 背景及び概観.....	5
2.7.3.1.1 MRA632JP 試験.....	6
2.7.3.1.1.1 試験デザイン.....	6
2.7.3.1.1.2 試験実施方法.....	7
2.7.3.1.1.2.1 対象患者.....	7
2.7.3.1.1.2.2 治験薬及び併用薬の投与方法.....	7
2.7.3.1.1.3 有効性の評価項目.....	8
2.7.3.1.1.4 有効性の評価方法.....	9
2.7.3.1.2 WA28119 試験.....	10
2.7.3.1.2.1 試験デザイン.....	10
2.7.3.1.2.2 試験実施方法.....	11
2.7.3.1.2.2.1 対象患者.....	11
2.7.3.1.2.2.2 治験薬及び併用薬の投与方法.....	12
2.7.3.1.2.3 有効性の評価項目.....	12
2.7.3.1.2.4 有効性の評価方法.....	13
2.7.3.1.3 MRA632JP 試験と WA28119 試験の比較.....	14
2.7.3.2 個々の試験結果の要約.....	14
2.7.3.2.1 MRA632JP 試験.....	14
2.7.3.2.2 WA28119 試験.....	16
2.7.3.3 全試験を通しての結果の比較と解析.....	17
2.7.3.3.1 試験対象集団.....	17
2.7.3.3.1.1 人口統計学的特性及びベースライン時特性.....	18
2.7.3.3.1.2 投与状況.....	19
2.7.3.3.2 全有効性試験の結果の比較検討.....	20
2.7.3.3.2.1 MRA632JP 試験.....	20
2.7.3.3.2.2 WA28119 試験.....	28
2.7.3.3.2.3 トシリズマブによる高安動脈炎の症例報告.....	35
2.7.3.3.3 部分集団における結果の比較.....	38
2.7.3.3.3.1 MRA632JP.....	38
2.7.3.3.3.2 WA28119 試験.....	39
2.7.3.4 推奨用法・用量に関する臨床情報の解析.....	43
2.7.3.5 効果の持続, 耐薬性.....	45
2.7.3.6 参考文献.....	46
2.7.3.7 付録.....	49

2.7.3.7.1	MRA632JP 試験.....	51
2.7.3.7.2	WA28119 試験.....	83
2.7.3.7.3	MRA632JP 試験と WA28119 試験.....	114

2.7.3 臨床的有効性

2.7.3.1 背景及び概観

トシリズマブ皮下注製剤（以降、MRA-SC 又は本剤）の有効性の評価には、国内で実施された高安動脈炎患者を対象とした第 III 相試験（以降、MRA632JP 試験）と海外で実施された巨細胞性動脈炎患者を対象とした第 III 相試験（以降、WA28119試験）の結果を用いた。試験の概要を表 2.7.3.1-1に示す。

表 2.7.3.1-1 本剤の有効性の評価に用いた試験の概要

国内／海外	相	試験番号 評価/参考 資料番号	デザイン	対象	試験の目的	投与群・投与例数 解析対象例	投与期間
国内	III	MRA632JP 評価資料 5.3.5.1-1 5.3.5.1-7 ¹⁾	多施設共同 【二重盲検期 間】 ランダム化二 重盲検 【非盲検期 間】 非盲検	高安動脈 炎患者	<ul style="list-style-type: none"> ・有効性 ・安全性 ・薬物動態 ・薬力学 	【二重盲検期間】 プラセボ群：18例 MRA-SC 群：18例 ITT：36例 PPS：33例 Safety：36例 【非盲検期間】 162 mg/週：36例	【二重盲検期間】 高安動脈炎の再発が認められた被験者は再発が認められた日から4週間以内に実施された二重盲検期間の最終観察日までとし、残りの被験者は再発した被験者数が計19例に達した時点から4週間以内に実施された二重盲検期間最終観察日までとした。 【非盲検期間】 二重盲検期間終了後から製造販売承認が得られるまで（現在実施中）
海外	III	WA28119 評価資料 5.3.5.1-3 ²⁾	多施設共同 【二重盲検期 間】 ランダム化二 重盲検 【非盲検期 間】 非盲検	巨細胞性 動脈炎患 者	<ul style="list-style-type: none"> ・有効性 ・安全性 ・薬物動態 ・薬力学 	【二重盲検期間】 プラセボ+26週群 ：50例 プラセボ+52週群 ：51例 MRA-SC QW 群 ：100例 MRA-SC Q2W 群 ：49例 ITT：250例 Safety：250例	【二重盲検期間】 52週間 【非盲検期間】 104週間（現在実施中）

1)：2016年11月10日データカットオフ（全例が非盲検期間でトシリズマブを52週間投与終了した時点）

2)：2016年4月11日データカットオフ（全例が二重盲検期間の最終観察を終了した時点）

MRA-SC 群：162 mg/週投与

プラセボ+26週群：プラセボ/週投与と26週間の副腎皮質ステロイド漸減投与

プラセボ+52週群：プラセボ/週投与と52週間の副腎皮質ステロイド漸減投与

MRA-SC QW 群：162 mg/週投与と26週間の副腎皮質ステロイド漸減投与

MRA-SC Q2W 群：162 mg/2週投与と26週間の副腎皮質ステロイド漸減投与

2.7.3.1.1 MRA632JP 試験

本試験では、高安動脈炎患者を対象に MRA-SC 162 mg/週（以降、MRA-SC 群）又は MRA-SC プラセボ 162 mg/週（以降、プラセボ群）を用いた二重盲検並行群間比較法で、プラセボに対する MRA-SC の有効性、安全性、薬物動態及び薬力学の検討を行った。二重盲検期間終了後、非盲検下で MRA-SC 162 mg/週長期投与における安全性、有効性、薬物動態及び薬力学の検討を行った。

本試験では、19例の再発が観察された時点で二重盲検期間を終了し、その直後に再発があった1例を合わせた20例の再発例を含む全例を4週間以内に非盲検期間へ移行した。本試験での有効性については、主要評価項目の二重盲検期間での高安動脈炎の再発までの期間を、19例の再発が観察された時点でのデータを用いて評価した。

2.7.3.1.1.1 試験デザイン

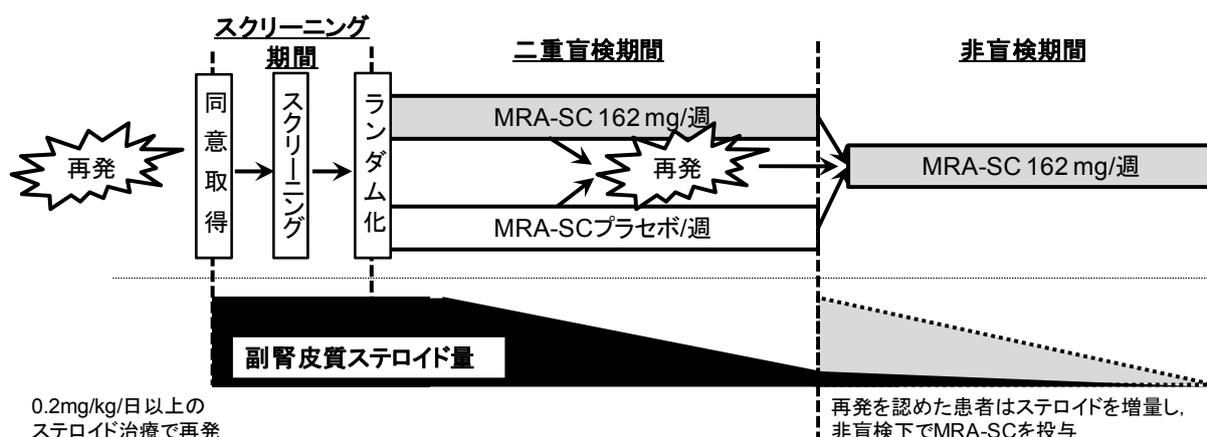
現時点で高安動脈炎に対して有効性が検証されている薬剤は存在しないことから、本試験ではプラセボを対照とした臨床試験を実施した。高安動脈炎は、血管の線維化等、時に不可逆的な転帰を辿るため、症状を有する患者にプラセボを投与することの倫理性を考慮し、症状が寛解した患者を対象とした試験デザインとした。高安動脈炎の臨床評価に関連したガイドラインは存在せず、評価方法は統一されていないものの、高安動脈炎のアウトカム指標として最も汎用されている副腎皮質ステロイドの減量効果を評価する試験デザインとし、規定されたペースで副腎皮質ステロイドを減量投与（2.7.3.1.1.2.2(2)項参照）した時の高安動脈炎再発までの期間を主要評価項目とした。高安動脈炎再発の定義については、US National Institutes of Health (NIH) により提唱されている Kerr の定義¹⁾が最も汎用されているため、これをベースとして実臨床における再発の判定基準と ITAS2010²⁾を参考に策定した。

高安動脈炎は、初発年齢が20歳前後の就学期及び就労期の若年女性に好発することからより利便性の高い皮下注製剤が適切であること、不可逆的に進行する疾患であることから、持続的かつ確実に炎症を抑制し、再発防止に重きを置く治療方針が適切と考えられるため、常に十分な血清中トシリズマブ濃度を維持できる用法・用量が必要である。また、過去の臨床試験成績から血清中トシリズマブトラフ濃度上昇に伴う安全性の懸念が認められていないことから、MRA-SC 162 mg の1週間隔投与が妥当と判断した。

本試験では、登録前の12週間以内に0.2 mg/kg/日以上副腎皮質ステロイド（以降、副腎皮質ステロイドはすべてプレドニゾロン換算値で表示）による治療中にも関わらず高安動脈炎の再発（定義は2.7.3.1.1.3(1)項参照）が認められた患者を登録した。登録された患者は、高安動脈炎再発時の倍量以上の副腎皮質ステロイド投与により寛解を1週間以上維持したことを確認された後、ランダム化時の副腎皮質ステロイド投与量（0.6 mg/kg 未満、0.6 mg/kg 以上0.8 mg/kg 未満、0.8 mg/kg 以上）を層別因子として MRA-SC 群とプラセボ群の2群に1:1に割り付けられた。副腎皮質ステロイドを規定どおりに0.1 mg/kg/日まで減量しながら、二重盲検下で MRA-SC 162 mg 又はプラセボを1週間隔で皮下投与した。二重盲検期間で高安動脈炎の再発が認められた被験者は、再発が認められた日から4週間以内に非盲検期間に移行し、副腎皮質ステロイドを増量し、MRA-SC 162 mg/週の投与を受けた。また、二重盲検期間で高安動脈炎の再発の定義（2.7.3.7.1(1)~2.7.3.7.1(3)）には合致しないものの、高安動脈炎の病勢進行等により二重盲検期間の継続が困難と判断された被験者は、医学専門家と治験依頼者で協議の上、非盲検期間へ移行することも可能とした。

盲検下レビューの結果、年齢のカテゴリ（18歳未満、18歳以上65歳未満、65歳以上）間で高安動脈炎の再発数に偏りがみられ、年齢のカテゴリが主要評価項目に影響する因子であることが示唆された。そのため、有効性の主要評価項目の解析方法を、上記の年齢のカテゴリを層別因子とした層別 Log-rank 検定及び層別 Cox 比例ハザードモデルに変更した。

図 2.7.3.1.1.1-1 MRA632JP の試験デザイン



2.7.3.1.1.2 試験実施方法

2.7.3.1.1.2.1 対象患者

本試験では、12歳以上の患者を対象とした。高安動脈炎の好発年齢は、女性では20歳前後と報告されており^{3),4)}、20歳未満の患者も多く存在することが示唆され、幅広い治療機会を提供する必要があると考えて本試験の対象に組み入れた。12歳以上の平均体重は男女とも40 kg を越えており⁵⁾、関節リウマチで実施した国内臨床試験の経験を大きく下回ることはないと推察されること、また、トシリズマブは既適応の全身型若年性特発性関節炎で得られている8 mg/kg/2週の点滴静脈内投与での血清中トシリズマブ濃度を、162 mg/週の皮下投与が上回る可能性は低いと考えられるため、小児に対する本剤の1週間隔投与でのトシリズマブの曝露は忍容可能な範囲であり、12歳以上の患者を組み込むことは妥当であると考えた。

なお、MRA632JP 試験の選択基準、除外基準及び患者背景の詳細は、「2.7.6 個々の試験のまとめ」に示す。選択基準及び除外基準は、血管炎症候群の診療ガイドライン (JCS 2008)³⁾、アクテムラ点滴静注用の添付文書、アクテムラ皮下注の添付文書及びトシリズマブ使用ガイドラインに準拠して設定した。

2.7.3.1.1.2.2 治験薬及び併用薬の投与方法

(1) 本剤

1) 二重盲検期間

治験薬初回投与は、治験薬初回投与1週間以前から高安動脈炎の寛解 (2.7.3.6項参照) が継続していることを確認後に実施した。登録された被験者は二重盲検下で MRA-SC 162 mg 又はプラセボを週1回投与された。また、副腎皮質ステロイドは2.7.3.1.1.2.2(2)1)項に従って減量した。

2) 非盲検期間

二重盲検期間に高安動脈炎を再発した被験者は、非盲検期間に移行し、副腎皮質ステロイドを増量して MRA-SC 162 mg/週の投与を受けた。また、二重盲検期間終了後には、全例、非盲検期間に移行した。非盲検期間中の副腎皮質ステロイド量は治験責任医師又は治験分担医師の裁量によって変更可能とした。

(2) 副腎皮質ステロイド

1) 二重盲検期間

試験中に併用する副腎皮質ステロイドは、実施医療機関で市販のものを入手し使用した。副腎皮質ステロイド使用量は、二重盲検期間では治験薬初回投与後4週間は減量しないこととし、

それ以降は以下の計算式に従って毎週10%ずつ減量した。

$$\text{計算式：N週目の投与量} = \text{治験薬初回投与時の用量} \times 0.9^{(N-3)}$$

二重盲検期間で0.1 mg/kg/日まで減量した場合は、それ以上は減量しないこととした。なお、副腎皮質ステロイド使用量はすべてプレドニゾロン換算とした。

二重盲検期間中に再発し、非盲検期間へ移行するまでの間は、治験責任医師の裁量によって副腎皮質ステロイド量を調整して投与した。

2) 非盲検期間

治験責任医師の裁量によって副腎皮質ステロイド量を調整して投与した。

2.7.3.1.1.3 有効性の評価項目

有効性評価項目の再発までの期間と副腎皮質ステロイド投与量について以下に記載した。

(1) 再発までの期間

1) 再発の定義

再発までの期間は、ランダム化から再発までの期間とした。再発は、客観的評価での全身症状、主観的評価での全身症状、炎症マーカーの上昇、血管病変、臓器病変を伴う虚血症状、画像評価の該当項目によって定義され（表 2.7.3.1.1.3-1）、主要評価項目では再発までの期間、副次的評価項目では Kerr の定義による再発までの期間、臨床症状による再発までの期間の3種類に分けて評価した。主要評価項目は、客観的評価での全身症状、主観的評価での全身症状、炎症マーカーの上昇、血管病変、臓器病変を伴う虚血症状の5項目中2項目以上で再発の徴候ありと判定された場合に再発と定義した。

再発の定義については、US National Institutes of Health (NIH) により提唱されている Kerr の定義¹⁾が最も汎用されているため、これをベースとして実臨床における再発の判定基準と ITAS2010²⁾を参考に策定した。

表 2.7.3.1.1.3-1 高安動脈炎の再発の定義

		項目						再発の定義
		客観的評価による全身症状	主観的評価による全身症状	炎症マーカーの上昇	血管病変	臓器病変を伴う虚血症状	画像評価	
主要評価項目	高安動脈炎の再発	○	○	○	○	○	×	2/5 項目以上
副次的評価項目	Kerr の定義による高安動脈炎の再発	○		○	○		○	2/4 項目以上
	臨床症状による高安動脈炎の再発	○	○	×	○	○	×	1/4 項目以上

○：該当項目 ×：非該当項目

2) 再発の各項目

「高安動脈炎の再発及び寛解の定義（MRA632JP 試験）」に詳細を記載した。

3) 再発の評価日と打ち切り例

再発日は医師による評価日とした。解析時点で再発が起きていない被験者は、再発が起きていないことが確認されている最終の高安動脈炎徴候の評価日で打ち切りとした。

客観的評価での全身症状、主観的評価での全身症状、炎症マーカーの上昇、血管病変につ

いては、2回以上の連続した評価により、高安動脈炎以外の原因を除外した。ただし、緊急の治療を要する場合は1回のみでの評価を可とした。2回以上の評価を実施した際の再発日は1回目の評価日とした。

(2) 副腎皮質ステロイド投与量

二重盲検期間では、再発時又は二重盲検期間の最終観察時の副腎皮質ステロイド投与量を、非盲検期間では、副腎皮質ステロイド投与量の推移を評価した。

2.7.3.1.1.4 有効性の評価方法

(1) 必要症例数の設定と中間解析

高安動脈炎再発までの期間の分布に指数分布を仮定し、プラセボ群の24週無再発率を25.0%^{*1}、MRA-SC 群の24週無再発率を75.0%^{*2}（ハザード比：0.2075）、有意水準両側5%、検出力90%、24週間での脱落率を20%とし、Log-rank 検定で群間比較するとした。また、イベントが12（必要イベント数の約62%）発生した時点で無益性及び有効性の中間解析を計画した。有効性の中間解析に伴う第1種の過誤確率の上昇を防ぐため、中間解析時及び最終解析時（二重盲検期間終了時）の有意水準の導出には O'Brien-Fleming タイプの Lan & DeMets の α 消費関数⁶⁾を用いた。なお、上記の情報分数が与えられた下での有効性の中間解析及び最終解析時有意水準は、それぞれ0.0096、0.0470であった。また、無益性の中間解析に伴う試験全体の検出力を確保するため、O'Brien-Fleming タイプの Lan & DeMets の β 消費関数を用いた。この場合、最終解析の必要イベント数は19イベント、中間解析時の必要イベント数は12イベントとなった。登録期間を52週間、追跡期間を76週間、24週間の脱落割合を両群それぞれ20%とすると、必要症例数は33例となったため、1群17例、計34例を必要症例数とした。

*1：プラセボ群の24週無再発率は、以下のように推定した。

副腎皮質ステロイドを10 mg/日以下に減量すると、6カ月の無再発率は28%との報告がある⁷⁾。本試験では、症例報告よりも早いスピードでステロイドを減量させるため、プラセボ群の24週時無再発率は25%と仮定した。

*2：MRA-SC 群の24週無再発率は、以下のように推定した。

トシリズマブ（IV 8 mg/kg/4週）投与後に報告者の評価でトシリズマブが有効と判断された割合は79.6%（43/54例）であった⁸⁾⁻²²⁾。保守的に見積もり、MRA-SC 群の24週時無再発率は75%と仮定した。

以上より、両群併せた目標症例数を34例（各群17例）と設定し、本試験の早期有効中止及び早期無益性中止の可否を検討するために、12件（必要イベント数の約63%）のイベントが観察された時点をそれぞれデータカットオフ日とし、中間解析を実施することとした。実際には、13件の再発が観察された時点で中間解析を実施し、試験を継続した。

(2) 統計学的手法

主要評価項目の高安動脈炎再発までの期間の分布及び中央値は、Kaplan-Meier 法を用いて群ごとに推定し、二重対数変換の Brookmeyer-Crowley 法を用いて中央値の信頼区間を合わせて推定した。なお、本試験では MRA-SC 群の高安動脈炎再発までの期間の中央値は推定できない可能性を考慮し、時期ごとに高安動脈炎無再発率も推定した。治療効果の推定値として、Cox 比例ハザードモデルを仮定し、プラセボ群に対する MRA-SC 群のハザード比とその信頼区間を推定した。

本試験の主要解析では、プラセボ群に対する MRA-SC 群の優越性を評価するため、年齢カテゴリ（18歳未満、18歳以上65歳未満、65歳以上）で層化調整した Log-rank 検定を実施し、両側 P 値が解析時点の有意水準を下回るかで仮説検定した。

解析時点の信頼区間の信頼係数及び有意水準は、中間解析に伴う第1種の過誤確率の上昇を考慮して、O'Brien-Fleming タイプの α 消費関数に基づいて決定された。また、感度解析として割付因子で層化調整した Log-rank 検定及び Cox 回帰の解析結果も報告した。

2.7.3.1.2 WA28119試験

2.7.3.1.2.1 試験デザイン

WA28119試験では、プラセボ対照二重盲検並行群間比較法により、巨細胞性動脈炎患者を対象として副腎皮質ステロイドの減量下で MRA-SC 162 mg/週、MRA-SC 162 mg/2週又はプラセボを投与し、本剤の有効性、安全性の検討を行った。二重盲検期間の52週間 (Part 1) 終了後、104週間の非盲検期間 (Part 2) で MRA-SC 162 mg/週の長期投与での安全性、有効性の検討を行うこととした。

目標症例数は、MRA-SC 162 mg/週群100例、MRA-SC 162 mg/2週群50例及びプラセボ2群各50例の4群250例に設定し、試験開始時の副腎皮質ステロイド量 (プレドニゾン換算量で30 mg/日以下、30 mg/日超、以降すべてプレドニゾン換算値で表示) を層別因子として、以下の4群に2:1:1:1の比で割り付けた。

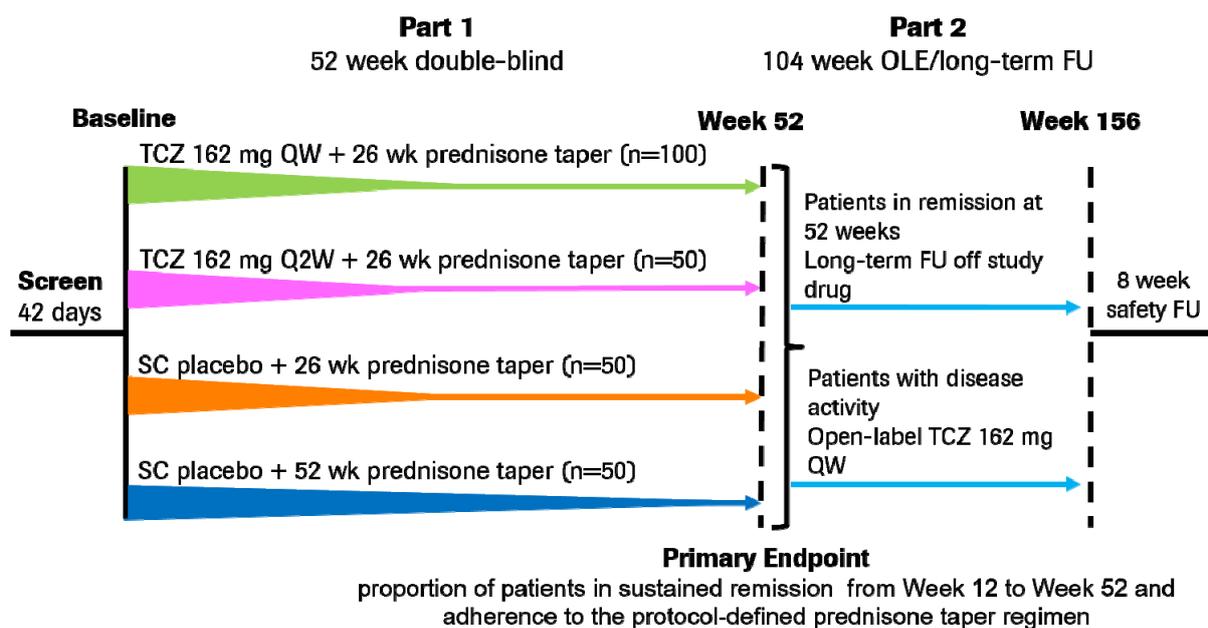
- MRA-SC 162 mg/週と26週間の副腎皮質ステロイド漸減投与 (以降、MRA-SC QW 群)
- MRA-SC 162 mg/2週と26週間の副腎皮質ステロイド漸減投与 (以降、MRA-SC Q2W 群)
- プラセボ/週と26週間の副腎皮質ステロイド漸減投与 (以降、プラセボ+26週群)
- プラセボ/週と52週間の副腎皮質ステロイド漸減投与 (以降、プラセボ+52週群)

本試験では、ランダム化後12週以内に巨細胞性動脈炎の症状が寛解導入され、52週時まで再発を認めなかった被験者を「寛解を維持していた被験者」(以降、レスポnder) とした。ランダム化後12週以内に寛解導入し、52週間の二重盲検期間 (Part 1) に MRA-SC 162 mg/週、MRA-SC 162 mg/2週又はプラセボを二重盲検下で投与し、副腎皮質ステロイド量を規定どおりに漸減することにより再発を誘導しても、再発せず寛解を維持しているレスポnderの割合から本剤の有効性を評価した。

主要評価項目は、52週時の寛解維持割合とし、26週間の副腎皮質ステロイド漸減投与下のプラセボ (プラセボ+26週群) に対する MRA-SC の優越性を検証した (有意水準: 0.005)。なお、ランダム化後12週以内に疾患症状が寛解に至らなかった場合、治験実施計画書の規定通りの副腎皮質ステロイドの漸減投与ができなかった場合、52週までに再発又は中止した場合は、ノンレスポnderとして副腎皮質ステロイドの救済治療 (escape therapy) (2.7.3.1.2.2.2(2)) を受けることとした。

本試験では、ベースライン前の6週以内に新たに巨細胞性動脈炎と診断された「新規発症の患者」、又はプレドニゾン換算値で40 mg/日以上副腎皮質ステロイドによる2週間以上の連続した治療歴があり、ベースラインの6週よりも前に巨細胞性動脈炎と診断された「再発患者」を対象とした。

図 2.7.3.1.2.1-1 WA28119の試験デザイン



TCZ : MRA-SC

2.7.3.1.2.2 試験実施方法

2.7.3.1.2.2.1 対象患者

巨細胞性動脈炎の発症年齢は50歳以上が多く、50歳以下は稀で、60～70代にピークがある^{3,4)}。本試験では、50歳以上かつ過去に ESR 50 mm/時であった患者を対象とした。また、以下の (1) 又は (2) のいずれかで巨細胞性動脈炎と診断され、かつ (3) 又は (4) のいずれかの症状が認められる患者を対象とした。

なお、WA28119試験の対象の選択基準、除外基準及び患者背景の詳細は、「2.7.6 個々の試験のまとめ」に示した。

- (1) 巨細胞性動脈炎を特徴づける側頭動脈の生検所見
- (2) 血管造影又は断層像 (MRA, CTA, PET-CT など) (以降, 画像判定) による大型血管炎の診断
- (3) 明確な巨細胞性動脈炎の頭部の症状 (新規発症の限局的な頭痛, 頭皮の圧痛, 側頭動脈痛又は脈拍減弱, 局所貧血に関連した失明, その他咀嚼時の口や顎の原因不明の痛み)
- (4) リウマチ性多発筋痛症 (以降, PMR) の症状 (炎症性の朝のこわばりを伴う肩及び/又は腰帯痛)

更に、以下に示す新規発症又は再発した患者であり、ベースライン時の6週以内に疾患活動性が認められた (頭部の症状又は PMR の症状や徴候があり, ESR が30 mm/時以上又は CRP が1 mg/dL 以上) 患者を対象とした。

新規発症の患者 : ベースライン前の6週以内に新たに巨細胞性動脈炎と診断

再発の患者 : ベースライン時の6週より以前に巨細胞性動脈炎と診断され, 40 mg/日以上の副腎皮質ステロイドによる2週間以上の連続した治療歴がある

2.7.3.1.2.2 治験薬及び併用薬の投与方法

(1) 本剤

1) 二重盲検期間

MRA-SC 162 mg を週1回又は2週に1回、又はプラセボを週1回投与された。

2) 非盲検期間

52週間の二重盲検期間を終了した被験者は、非盲検期間に移行した。52週時に寛解している場合は、非盲検期間では本剤投与を中止して寛解維持の評価を継続した。再発又は疾患活動性が認められる場合は、その疾患活動性に基づいて医師の裁量により本剤の週1回投与及び/又は副腎皮質ステロイド若しくはメトトレキサート（以降、MTX）へ投与を変更することとした。

(2) 副腎皮質ステロイド

1) 二重盲検期間

副腎皮質ステロイド投与については、治験薬投与の二重盲検期間内に、副腎皮質ステロイド投与の非盲検期間と盲検期間を設定し、「表 2.7.3.7.2-1 副腎皮質ステロイド漸減投与スケジュール」に従った。副腎皮質ステロイドの非盲検期間では、疾患活動性とその病状から20～60 mg/日から投与を開始し、20 mg/日まで減量した。引き続き、副腎皮質ステロイドの盲検期間では、治験実施計画書に規定した方法により0 mg まで漸減投与した。ただし、治験薬の二重盲検期間中の再発時、又は疾患活動性の持続によって副腎皮質ステロイドを予定どおり漸減投与できなかった時は、その時期が副腎皮質ステロイドの非盲検期間中の場合は漸減投与を中止し、医師の裁量により副腎皮質ステロイドを調整し、副腎皮質ステロイドの盲検期間中の場合も漸減投与を中止し、副腎皮質ステロイドの非盲検期間下に移行して20 mg/日以上へ増量後、医師の裁量により調整した [救済治療 (escape therapy)] 。

2) 非盲検期間

治験責任医師の裁量によって副腎皮質ステロイド量を調整して投与した。

2.7.3.1.2.3 有効性の評価項目

(1) 52週時の寛解維持割合、再発までの期間

1) 巨細胞性動脈炎の再発と寛解の定義

巨細胞性動脈炎の再発及び寛解の定義については、以下に主な概要を示した。

① 再発

以下の疾患症状や徴候があると治験責任医師又は治験分担医師が判断した場合、又は ESR が30 mm/時以上の場合。

- 熱（38°C 又は100.4°F 以上）
- PMR の症状（肩及び/又は腰帯の朝のこわばり及び/又は痛み）
- 限局的な頭痛、側頭動脈痛、頭皮の圧痛
- 動脈炎性前方虚血性視神経症（A-AION）による急性又は亜急性の失明、一過性の視界不良（一般的に単眼又は一度に少なくとも一方の眼に影響し、潜在的に両眼に影響する）のような視覚に関する症状や徴候
- 顎や口の痛み
- 新規又は悪化した四肢の間欠性跛行
- 巨細胞性動脈炎又は PMR の再発と一致して治験責任医師によって判断されるその他の特徴

② 寛解

再発がなく、CRP が正常化（1 mg/dL 未満）の状態。

(2) 副腎皮質ステロイド累積投与量

52週までの副腎皮質ステロイド累積投与量を算出した。

2.7.3.1.2.4 有効性の評価方法

(1) 必要症例数の設定と中間解析

MRA-SC QW 群及び MRA-SC Q2W 群がプラセボ+26週群に対して52週時点での寛解維持例の割合で群間差を検出するためには、検出力は少なくとも90%以上、両側で α レベルを0.01として、MRA-SC QW 群100例、MRA-SC Q2W 群、プラセボ+26週群及びプラセボ+52週群各50例の計250例とした。この症例数は、52週時の寛解維持割合の差が40%であるという仮説に基づいている（副腎皮質ステロイド30%に対してトシリズマブ70%と仮定した場合）。

なお、中間解析は実施しなかった。

(2) 統計学的手法

1) 52週時の寛解維持割合

52週時の寛解維持割合を指標とした、プラセボ+26週群に対する MRA-SC 群の有効性（主要評価項目）とプラセボ+52週群に対する MRA-SC 群の有効性（主要な副次的評価項目）は、合わせて両側1% ($\alpha = 0.01$) で検定した。二つの独立したトシリズマブ投与の仮説族の階層を設定し、各階層では多重比較による第1種の過誤を避けるために α レベルを等分した（表 2.7.3.1.2.4-1）。両階層は、多重性を更にコントロールするためにあらかじめ固定した一連の順序に基づいて検定した。ただし、各階層の順序1で P 値が0.005未満でない限り、順序2での検定は実施しないこととした。

表 2.7.3.1.2.4-1 多重比較による第1種の過誤の制御のための独立した投与群の階層

	階層1（高用量, $\alpha = 0.005$ ）	階層2（低用量, $\alpha = 0.005$ ）
順序1	MRA-SC QW 群がプラセボ+26週群に優越性を示す（主要評価項目）。	MRA-SC Q2W 群がプラセボ+26週群に優越性を示す（主要評価項目）。
順序2	MRA-SC QW 群がプラセボ+52週群に非劣性を示す（主要な副次的評価項目）。	MRA-SC Q2W 群がプラセボ+52週群に非劣性を示す（主要な副次的評価項目）。

すべての他の副次的、探索的評価項目では、上記のような手順での検定は行わないこととした。また、すべての評価項目では、特別なことがない限り、ITT 対象で記述的に要約することとした。

2) 副腎皮質ステロイド累積投与量

52週までの副腎皮質ステロイドの予想累積投与量は、副腎皮質ステロイド投与開始量、26週間又は52週間の漸減投与スケジュール、及び漸減投与が正しく実施されるという仮定に基づいて算出し、実累積投与量は、救済治療（escape therapy）へ移行後の副腎皮質ステロイド、漸減投与に用いた副腎皮質ステロイド、使用した治験薬ではない市販の副腎皮質ステロイドをすべてまとめて算出した。

副腎皮質ステロイド累積投与量は、非正規分布を示すという想定に基づいて試験開始時の副

腎皮質ステロイド投与量（30 mg/日以下，30 mg/日超）を層別因子とした van Elteren 検定を用いて評価することとした。しかし，副腎皮質ステロイド累積投与量が正規分布を示す場合は，試験開始時の副腎皮質ステロイド量で層別化した，適切なパラメトリックな解析を行うこととした。

治験実施計画書に規定された副腎皮質ステロイドの漸減投与方法からの服用漏れが発生した場合は，盲検下の副腎皮質ステロイドが日ごとに分けられたプラスチック容器内の最小量の副腎皮質ステロイドを服用したと仮定して見積もった。規定どおりに副腎皮質ステロイドの漸減投与ができず増量した被験者は，当初割り付けられた投与群で解析された。

2.7.3.1.3 MRA632JP 試験と WA28119試験の比較

MRA632JP 試験と WA28119試験の主な試験デザインの比較表を表 2.7.3.7.3-1に示す。両試験の共通点は，副腎皮質ステロイドの規定された減量下での二重盲検比較試験を行うことにより，本剤の再発抑制効果をみることである。一方，主な相違点は，対象疾患（MRA632JP 試験：高安動脈炎，WA28119試験：巨細胞性動脈炎，以下同様），対象とする患者集団（再発例，新規発症例及び再発例），主要評価項目（再発までの期間，52週時の寛解維持割合），再発の定義（2.7.3.1.1.3(1)1），2.7.3.1.2.3(1)1）である。よって，両試験を直接比較することは困難であるものの，両試験では副腎皮質ステロイド漸減投与下の再発抑制効果を評価することは共通していることから，高安動脈炎及び巨細胞性動脈炎に対する本剤投与による副腎皮質ステロイドの減量効果を両試験の結果から説明することにより，大型血管炎に対する本剤の有効性を説明することは可能と考える。

2.7.3.2 個々の試験結果の要約

2.7.3.2.1 MRA632JP 試験

本試験では，ランダム化された全例を主要解析対象集団（ITT）とし，プラセボ群18例，MRA-SC 群18例の計36例に治験薬が投与された。本試験の有効性の解析では，ITT を主たる解析対象とし，PPS は参考の解析対象とした。

主要評価項目の二重盲検期間での再発までの期間，副次的評価項目の二重盲検期間での Kerr の定義による再発までの期間，臨床症状による再発までの期間は，19イベントの再発が観察された時点でのデータを用いて本剤の有効性を評価した（20イベント以降の高安動脈炎の再発のデータは含まず，19イベントの高安動脈炎の発現日でデータを打ち切った）。副腎皮質ステロイド投与量に関しては，20イベントの再発が観察された時点でのデータを用いた。

以下に主要な評価項目の有効性の結果を示す。

(1) 再発までの期間

高安動脈炎の再発までの期間の年齢カテゴリで層化調整した Log-rank 検定による P 値は 0.0596で，事前に規定した有意水準0.0459を下回らなかった。再発までの期間の年齢カテゴリを層別因子とした Cox 比例ハザードモデルによるプラセボ群に対する MRA-SC 群のハザード比は0.41で，95.41%信頼区間は0.15～1.10であった。

Kerr の定義による再発までの期間と臨床症状による再発までの期間の結果は，表 2.7.3.2.1-1 に示した。

(2) 副腎皮質ステロイド投与量

二重盲検期間での再発時又は最終観察時の副腎皮質ステロイド投与量の中央値（最小値～最大値）は，プラセボ群で11.91 mg/日（4.0～20.0 mg/日），MRA-SC 群で9.05 mg/日（4.0～32.0 mg/日）であり，プラセボ群に比べて低かった。再発時又は最終観察時に副腎皮質ステロイド投与量を10 mg/日以下まで減量した被験者は，プラセボ群で7/18例（38.9%），MRA-SC 群で

11/18例（61.1%）であった。その内、再発が認められなかった被験者は、プラセボ群は5/7例、MRA-SC 群で8/11例であった。

医師の裁量により調節した非盲検期間の副腎皮質ステロイド1日平均投与量（中央値）は、半数以上の評価例数のある期間で本剤投与回数が増加に伴って減少した。非盲検期間の2016年11月10日のデータカットオフ時点の副腎皮質ステロイド投与量（以降、非盲検期間の副腎皮質ステロイド最終投与量）は、10 mg/日以下が26/36例（72.2%）であった。

(3) 再発率

二重盲検期間が終了した被験者は36例であり、全例が非盲検期間に移行した。その内の7例は非盲検期間に試験を中止し、29例が2016年11月10日のデータカットオフ時点で治験薬投与を継続中であった。二重盲検期間では、プラセボ群12例、MRA-SC 群8例が再発した。非盲検期間では8/36例（22.2%）が再発し、その内訳は二重盲検期間のプラセボ群が7例（二重盲検期間での再発例6例、未再発例1例）、MRA-SC 群は1例（二重盲検期間での再発例）であった。

二重盲検期間の高安動脈炎の再発率は、100人・年あたりの再発率（Events / 100 Patient Years, 以降 Events / 100 PYs）で表示した場合、プラセボ群が203.1 Events / 100 PYs, MRA-SC 群が101.1 Events / 100 PYs であり、MRA-SC 群の再発率はプラセボ群の約半分であった。

非盲検期間の高安動脈炎の再発率は、23.6 Events / 100 PYs であり、二重盲検期間のプラセボ群の再発率の約1/9, MRA-SC 群の再発率の約1/4であった。

表 2.7.3.2.1-1 有効性成績の概要（MRA632JP 試験, ITT）

	二重盲検期間		非盲検期間
	プラセボ群 18例	MRA-SC 群 18例	MRA-SC 36例
再発までの期間の中央値（95%CI） （週）	12.1 (10.7~16.0)	推定不能 (12.1~推定不能)	-
プラセボ群に対する MRA-SC 群のハザード比 ¹⁾ (95.41%CI)	-	0.41 (0.15~1.10)	-
P 値 (Log-rank 検定) ²⁾	-	0.0596	-
Kerr の定義による再発までの期間の中央値 (95%CI) (週)	12.1 (10.7~16.0)	推定不能 (12.1~推定不能)	-
プラセボ群に対する MRA-SC 群のハザード比 ¹⁾ (95.41%CI)	-	0.41 (0.15~1.10)	-
臨床症状による再発までの期間の中央値 (95%CI) (週)	12.0 (8.3~16.0)	16.0 (8.1~推定不能)	-
プラセボ群に対する MRA-SC 群のハザード比 ¹⁾ (95.41%CI)	-	0.70 (0.29~1.70)	-
副腎皮質ステロイド最終投与量の中央値 (最小値~最大値) (mg/日) ³⁾	11.91 (4.0~20.0)	9.05 (4.0~32.0)	7.00 (0~30.0)
副腎皮質ステロイド最終投与量10 mg/日以下の例数 (%)	7/18例 (38.9%)	11/18例 (61.1%)	26/36例 (72.2%)
再発率 (Events / 100 PYs)	203.1	101.1	23.6

1): 年齢カテゴリ（18歳未満, 18歳以上65歳未満, 65歳以上）を層別因子とした Cox 比例ハザードモデルによりプラセボ群に対する MRA-SC 群のハザード比及び信頼区間を算出。

2): 年齢カテゴリで層化調整した Log-rank 検定結果。事前に規定した有意水準0.0459で検定した。

3): 二重盲検期間は再発時又は最終観察時, 非盲検期間は2016年11月10日のデータカットオフ時点。

[5.3.5.1-1 表 11.4.1.1-1, 表 11.4.1.2-1, 表 11.4.1.2-2, 表 16.2.6-2, 5.3.5.1-1 総括報告書改訂書3版 表 11.4.1.2-4 (表 15.2.1-26), 表 16.2.5-2, 表 2.7.3.7.1-2, 表 2.7.3.7.1-3, 表 2.7.3.7.1-4, 表 2.7.3.7.1-5, 表 2.7.3.7.1-8を改変]

(4) 低用量副腎皮質ステロイド投与時の本剤の再発抑制効果

二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に、副腎皮質ステロイド量が

10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満（以降、ステロイド減量目標値）を一回でも達成した被験者数は30/36例（83.3%）であり（表 2.7.3.7.1-8），その内の25例は、2016年11月10日のデータカットオフ時点で再発又は再発の徴候に伴う副腎皮質ステロイドの増量がなく、ステロイド減量目標値を達成している。25例のステロイド減量目標値達成後の維持期間の中央値（最小値～最大値）は379.0日（84～630日）であり、25例中22例（88.0%）が少なくとも半年間は副腎皮質ステロイドを低用量で維持した上で再発抑制効果を示した。

2.7.3.2.2 WA28119試験

本試験の有効性の解析では、ITT を主たる解析対象とした。ITT 対象は250例であった。以下に主要な評価項目の有効性の結果を示す。なお、52週時の寛解維持割合以外の有効性評価項目では、検定結果と P 値を探索的な結果として示した。

(1) 52週時の寛解維持割合

52週時の寛解維持割合は、プラセボ+26週群で14.0%，MRA-SC QW 群で56.0% [リスク差：42.00%（99.5%信頼区間：18.00～66.00）]，試験開始時の副腎皮質ステロイド量を層別因子とした CMH 検定による P 値：0.0001未満]，MRA-SC Q2W 群で53.1% [リスク差：39.06%（99.5%信頼区間：12.46～65.66）]，CMH 検定による P 値：0.0001未満] であり、プラセボ+26週群に対する MRA-SC QW 群と MRA-SC Q2W 群の優越性が示された。

52週時の寛解維持割合は、プラセボ+52週群で17.6%，MRA-SC QW 群で56.0% [リスク差：38.35%（99.5%信頼区間：17.89～58.81）]，試験開始時の副腎皮質ステロイド量を層別因子とした CMH 検定による P 値：0.0001未満]，MRA-SC Q2W 群で53.1% [リスク差：35.41%（99.5%信頼区間：10.41～60.41）]，CMH 検定による P 値：0.0002] であり、プラセボ+52週群に対する MRA-SC QW 群と MRA-SC Q2W 群の非劣性と優越性が示された（非劣性マージン：-22.5%）。

(2) 再発までの期間

二重盲検期間の再発までの期間については、試験開始時の副腎皮質ステロイド量（30 mg/日以下，30 mg/日超）を層別因子とした Cox 比例ハザードモデルにより、プラセボ群に対する MRA-SC 群のハザード比及び信頼区間をそれぞれ算出した。再発までの期間の MRA-SC 群のプラセボ+26週群に対するハザード比は、MRA-SC QW 群で0.23（99%信頼区間：0.11～0.46，P 値：0.0001未満），MRA-SC Q2W 群で0.28（99%信頼区間：0.12～0.66），P 値：0.0001] であった。MRA-SC 群のプラセボ+52週群に対するハザード比は、MRA-SC QW 群で0.39（99%信頼区間：0.18～0.82，P 値：0.0011），MRA-SC Q2W 群で0.48（99%信頼区間：0.20～1.16），P 値：0.0316] であった。

(3) 副腎皮質ステロイド投与量

副腎皮質ステロイド累積投与量（中央値）は、プラセボ+26週群では3296.00 mg，プラセボ+52週群では3817.50 mg であるのに対し、MRA-SC QW 群及び MRA-SC Q2W 群はいずれも1862.00 mg であり、プラセボ群より MRA-SC 群で少なかった。

試験開始時の副腎皮質ステロイド量を層別因子とした van Elteren 検定による副腎皮質ステロイド累積投与量のプラセボ+26週群に対する MRA-SC QW 群の P 値は0.0001未満であり、プラセボ+26週群に対する MRA-SC Q2W 群の P 値は0.0003であった。

(4) 再発率

再発率（1人年あたりの再発回数）の平均値は、プラセボ+26週群で1.74/年，プラセボ+52週群で1.30/年，MRA-SC QW 群で0.41/年，MRA-SC Q2W 群で0.67/年であり、プラセボ+26週群が最も高かった。再発率（中央値）は、プラセボ+26週群とプラセボ+52週群では1であったが、

MRA-SC QW 群と MRA-SC Q2W 群では0であった。

表 2.7.3.2.2-1 有効性成績の概要 (WA28119試験, ITT)

	プラセボ+26週群 50例	プラセボ+52週群 51例	MRA-SC QW 群 100例	MRA-SC Q2W 群 49例
52週時の寛解維持割合 (対プラセボ+26週群)				
レスポonder例 (%) ¹⁾	7 (14.0%)	–	56 (56.0%)	26 (53.1%)
リスク差 (99.5%CI)	–	–	42.00 (18.00, 66.00)	39.06 (12.46, 65.66)
P 値 ²⁾	–	–	< 0.0001	< 0.0001
52週時の寛解維持割合 (対プラセボ+52週群)				
レスポonder例 (%) ¹⁾	–	9 (17.6%)	56 (56.0%)	26 (53.1%)
リスク差 (99.5%CI)	–	–	38.35 (17.89, 58.81)	35.41 (10.41, 60.41)
P 値 ²⁾	–	–	< 0.0001	0.0002
再発までの期間				
再発例 (%)	34 (68.0%)	25 (49.0%)	23 (23.0%)	13 (26.5%)
再発までの期間の中央値 (最小値~最大値) (日)	165.0 (1~365)	295.0 (1~362)	推定不能 (1~367)	推定不能 (1~364)
プラセボ+26週群に対する ハザード比 ³⁾ (99%CI)	–	–	0.23 (0.11, 0.46)	0.28 (0.12, 0.66)
P 値	–	–	<0.0001	0.0001
プラセボ+52週群に対する ハザード比 ³⁾ (99%CI)	–	–	0.39 (0.18, 0.82)	0.48 (0.20, 1.16)
P 値	–	–	0.0011	0.0316
副腎皮質ステロイド累積投与量				
中央値 (95%CI) (mg)	3296.00 (2729.5, 4023.5)	3817.50 (2817.5, 4425.5)	1862.00 (1582.0, 1942.0)	1862.00 (1568.0, 2239.5)
P 値 (対プラセボ+26週群) ⁴⁾	–	–	<0.0001	0.0003
P 値 (対プラセボ+52週群) ⁴⁾	–	–	<0.0001	<0.0001
再発率 (1人年あたりの再発回数) の平均値	1.74	1.30	0.41	0.67

1) : 52週時に寛解を維持していた被験者の割合

2) : 試験開始時の副腎皮質ステロイド量 (30 mg/日以下, 30 mg/日超) を層別因子とした Cochran-Mantel-Haenszel 検定

3) : 試験開始時の副腎皮質ステロイド量 (30 mg/日以下, 30 mg/日超) を層別因子とした Cox 比例ハザードモデルに基づく

4) : 試験開始時の副腎皮質ステロイド量 (30 mg/日以下, 30 mg/日超) を層別因子とした van Elteren 検定

[5.3.5.1-3 Page 417, Table 23, Table 28, Table 29を改変]

2.7.3.3 全試験を通しての結果の比較と解析

2.7.3.3.1 試験対象集団

MRA632JP 試験では, ITT 対象例及び安全性評価例はプラセボ群, MRA-SC 群ともに18例であった。PPS 対象はプラセボ群が17例, MRA-SC 群が16例であった。

WA28119試験では, ITT 対象例及び安全性評価例は, いずれもプラセボ+26週群50例, プラセボ+52週群51例, MRA-SC QW 群100例, MRA-SC Q2W 群49例の計250例であった (表 2.7.3.1-1)。

2.7.3.3.1.1 人口統計学的特性及びベースライン時特性

(1) MRA632JP 試験と WA28119試験の人口統計学的特性及びベースライン時特性

MRA632JP 試験及び WA28119試験の主な被験者背景を表 2.7.3.3.1.1-1に示す。男女の割合は、両試験でそれぞれ群間の大きな偏りは認められなかった。年齢の中央値は、MRA632JP 試験では各群20歳代半ばであるが、WA28119試験では各群70歳前後であった。MRA632JP 試験は高安動脈炎患者、WA28119試験は巨細胞性動脈炎患者を対象としており、それらの男女比及び年齢は市販後に使用が想定される患者と同様であると考えられた。罹病期間は、両試験とも患者によってばらつきがあるが、罹病期間の中央値は、MRA632JP 試験では各群約3年であるが、WA28119試験では各群で41～80日であった。MRA632JP 試験では、疾患の再発例を対象としているが、WA28119試験では、再発例（ベースラインの6週より以前に巨細胞性動脈炎と診断され、40 mg/日以上副腎皮質ステロイドによる2週間以上の連続した治療歴）と新規発症例（ベースライン前の6週以内に新たに巨細胞性動脈炎と診断）を対象としており、新規発症例が全群合わせて47%に対して、再発例は53%であった。試験開始時の副腎皮質ステロイド投与量の中央値は、MRA632JP 試験の体重の中央値から換算すると約30 mg/日、WA28119試験では30.00～35.00 mg/日であるため、両試験で差はないと考えた。

なお、MRA632JP 試験の人口統計学的特性及びベースライン時特性を表 2.7.3.7.1-1、WA28119試験の人口統計学的特性及びベースライン時特性を表 2.7.3.7.2-2～表 2.7.3.7.2-4に示す。

表 2.7.3.3.1.1-1 MRA632JP 試験及び WA28119試験の主な被験者背景

試験番号	MRA632JP		WA28119			
	プラセボ群 18例	MRA-SC 群 18例	プラセボ+26週 群 50例	プラセボ+52週 群 51例	MRA-SC QW 群 100例	MRA-SC Q2W 群 50例
女性 (%)	15 (83.3)	16 (88.9)	38 (76.0)	37 (72.5)	78 (78.0)	35 (70.0)
男性 (%)	3 (16.7)	2 (11.1)	12 (24.0)	14 (27.5)	22 (22.0)	15 (30.0)
年齢 (歳) の 中央値 (最小値～最大値)	27.0 (17～68)	26.5 (13～66)	70.5 (52～83)	68.0 (52～84)	71.0 (51～85)	71.0 (53～91)
65歳以上	1 (5.6%)	2 (11.1%)	34 (68.0%)	34 (66.7%)	68 (68.0%)	33 (66.0%)
体重 (kg) の 中央値 (最小値～最大値)	57.90 (39.4～ 99.7)	53.05 (32.9～ 97.4)	66.65 (47.7～ 120.0)	70.60 (48.5～ 108.0)	67.50 (48.0～ 105.0)	69.20 (46.4～ 124.1)
罹病期間の 中央値 (最小値～最大値)	2.89年 (0.1～16.5年)	3.33年 (0.4～22.8年)	80.00日 (12.0～2698.0 日)	53.00日 (8.0～1789.0 日)	52.00日 (9.0～2856.0 日)	41.50日 (13.0～2708.0 日)
新規発症例 ²⁾	–	–	23 (46.0%)	23 (45.1%)	47 (47.0%)	26 (52.0%)
試験開始時の 副腎皮質ステ ロイド投与量 の中央値 (最 小値～最大 値)	0.45 mg/kg/日 (0.4～0.9 mg/kg/日)	0.50 mg/kg/日 (0.4～1.0 mg/kg/日)	30.00 mg/日 (20.0～60.0 mg/日)	30.00 mg/日 (5.0～60.0 mg/日)	30.00 mg/日 (10.0～60.0 mg/日)	35.00 mg/日 (5.0～60.0 mg/日)

1) : MRA632JP 試験は ITT, WA28119試験は ALL で集計した。

2) : ベースライン前の6週以内に新たに巨細胞性動脈炎と診断された被験者。

[5.3.5.1-1 表 11.2-1, 5.3.5.1-3 Table 10, Table 12を改変]

(2) WA28119試験でMRA632JP試験と共通する病変部位を持つ患者

巨細胞性動脈炎には、大動脈などが障害される大血管型 (large vessel) 巨細胞性動脈炎があり、高安動脈炎と病変部位が共通している可能性が考えられる。そこで、画像判定で大血管の血管炎の存在が確認された患者集団 (①)、更に高安動脈炎に非特異的な病変や症状を除いた集団として①に加えて側頭動脈の生検結果が陽性でない患者集団 (②)、及び②に加えて頭部の症状のない患者集団 (③) の3つの部分集団について有効性を検討した。巨細胞性動脈炎は、側頭動脈に特徴的な病変が認められることから、側頭動脈に病変部位が認められず、頭部の症状のない患者は、高安動脈炎と共通する大血管に病変部位が存在する可能性がある集団から、高安動脈炎に非特異的な病変や症状を除いた患者集団と考えられる。そこで、以下の3つの患者集団を設定して有効性を評価することにした。

なお、①の患者を大血管型巨細胞性動脈炎と定義し、その詳細は2.5.1.1(1)項に記載した。

- ① 画像判定で大血管の血管炎の存在が確認された患者集団
- ② ①で側頭動脈の生検結果で陽性でない患者集団
- ③ ②で頭部の症状のない患者集団

表 2.7.3.3.1.1-2 高安動脈炎と共通する大型血管に病変部位が存在する可能性がある患者集団と該当する選択基準 (WA28119試験)

	(1) 巨細胞性動脈炎を特徴づける側頭動脈の生検	(2) 血管造影又は断層像 (MRA, CTA, PET-CT など) による大型血管炎の診断	(3) 明確な巨細胞性動脈炎の頭部の症状	(4) リウマチ性多発筋痛症 (炎症性疾患の朝のこわばりに関連した肩及び/又は腰帯痛) の症状
①	陽性/陰性/未実施	○	いずれか又は両方に○	
②	陰性/未実施	○	いずれか又は両方に○	
③		○	×	○

①～③は、直前の記載である2.7.3.3.1.1(2)と同じ患者集団を指す。

画像検査は139例で実施され、その内①に該当したのは115/139例 (83%) であり、その内訳はプラセボ+26週群が19例、プラセボ+52週群が23例、MRA-SC QW 群が50例、MRA-SC Q2W 群が23例であった。②は94/139例 (68%) であり、その内訳はプラセボ+26週群が14例、プラセボ+52週群が21例、MRA-SC QW 群が43例、MRA-SC Q2W 群が16例であった。③は42/139例 (30%) であり、その内訳はプラセボ+26週群が8例、プラセボ+52週群が7例、MRA-SC QW 群が18例、MRA-SC Q2W 群が9例であった。

2.7.3.3.1.2 投与状況

MRA632JP試験とWA28119試験の治験薬投与状況を表 2.7.3.3.1.2-1に示す。

MRA632JP試験では、36例にプラセボ又は本剤が投与され、全例が非盲検期間に移行した。二重盲検期間での治験薬投与期間の中央値 (最小値～最大値) はプラセボ群で12.86週 (8.0～55.9週)、MRA-SC 群で19.00週 (5.0～52.0週) であった。二重盲検期間と非盲検期間の全期間での本剤投与期間の中央値 (最小値～最大値) は70.43週 (8.1～108.0週) であった。全期間を通して本剤を52週以上投与した被験者数は31例であった。

WA28119試験では、二重盲検期間での治験薬投与期間の最小値及び最大値は各群で異なるが、中央値はいずれも358.0日であった。

表 2.7.3.3.1.2-1 治験薬投与状況 (MRA632JP 試験, WA28119試験, ITT)

	MRA632JP		WA28119			
	プラセボ群 18例	MRA-SC 群 18例	プラセボ +26週群 50例	プラセボ +52週群 51例	MRA-SC QW 群 100例	MRA-SC Q2W 群 49例
二重盲検期間						
治験薬の投与期間 の中央値 (最小値～最大 値)	12.86週 (8.0～55.9週)	19.00週 (5.0～52.0週)	358.0日 (44～368日)	358.0日 (43～369日)	358.0日 (9～365日)	358.0日 (6～371日)
全期間 ¹⁾						
観察期間の中央値 (最小値～最大 値) (週)	70.14 (8.3～107.1)	-	-	-	-	-
本剤投与期間の中 央値 (最小値～最大 値) (週)	70.43 (8.1～108.0)	-	-	-	-	-
本剤累積投与量の 中央値 (最小値～ 最大値) (mg)	11421.0 (1296～17496)	-	-	-	-	-
本剤52週以上投与 例数 ²⁾	31	41	41	46	82	40

1) : 二重盲検期間と非盲検期間を合わせた期間

2) : MRA632JP 試験では、二重盲検期間と非盲検期間の全期間を通じた本剤投与例数

[5.3.5.1-1 表 12.1-1, 5.3.5.1-3 Table 6, Table 8, 5.3.5.1-7 表 11.1-1, 表 11.1-5, 5.3.5.1-3 Table 35を改変]

2.7.3.3.2 全有効性試験の結果の比較検討

2.7.3.3.2.1 MRA632JP 試験

(1) 再発までの期間 (ITT, 主要評価項目)

二重盲検期間の高安動脈炎の再発までの期間について、年齢カテゴリ (18歳未満, 18歳以上65歳未満, 65歳以上) で層化調整した Log-rank 検定を実施し、同様に年齢カテゴリを層別因子とした Cox 比例ハザードモデルによりプラセボ群に対する MRA-SC 群のハザード比及び信頼区間を算出した結果を表 2.7.3.3.2.1-1に示す。仮説を評価するための信頼区間の信頼係数及び有意水準は、中間解析に伴う第1種の過誤確率の上昇を考慮して O'Brien-Fleming タイプの α 消費関数に基づいてそれぞれ95.41%及び4.59%とした。高安動脈炎再発までの期間の Kaplan-Meier 曲線を図 2.7.3.3.2.1-1に示す。

Kaplan-Meier 法により推定される再発までの期間の中央値 (95%信頼区間) は、プラセボ群では12.1週 (10.7～16.0週), MRA-SC 群では推定不能 (12.1週～推定不能)であった。

再発までの期間の年齢カテゴリで層化調整した Log-rank 検定による P 値は0.0596で、事前に規定した有意水準0.0459を下回らなかった。

再発までの期間の年齢カテゴリを層別因子とした Cox 比例ハザードモデルによるプラセボ群に対する MRA-SC 群のハザード比は0.41で、95.41%信頼区間は0.15～1.10であった (相対リスク減少率59%)。初回投与後24週の高安動脈炎無再発率の推定値は、プラセボ群で22.92%, MRA-SC 群で50.60%であった。

中止理由及び副腎皮質ステロイド減量時に規定よりも多く使用したという逸脱を考慮した場合、再発の評価の欠測を考慮した場合の再発までの期間の感度分析では、いずれも主要評価項目の結果と変わらなかった (5.3.5.1-1 11.4.3.2(1))。

表 2.7.3.3.2.1-1 二重盲検期間での再発までの期間-19 events (ITT) (MRA632JP 試験)

ttet01n_tfr_itt Relapse Free of Takayasu Arteritis (19 events)
 Protocol: MRA632JP
 Analysis: ITT

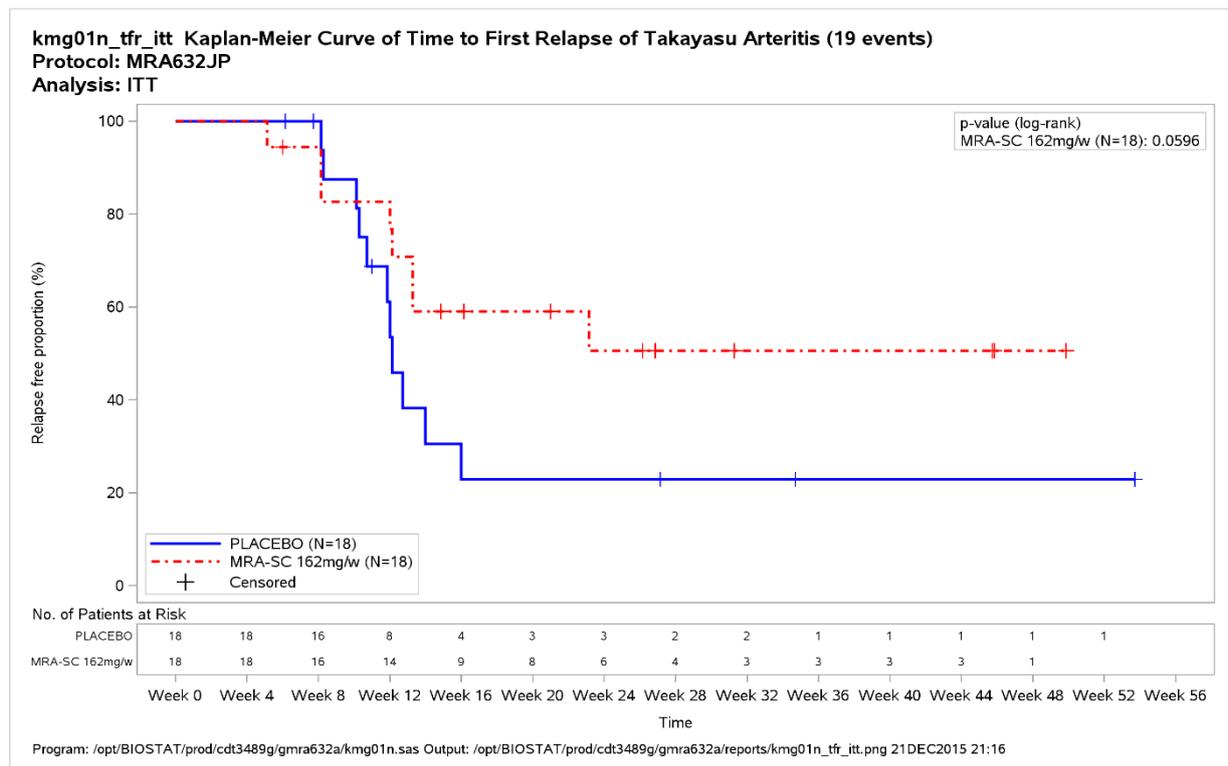
ASSESSMENT OF RELAPSE FOR TAKAYASU ARTERITIS

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Patients with event (%)	11 (61.1%)	8 (44.4%)
Patients without event (%)	7 (38.9%)	10 (55.6%)
Time to event (weeks)#		
Median	12.1	NE
95% CI	(10.7, 16.0)	(12.1, NE)
25% and 75%-ile	10.5, 16.0	12.1, NE
Range##	6* to 54*	5 to 50*
Unstratified Analysis		
p-value (log-rank)		0.1060
Hazard Ratio		0.48
95.41% CI		(0.19, 1.23)
Stratified Analysis**		
p-value (log-rank)		0.0596
Hazard Ratio		0.41
95.41% CI		(0.15, 1.10)
Time Point at 24 weeks#		
Patients remaining at risk	3	6
Event Free Rate (%)	22.92	50.60
95% CI	(0.43, 45.40)	(25.40, 75.80)

* censored
 ** stratified by age category: <18, 18-<65, 65-
 # Kaplan-Meier estimate
 ## including censored observations
 Significance level: 0.0459

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/ttet01n.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/ttet01n_tfr_itt.out
 22DEC2015 15:30

図 2.7.3.3.2.1-1 二重盲検期間での再発までの期間の Kaplan-Meier 曲線-19 events (ITT)
(MRA632JP 試験)



[5.3.5.1-1 図 11.4.1.1-1を再掲]

(2) 再発までの期間 (PPS)

PPS 対象での二重盲検期間の高安動脈炎の再発までの期間について、年齢カテゴリを層別因子とした Log-rank 検定を実施し、同様に年齢カテゴリを層別因子とした Cox 比例ハザードモデルによりプラセボ群に対する MRA-SC 群のハザード比及び信頼区間を算出した結果を表 2.7.3.3.2.1-2に示す。

Kaplan-Meier 法により推定される再発までの期間の中央値 (95%信頼区間) は、プラセボ群では12.1週 (10.7~14.0週) , MRA-SC 群では推定不能 (13.3~推定不能) であった。

再発までの期間の年齢カテゴリで層化調整した Log-rank 検定による P 値は0.0345であった。再発までの期間の年齢カテゴリを層別因子とした Cox 比例ハザードモデルによるプラセボ群に対する MRA-SC 群のハザード比は0.34で、95.41%信頼区間は0.11~1.00であった。

表 2.7.3.3.2.1-2 二重盲検期間での再発までの期間-19 events (PPS) (MRA632JP 試験)

ttet01n_tfr_pp Relapse Free of Takayasu Arteritis (19 events)
 Protocol: MRA632JP
 Analysis: PPS

ASSESSMENT OF RELAPSE FOR TAKAYASU ARTERITIS

	PLACEBO (N=17)	MRA-SC 162mg/w (N=16)
Patients with event (%)	11 (64.7%)	7 (43.8%)
Patients without event (%)	6 (35.3%)	9 (56.3%)
Time to event (weeks)#		
Median	12.1	NE
95% CI	(10.7, 14.0)	(13.3, NE)
25% and 75%-ile	10.3, 15.0	12.1, NE
Range##	6* to 54*	5 to 50*
Unstratified Analysis		
p-value (log-rank)		0.0399
Hazard Ratio		0.38
95.41% CI		(0.14, 1.02)
Stratified Analysis**		
p-value (log-rank)		0.0345
Hazard Ratio		0.34
95.41% CI		(0.11, 1.00)
Time Point at 24 weeks#		
Patients remaining at risk	2	6
Event Free Rate (%)	16.67	51.66
95% CI	(0.00, 37.54)	(25.32, 77.99)

* censored
 ** stratified by age category: <18, 18-<65, 65-
 # Kaplan-Meier estimate
 ## including censored observations
 Significance level: 0.0459

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/ttet01n.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/ttet01n_tfr_pp.out
 15FEB2016 17:54

[5.3.5.1-1 表 11.4.3.6-1を再掲]

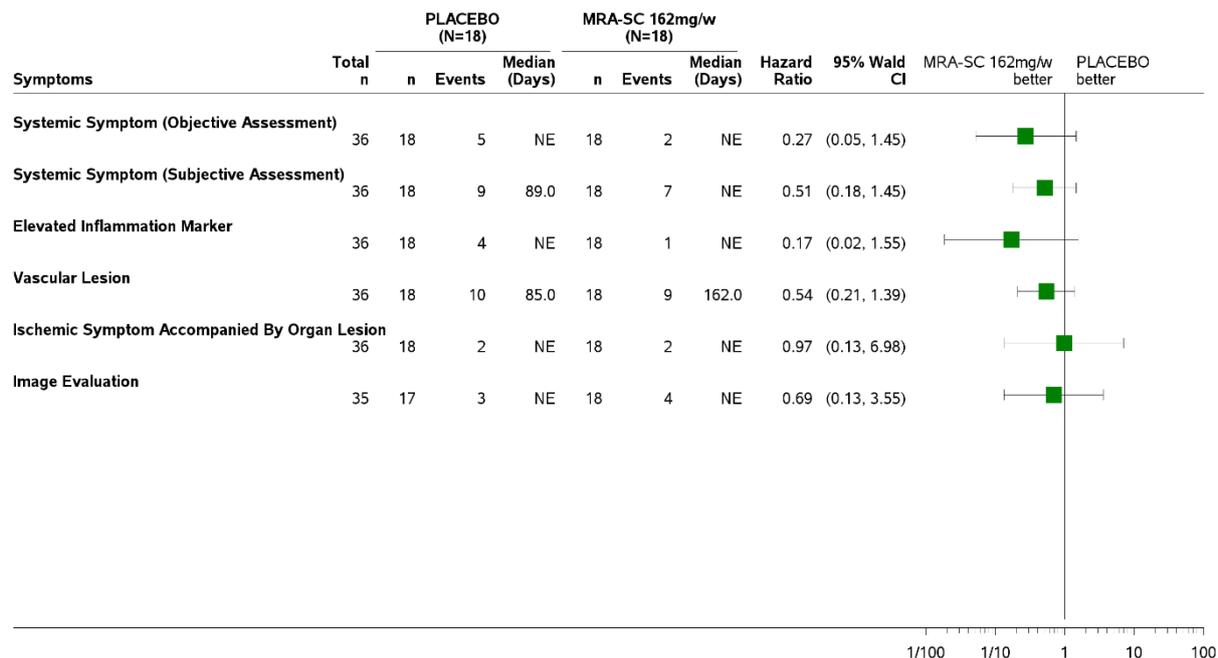
(3) 高安動脈炎の再発を定義した各大項目の発現

高安動脈炎の再発の大項目には、客観的評価による全身症状、主観的評価による全身症状、炎症マーカーの上昇、血管病変、臓器病変を伴う虚血症状、画像評価がある。これらの各大項目から定義される二重盲検期間の再発までの期間について、年齢カテゴリ（18歳未満、18歳以上65歳未満、65歳以上）を層別因子とした Cox 比例ハザードモデルによりプラセボ群に対する MRA-SC 群のハザード比及び信頼区間を算出した結果を図 2.7.3.3.2.1-2に示す。

再発のすべての大項目でハザード比の点推定値は1未満であり、MRA-SC 群で再発のリスクを低下させる傾向が一貫して認められた。

図 2.7.3.3.2.1-2 再発の各大項目から定義される二重盲検期間での再発までの期間のハザード比と信頼区間-19 events (MRA632JP 試験, ITT)

kmcoxfrs_st_n_itt Forest plot for HR of each symptom (Stratified Cox regression, 19 events)
 Protocol: MRA632JP
 Analysis: ITT



stratified by age category: <18, 18-<65, 65-

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/kmcoxfrs.sas Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/kmcoxfrs_st_n_itt.png 03AUG2016 17:46

[5.3.5.3-1 図 2.1.1-1を再掲]

(4) 副腎皮質ステロイド投与量

1) 二重盲検期間

二重盲検期間の再発時又は最終観察時の副腎皮質ステロイド投与量の要約統計量を表 2.7.3.3.2.1-3に示す。

再発時又は最終観察時の副腎皮質ステロイド投与量は、主要評価項目で高安動脈炎再発の徴候ありと判定された被験者は最終観察時又は最終観察時の直前（副腎皮質ステロイド投与量の増加前）の副腎皮質ステロイド投与量、再発が確認されなかった被験者は最終観察時の副腎皮質ステロイド投与量とした。

再発時又は最終観察時の副腎皮質ステロイド投与量の中央値（最小値～最大値）は、プラセボ群で11.91 mg/日（4.0～20.0 mg/日）、MRA-SC 群で9.05 mg/日（4.0～32.0 mg/日）であった。また、再発時又は最終観察時の体重あたりの副腎皮質ステロイド投与量の中央値（最小値～最大値）は、プラセボ群で0.195 mg/kg/日（0.10～0.46 mg/kg/日）、MRA-SC 群で0.174 mg/kg/日（0.09～0.87 mg/kg/日）であり、プラセボ群に比べて低かった。

再発時又は最終観察時に副腎皮質ステロイド投与量を10 mg/日以下まで減量した被験者は、プラセボ群が7/18例（38.9%）、MRA-SC 群が11/18例（61.1%）であった（5.3.5.1-1 Listing 16.2.5-2, 16.2.6-2）。その内、再発が認められなかった被験者は、プラセボ群が5/7例、MRA-SC 群が8/11例であった。

表 2.7.3.3.2.1-3 二重盲検期間の再発時又は最終観察時の
副腎皮質ステロイド投与量の要約統計量-20 events (ITT) (MRA632JP 試験)

sumcs_itt Corticosteroid at last observation
Protocol: MRA632JP
Analysis: ITT

Parameter	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Corticosteroids (mg Equivalent to Prednisolone)		
n	18	18
Mean (SD)	12.21 (4.64)	10.78 (6.77)
Min - Max	4.0 - 20.0	4.0 - 32.0
Median	11.91	9.05
Corticosteroids (mg/kg Equivalent to Prednisolone)		
n	18	18
Mean (SD)	0.215 (0.102)	0.218 (0.187)
Min - Max	0.10 - 0.46	0.09 - 0.87
Median	0.195	0.174

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/sumcs.sas
Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/sumcs_itt.out
03OCT2016 14:38

[5.3.5.1-1 総括報告書改訂書3版 表 11.4.1.2-4 (表 15.2.1-26) を再掲]

1) 非盲検期間

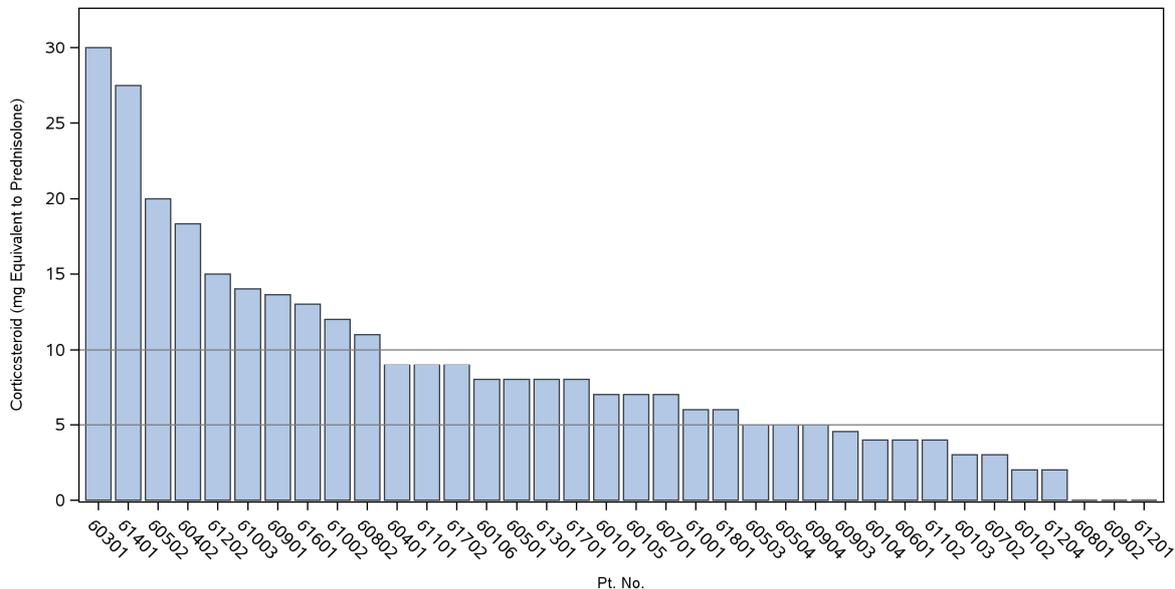
非盲検期間の副腎皮質ステロイド1日平均投与量の中央値は、半数以上の評価例数のある期間で本剤投与回数の増加に伴って減少した (表 2.7.3.7.1-4)。

副腎皮質ステロイド投与量の中央値は、登録前再発時で12.0 mg/日 (0.22 mg/kg/日)、非盲検期間の2016年11月10日のデータカットオフ時点 (以降、非盲検期間の副腎皮質ステロイド最終投与量) で7.00 mg/日 (0.13 mg/kg/日) であり、非盲検期間の副腎皮質ステロイド最終投与量の中央値は、登録前再発時の副腎皮質ステロイド投与量の中央値を下回った (表 2.7.3.7.1-4, 表 2.7.3.7.1-8)。

非盲検期間の副腎皮質ステロイド最終投与量が10 mg/日以下の被験者は26/36例 (72.2%) (表 2.7.3.7.1-5)、副腎皮質ステロイドが離脱に至った被験者は3例 (症例番号: 60902, 61201, 60801) に認められ、離脱後も2016年11月10日のデータカットオフ時まで再発はなかった (5.3.5.1-7 表 11.4-6, 図 11.2-5)。非盲検期間の副腎皮質ステロイド最終投与量が10 mg/日以下の維持期間の中央値 (最小値~最大値) は349.0日 (14~587日) であった (表 2.7.3.7.1-6)。非盲検期間の副腎皮質ステロイド最終投与量が登録前再発時の副腎皮質ステロイド量を下回った被験者は、31/36例 (86.1%) であった (表 2.7.3.7.1-8)。

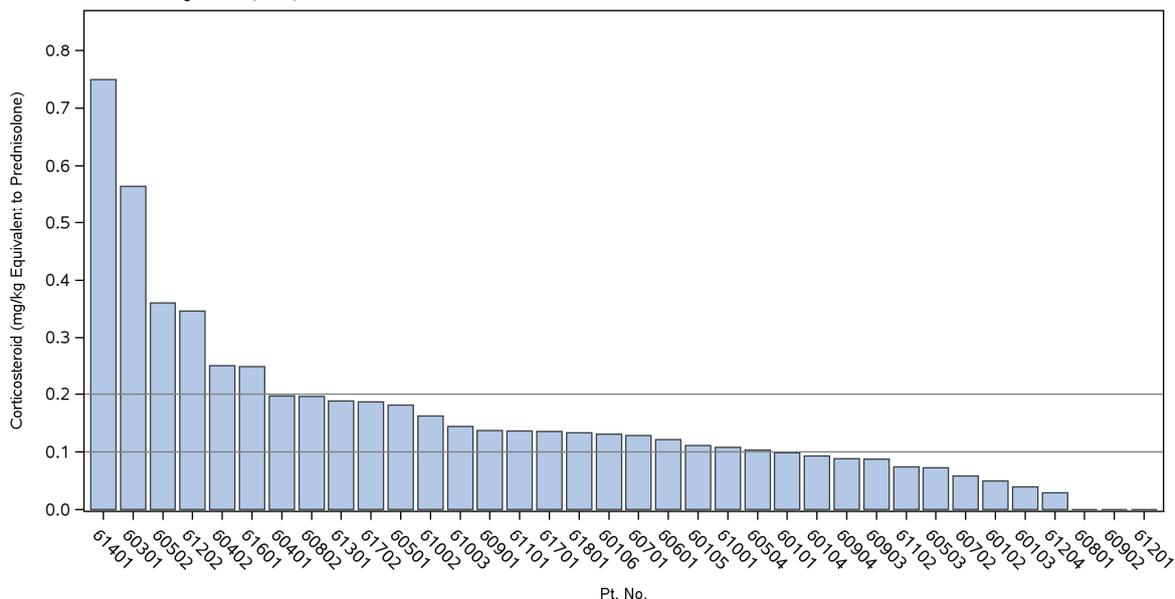
図 2.7.3.3.2.1-3 非盲検期間の副腎皮質ステロイド最終投与量 (mg/日) の Waterfall-plot (ITT) (MRA632JP 試験) (上 : mg/日, 下 : mg/kg/日)

wfg01_mt_itt Waterfall plot for Corticosteroid at Last Obs -Open period
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Treatment: MRA-SC 162mg/W Total(N=36)



Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/wfg01.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/wfg01_mt_itt.png
12JAN2017 17:21

wfg01_mt_itt Waterfall plot for Corticosteroid at Last Obs -Open period
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Treatment: MRA-SC 162mg/W Total(N=36)



Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/wfg01.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/wfg01_mt_itt.png
12JAN2017 17:21

(5) 再発率

二重盲検期間に再発した被験者は、プラセボ群12/18例（66.7%）、MRA-SC 群8/18例（44.4%）であった。非盲検期間に再発した被験者は8/36例（22.2%）であり、その内訳は二重盲検期間のプラセボ群が7例、MRA-SC 群は1例であった（表 2.7.3.7.1-7）。

二重盲検期間の高安動脈炎の再発率は、100人・年あたりの再発率（Events / 100 Patient Years, 以降 Events / 100 PYs）で表示した場合、プラセボ群が203.1 Events / 100 PYs, MRA-SC 群が101.1 Events / 100 PYs であった（表 2.7.3.7.1-2）。非盲検期間の高安動脈炎の再発率は、23.6 Events / 100 PYs であり（表 2.7.3.7.1-3）、二重盲検期間での MRA-SC 群の再発率は、プラセボ群の約半分であり、非盲検期間の再発率は二重盲検期間のプラセボ群の約1/9, MRA-SC 群の約1/4であった。

(6) 低用量副腎皮質ステロイド投与時の本剤の再発抑制効果

二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に、「副腎皮質ステロイド量が10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満（以降、ステロイド減量目標値）」を一回でも達成した被験者数は30例であり、未達は6例であった（表 2.7.3.7.1-8）。ステロイド減量目標値未達の6例の内、2016年11月10日のデータカットオフ時点で治験中止例が4例、治験継続例が2例であった（5.3.5.1-7 表 11.4-1）。治験中止例の中止理由は、効果不十分が3例、治療拒否／協力を得られずが1例であった。治験継続例の1例は非盲検期間の副腎皮質ステロイド漸減投与中に再発後に増量し、1例は非盲検期間の副腎皮質ステロイド漸減投与中であり、ステロイド減量目標値を今後達成する可能性はあるものの、2016年11月10日のデータカットオフ時点では達成していない。

ステロイド減量目標値を達成した30例中25例は、2016年11月10日のデータカットオフ時点で再発又は再発の徴候に伴う副腎皮質ステロイドの増量がなく、ステロイド減量目標値を達成している。25例のステロイド減量目標値達成後の維持期間の中央値（最小値～最大値）は379.0日（84～630日）であり、25例中22例（88.0%）が少なくとも半年間は副腎皮質ステロイドを低用量で維持した上で再発抑制効果を示した。一方、30例中5例は、再発又は再発の徴候から副腎皮質ステロイドが増量投与され、その内1例は中止時検査で再発が認められた。再発又は再発の徴候から副腎皮質ステロイドを増量した5例では、ステロイド減量目標値達成後の維持期間はそれぞれ27日、28日、29日、58日、321日であった。以上より、MRA632JP 試験では、0.2 mg/kg/日以上副腎皮質ステロイド投与量で再発した被験者を対象とし、非盲検期間の副腎皮質ステロイド最終投与量の0.2 mg/kg/日以下と10 mg 以下がほぼ同じ基準と考えられるため（表 2.7.3.7.1-5, 図 2.7.3.3.2.1-3）、副腎皮質ステロイド量が10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満のステロイド減量目標値を達成した36例中25例（69.4%）で、本剤投与により副腎皮質ステロイドを低用量で維持した上での再発抑制効果が示された。また、ステロイド減量目標値達成後の維持期間の中央値が379.0日間に達しており、Maksimowicz-McKinnon らの報告⁷⁾では、副腎皮質ステロイド投与量を10 mg/日未満に減量した場合、必要に応じて免疫抑制剤や生物学的製剤を併用する中で、6カ月間寛解を維持できた患者の割合は28%であったことから、高安動脈炎に対する本剤の有効性は比較的長期間にわたり再発抑制効果を示すことが認められた。

表 2.7.3.3.2.1-4 ステロイド減量目標値の達成及び再発の有無による被験者の分類 (MRA632JP 試験, ITT)

分類	ステロイド減量目標値 ^a の達成		ステロイド減量目標値 ^a の未達成	
	再発又は再発の徴候によるステロイド減量目標値を超える増量なし	再発又は再発の徴候によるステロイド減量目標値を超える増量あり		
例数	25例	5例	6例	
症例番号	60102 60103 60104 60105 ^b 60106 60501 60503 60504 ^b 60601 60701 ^c 60702 ^c 60801 60101 ^g (中止例) 60401 ^l (中止例)	60902 ^b 60903 61001 61101 ^e 61102 61201 ^b 61204 ^d 61301 ^c 61701 ^e 61702 ^e 61801	60301 60402 61002 61003 60904 ^{b,f,g} (中止例)	60502 ^j 60802 60901 ⁱ (中止例) 61202 ^{i,k} (中止例) 61401 ^h (中止例) 61601 ⁱ (中止例)

- a : 二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に、副腎皮質ステロイド量が10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満
- b : プラセボ群に割り付けられ、二重盲検期間に副腎皮質ステロイド減量目標値を達成し、非盲検期間移行後に本剤投与下で目標値以下を維持した症例
- c : 二重盲検期間でステロイド減量目標値以下を達成した後に再発が認められ、非盲検期間でステロイド減量目標値以下を達成した症例
- d : 非盲検期間の Day 97 に副腎皮質ステロイドを増量したが再発の徴候はなく、「再発の徴候による副腎皮質ステロイド増量あり」に該当しない症例
- e : 非盲検期間で再発が認められ、副腎皮質ステロイドを増量をした後にステロイド減量目標値を達成した症例
- f : 中止時検査で再発が認められ、副腎皮質ステロイドの増量のない症例
- g : 併用禁止療法による中止例
- h : 治療拒否/協力を得られずによる中止例
- i : 効果不十分による中止例
- j : 本剤投与開始時以降、ステロイド減量目標値以下を14日間達成したが、本剤投与による減量効果ではないため対象外とした症例
- k : 副腎皮質ステロイドの投与が行われなかった非盲検期間の Day 26~Day 28は対象外とした症例
- l : 同意の撤回による中止例

2.7.3.3.2.2 WA28119試験

(1) 52週時の寛解維持割合

1) プラセボ+26週群に対する MRA-SC の有効性 (主要評価項目)

MRA-SC 群とプラセボ+26週群の52週時点での寛解維持割合の群間比較には、試験開始時の副腎皮質ステロイド量 (30 mg/日以下, 30 mg/日超) を層別因子とした CMH 法を用いた (表 2.7.3.3.2.2-1)。

52週時の寛解維持割合は、プラセボ+26週群で14.0%, MRA-SC QW 群で56.0% [リスク差: 42.00% (99.5%信頼区間: 18.00~66.00), CMH 検定による P 値: 0.0001未満], MRA-SC Q2W 群で53.1% [リスク差: 39.06% (99.5%信頼区間: 12.46~65.66), CMH 検定による P 値: 0.0001未満] であり、プラセボ+26週群に対する MRA-SC QW 群と MRA-SC Q2W 群の優越性が示された。

本試験では、再発がなく、CRP が正常化 (1 mg/dL 未満) の状態を寛解と定義したが、急性期反応物質に対するトシリズマブの既知の薬力学的効果による結果へのバイアスの可能

性を緩和するために、CRP 値に関わらず巨細胞性動脈炎の症状や徴候のみで評価した際の52週時の寛解維持割合の感度分析では、52週時の寛解維持割合はプラセボ+26週群で20.0%、MRA-SC QW 群で59.0% [リスク差：39.00% (99.5%信頼区間：14.77～63.23)]，CMH 検定による P 値：0.0001未満]，MRA-SC Q2W 群で55.1% [リスク差：35.10% (99.5%信頼区間：7.80～62.40)]，CMH 検定による P 値：0.0004] であり、主要評価項目の結果と一貫していることから、本試験結果の頑健性が確認された (5.3.5.1-3 Table 15)

2) プラセボ+52週群に対する MRA-SC の有効性 (主要な副次的評価項目)

主要評価項目と同じ52週時の寛解維持割合について、プラセボ+52週群に対する MRA-SC 群の非劣性を検証した (非劣性マージン：-22.5%)。MRA-SC 群とプラセボ+52週群の52週時点での寛解維持割合の群間比較には、試験開始時の副腎皮質ステロイド量 (30 mg/日以下、30 mg/日超) を層別因子とした CMH 法を用いた (表 2.7.3.3.2.2-1)。

52週時の寛解維持割合は、プラセボ+52週群で17.6%、MRA-SC QW 群で56.0% [リスク差：38.35% (99.5%信頼区間：17.89～58.81)]，CMH 検定による P 値：0.0001未満]，MRA-SC Q2W 群で53.1% [リスク差：35.41 (99.5%信頼区間：10.41～60.41)]，CMH 検定による P 値：0.0002] であり、プラセボ+52週群に対する MRA-SC QW 群と MRA-SC Q2W 群の非劣性と優越性が示された。

CRP 値に関わらず巨細胞性動脈炎の症状や徴候のみで評価した際の52週時の寛解維持割合は、プラセボ+52週群で33.3%、MRA-SC QW 群で59.0% [リスク差：25.67% (99.5%信頼区間：2.56～48.77)]，CMH 検定による P 値0.0030]，MRA-SC Q2W 群で55.1% [リスク差：21.77% (99.5%信頼区間：-5.46～48.99)]，CMH 検定による P 値0.0292] であった (5.3.5.1-3 Table 20)

表 2.7.3.3.2.2-1 52週時の寛解維持割合 (WA28119試験)

Summary and Analysis of the Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Responders	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Non-Responders	43 (86.0%)	42 (82.4%)	44 (44.0%)	23 (46.9%)
TCZ QW + 26 Week Prednisone Taper (N=100)				
Unadjusted Difference in Response Rates	42.00	38.35		
99.5% CI	(18.00, 66.00)	(17.89, 58.81)		
p-value (Cochran-Mantel-Haenszel)	<.0001	<.0001		
TCZ Q2W + 26 Week Prednisone Taper (N=49)				
Unadjusted Difference in Response Rates	39.06	35.41		
99.5% CI	(12.46, 65.66)	(10.41, 60.41)		
p-value (Cochran-Mantel-Haenszel)	<.0001	0.0002		

Patients in remission will be classed as responders.
 Patients are in sustained remission when they are responders from Week 12 to Week 52.
 Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
 Elevated ESR which attribute to GCA is reflected in Flare by investigator.
 Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
 Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
 Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
 Superiority comparison to 'PBO QW + 26 Week Taper' uses pooled SE. Non-inferiority comparison to 'PBO QW + 52 Week Taper' uses unpooled SE.
 The stratification factor, starting prednisone dose ($\leq 30\text{mg/day}$, $>30\text{mg/day}$) was included in the model.
 Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factor applied at Baseline.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ef_sum.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ef_sum_IT.out
 11JUL2016 23:17 Page 1 of 1

[5.3.5.1-3 Page 417を再掲]

(2) 再発までの期間

二重盲検期間の再発までの期間については、試験開始時の副腎皮質ステロイド量（30 mg/日以下，30 mg/日超）を層別因子とした Cox 比例ハザードモデルにより、プラセボ群に対する MRA-SC 群のハザード比及び信頼区間をそれぞれ算出した結果を表 2.7.3.3.2.2-2 に示す。なお、ベースライン時から12週間以内に寛解しなかった被験者は、ベースライン時で打ち切りとした。

再発までの期間の中央値（99%信頼区間）は、プラセボ+26週群165.0日（120.0～260.0），プラセボ+52週群295.0日（168.0～推定不能），MRA-SC QW 群及び MRA-SC Q2W 群では算出できなかった。

再発までの期間の MRA-SC 群のプラセボ+26週群に対するハザード比は、MRA-SC QW 群で 0.23（99%信頼区間：0.11～0.46，P 値：0.0001未満），MRA-SC Q2W 群で0.28（99%信頼区間：0.12～0.66），P 値：0.0001] であった。MRA-SC 群のプラセボ+52週群に対するハザード比は、MRA-SC QW 群で0.39（99%信頼区間：0.18～0.82，P 値：0.0011），MRA-SC Q2W 群で0.48（99%信頼区間：0.20～1.16），P 値：0.0316] であった。よって、プラセボ+26週群に対して、MRA-SC QW 群と MRA-SC Q2W 群で再発リスクを低下させた。また、プラセボ+52週群に対しても、MRA-SC QW 群と MRA-SC Q2W 群で再発リスクを低下させ、MRA-SC QW 群の方がより低下させることが示された。

再発までの期間の Kaplan-Meier 曲線は、12週時以降はプラセボ群より MRA-SC 群が上に位置していた（図 2.7.3.3.2.2-1）。試験開始から最初の数週間は、MRA-SC QW 群と MRA-SC Q2W 群の再発例数の違いにより、両曲線はかい離していたが12週時には重なった。しかし、盲検化された副腎皮質ステロイド投与量が0 mg/日になり始める20週時から24週時の間にかい離し、それ以降は MRA-SC Q2W 群より MRA-SC QW 群の曲線が上に位置していた。

表 2.7.3.3.2.2-2 再発までの期間 (WA28119試験)

Summary and Analysis of Time to First GCA Disease Flare Following Clinical Remission, by Treatment Group, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Patients included in analysis	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
Patients with event (%)	34 (68.0%)	25 (49.0%)	23 (23.0%)	13 (26.5%)
Patients without event (%)	16 (32.0%)	26 (51.0%)	77 (77.0%)	36 (73.5%)
Time to event (days)				
Median	165.0	295.0	NE	NE
99% CI for Median	(120.0, 260.0)	(168.0, NE)	NE	NE
25% and 75%-ile	92.0, NE	141.0, NE	NE	183.0, NE
Range	1 to 365	1 to 362	1 to 367	1 to 364
Stratified Analysis (vs PBO + 26 WK Taper)				
p-value			<.0001	0.0001
Hazard Ratio			0.23	0.28
99% CI			(0.11, 0.46)	(0.12, 0.66)
Stratified Analysis (vs PBO + 52 WK Taper)				
p-value			0.0011	0.0316
Hazard Ratio			0.39	0.48
99% CI			(0.18, 0.82)	(0.20, 1.16)

Patients who were never in remission are censored at Day 1.

Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

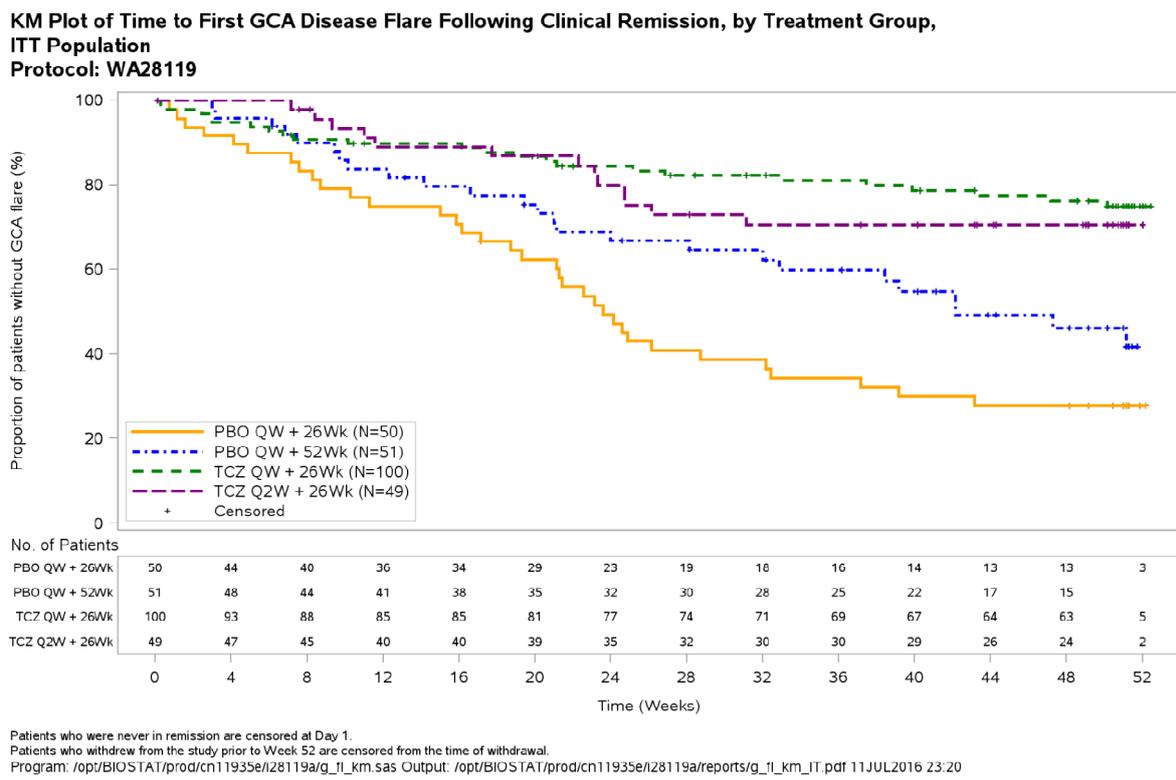
The treatment groups are compared to Placebo using a Cox proportional hazards model adjusting for the stratification factor of starting prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_fl_km.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_fl_km_IT.out
11JUL2016 23:17

Page 1 of 1

[5.3.5.1-3 Table 23を再掲]

図 2.7.3.3.2.2-1 再発までの期間の Kaplan-Meier 曲線 (WA28119試験)



[5.3.5.1-3 Figure 4を再掲]

(3) 副腎皮質ステロイド投与量

52週までの副腎皮質ステロイドの予想累積投与量は、26週間又は52週間の副腎皮質ステロイド漸減投与の開始量に基づいて算出し、実累積投与量は、副腎皮質ステロイドの救済治療 (escape therapy) へ移行後の副腎皮質ステロイド、使用した治験薬ではない市販の副腎皮質ステロイドをすべてまとめて算出した。副腎皮質ステロイド累積投与量は、試験開始時の副腎皮質ステロイド量 (30 mg/日以下, 30 mg/日超) を層別因子とした van Elteren 検定を用いて評価した (表 2.7.3.3.2.2-3)。また、52週までの副腎皮質ステロイドの累積投与量中央値の推移図を図 2.7.3.3.2.2-2に示した。

52週までの副腎皮質ステロイド予想累積投与量 (中央値) は、プラセボ+26週群では1337.00 mg, プラセボ+52週群では2607.50 mg, MRA-SC QW 群及び MRA-SC Q2W 群はそれぞれ 1337.00 mg, 1442.00 mg であり、副腎皮質ステロイド投与が52週時まで継続するプラセボ+52週群は他群より多かった。52週までの副腎皮質ステロイド実累積投与量 (中央値) は、プラセボ+26週群では3296.00 mg, プラセボ+52週群では3817.50 mg であるのに対し、MRA-SC QW 群及び MRA-SC Q2W 群はいずれも1862.00 mg であり、プラセボ群より MRA-SC 群で少なかった (表 2.7.3.3.2.2-3)。

試験開始時の副腎皮質ステロイド量を層別因子とした van Elteren 検定による副腎皮質ステロイド累積投与量の、プラセボ+26週群に対する MRA-SC QW 群の P 値は0.0001未満であり、プラセボ+26週群に対する MRA-SC Q2W 群の P 値は0.0003であった。

副腎皮質ステロイドの累積投与量 (中央値) は、22週時位までは26週間で副腎皮質ステロイドを漸減する MRA-SC QW 群及び MRA-SC Q2W 群, プラセボ+26週群とも同様に推移したが、それ以降は副腎皮質ステロイド投与量が増加しないと考えられる MRA-SC QW 群と MRA-SC Q2W 群ではほとんど上昇せず、プラセボの2群では上昇し、副腎皮質ステロイド投与が継続しているプラセボ+52週群が最も高く推移した (図 2.7.3.3.2.2-2)。

表 2.7.3.3.2.2-3 52週までの副腎皮質ステロイド累積投与量 (WA28119試験)

Summary and Analysis of Cumulative Corticosteroid (CS) Dose, ITT Population
Protocol: WA28119

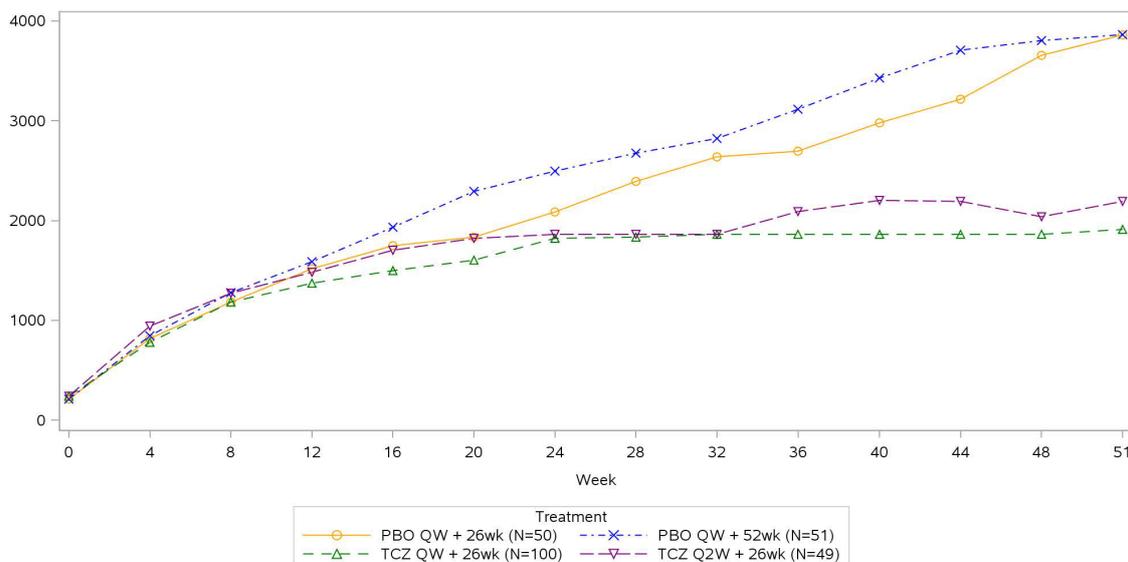
Statistics	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Expected Cumulative Dose (mg)				
n	50	51	100	49
Mean	1522.78	2694.52	1500.80	1606.93
Median	1337.00	2607.50	1337.00	1442.00
SD	540.10	732.88	567.75	571.83
Min - Max	952.0 - 2632.0	822.5 - 3902.5	350.0 - 2632.0	332.5 - 2632.0
Actual Cumulative Dose (mg)				
n	50	51	100	49
Mean	3765.19	4199.00	2097.84	2447.00
Median	3296.00	3817.50	1862.00	1862.00
SD	2022.45	2291.32	1248.45	1827.31
Min - Max	932.0 - 9777.5	822.5 - 10697.5	630.0 - 6602.5	295.0 - 9912.5
95% CI of the Median	(2729.5, 4023.5)	(2817.5, 4425.5)	(1582.0, 1942.0)	(1568.0, 2239.5)
P-Value				
PBO QW + 26 Week Prednisone Taper		0.8297	<.0001	0.0003
PBO QW + 52 Week Prednisone Taper			<.0001	<.0001

Van Elteren's test was used to calculate p-values. Analysis was stratified by starting prednisone dose (<=30mg/day, >30mg/day). For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack. Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group. Expected cumulative dose is based on a patient's starting prednisone dose in the taper and assumes they continued the taper without error. Actual cumulative dose is based on actual records of prednisone taken and includes all escape therapy and commercial prednisone as well as taper prednisone

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ex_cumvelt.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ex_cumvelt_IT.out
11JUL2016 23:20 Page 1 of 1

[5.3.5.1-3 Table 28を再掲]

図 2.7.3.3.2.2-2 52週までの副腎皮質ステロイドの累積投与量中央値の推移 (WA28119試験)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack. Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group. Patients who withdraw are excluded from the summaries for subsequent visits. Prednisone records are reported up to study day 364. Week 0 to Week 51 includes the 52 weeks of Part 1 prednisone exposure.

Program: /opt/BIOSTAT/prod/cn11935ei/28119a/g_ex_cumcs.sas
 Output: /opt/BIOSTAT/prod/cn11935ei/28119a/reports/g_ex_cumcs_IT.pdf
 11JUL2016 23:21

[5.3.5.1-3 Figure 5を再掲]

(4) 再発率

再発率（1人年あたりの再発回数）の平均値は、プラセボ+26週群で1.74/年、プラセボ+52週群で1.30/年、MRA-SC QW 群で0.41/年、MRA-SC Q2W 群で0.67/年であった。MRA-SC QW 群の1年あたりの再発率はプラセボ+26週群の約1/4、プラセボ+52週群の約1/3、MRA-SC Q2W 群はプラセボ+26週群の約1/3、プラセボ+52週群の約1/2であった。

再発率の中央値は、プラセボ+26週群とプラセボ+52週群では1であったが、MRA-SC QW 群とMRA-SC Q2W 群では0であった（表 2.7.3.7.2-5）。

2.7.3.3.2.3 トシリズマブによる高安動脈炎の症例報告

高安動脈炎患者でのトシリズマブの臨床使用実態を調べるために文献調査を行った。PubMed [検索式：("takayasu arteritis"[MeSH Terms] OR ("takayasu"[All Fields] AND "arteritis"[All Fields]) OR "takayasu arteritis"[All Fields]) AND ("tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields])] , Embase (検索式：'tocilizumab'/exp AND 'aorta arch syndrome'/exp) 及び医中誌 [検索式：(高安動脈炎/TH or 高安動脈炎/AL) AND (Tocilizumab/TH or トシリズマブ/AL)] を使用して検索した。その結果、PubMed では44件、Embase では168件、医中誌では33件が該当した（2016年6月22日現在）。その内、報告のあった Peer-reviewed journal の総説、メタ・アナリシス等の報告状況、日本人での高安動脈炎の有効性に関する文献情報を以下にそれぞれ示す。

- (1) 無作為化比較試験，薬物動態試験等の公表論文としての報告状況
 これまでにプロスペクティブな無作為化比較試験，薬物動態試験は報告されていない。
- (2) Peer-reviewed journal の総説，メタ・アナリシス等の報告状況
 トシリズマブによる高安動脈炎治療に関連する代表的な総説と，システマティック・レビューにおける記載内容を以下に示す。

- 1) Koster MJ, Matteson EL, Warrington KJ. Recent advances in the clinical management of giant cell arteritis and Takayasu arteritis. *Curr Opin Rheumatol*. 2016;28(3):211-7. ²³⁾

【目的・方法】生物学的治療での最近の報告にフォーカスして巨細胞性動脈炎及び高安動脈炎の治療の進歩をレビューした。

【結論】IL-6阻害剤は大型血管炎の再発例の治療に効果があると考えられる。しかし、新規に診断され免疫抑制剤を投与されることがない患者での使用は十分に確立されていない。アバタセプト及びウステキヌマブは大型血管炎の治療の有望な薬剤であるが、更なる調査が必要である。

【高安動脈炎に対するトシリズマブ】Nishimoto らによる高安動脈炎における臨床的有効性の最初の報告以来、再発性かつ難治性の疾患に対する観察コホートでのトシリズマブの使用報告が増えてきた。最近、Osman らによりトシリズマブで治療された高安動脈炎患者30例がレビューされた(2.7.3.3.2.3(2)3)参照)。そのレビュー以来、40例が追加で報告された。トシリズマブ8 mg/kg の4週ごとの静脈内投与は、80%を超える患者で3カ月までに臨床的及び臨床検査値上改善が認められたが、20%未満の患者で治療継続中に再発しており、総じて、高安動脈炎に対し効果があるようである。

これらの症例報告の最も重要な報告のうち、Goel らは副腎皮質ステロイドやセカンドラインの薬剤で再発する高安動脈炎患者10例のトシリズマブの使用経験を報告している。トシリズマブは急性期反応物質を正常化し、すべての患者で4回目の投与までに明らかに寛解導入が可能であったが、3例の患者で6回目の投与までに臨床的及び血管画像で再発が認められた。再発例では、急性期反応物質が正常の状況で画像上での悪化が認められた。同様に、他の症例報告ではトシリズマブで治療しているにもかかわらず無症状の血管炎の進行が報告されている。

- 2) Mekinian A, Comarmond C, Resche-Rigon M, Mirault T, Kahn JE, Lambert M, et al. Efficacy of Biological-Targeted Treatments in Takayasu Arteritis: Multicenter, Retrospective Study of 49 Patients. *Circulation*. 2015;132(18):1693-700. ²⁴⁾

【目的・方法】高安動脈炎患者での生物学的製剤(TNF- α 阻害剤, トシリズマブ)の安全性及び有効性を評価した。高安動脈炎であり、ACR 基準又はIshikawa 基準を満たす49例[女性80%, 年齢の中央値42歳(20~55歳), TNF- α 阻害剤(80%, 35例)又はトシリズマブ(20%, 14例)で治療]からなるレトロスペクティブな多施設試験であった。

【結果】高安動脈炎患者の88%は従来の免疫抑制剤ではコントロール不十分か、耐えられなかった。6カ月及び12カ月時に overall response (完全又は部分寛解)だったのはそれぞれ75%及び83%であった。生物学的製剤治療の12カ月後、CRP 及び副腎皮質ステロイドは減少した(ベースライン及び12カ月時でそれぞれ30 mg/L vs.6 mg/L, 15 mg vs. 7.5 mg)。3年時無再発生存率は生物学的製剤全体で90.9%であった。TNF- α 阻害剤とトシリズマブの有効性の違いはなかった。24カ月の追跡で、21%の患者が有害事象を発現し、6.6%の患者が治療を中止した。

【結論】高安動脈炎の患者の生物学的製剤による治療は有効性が高く、安全性プロファイルも受け入れられるものであった。

【高安動脈炎に対するトシリズマブ】、副腎皮質ステロイドを併用していた患者は治療開始時12.5 mg (4~75 mg/日, 11/14例)から12カ月後4.5 mg (1~14 mg/日, 4/7例)に減少し、全例(7/7例)が完全寛解であった。3年時無再発生存率は85.7%であった。

- 3) Osman M, Emery D, Yacyshyn E. Tocilizumab for treating takayasu's arteritis and associated stroke: A case series and updated review of the literature. *J Stroke Cerebrovasc Dis*. 2015;24(6):1291-8. ²⁵⁾

【目的・方法】レトロスペクティブにトシリズマブを投与された高安動脈炎患者をレビューし、疾患の寛解と副腎皮質ステロイドの減量を含むトシリズマブの有効性を評価した。日

付や言語の制限なく PubMed 及び MEDLINE で報告されたトシリズマブ投与を受けた高安動脈炎患者を集計し、高安動脈炎患者での寛解導入、副腎皮質ステロイド減量におけるトシリズマブの減量効果及び有害事象を評価した。

【結果】我々のコホートである高安動脈炎患者3例すべてでトシリズマブにより寛解に導入され、副腎皮質ステロイドは減量された。活動性の高安動脈炎の最初の兆候が脳卒中であった2例の患者で寛解が達成された。総計で、トシリズマブで治療された脳卒中を伴う高安動脈炎患者4例（自身の試験の2例及び他試験の2例）中3例が寛解及び疾患の安定に至った。また、文献からトシリズマブを投与された高安動脈炎患者30例を同定し、その内、76.7%が他の生物学的製剤で寛解を維持できなかつたにもかかわらず寛解に至っていた。更に、トシリズマブは、トシリズマブ使用前に比べて副腎皮質ステロイドの統計的に有意な減量をもたらした（中央値：-8.8 mg/日，四分位範囲：-19.4～-3.4 mg/日，Wilcoxon 検定による P 値：0.0002）。

【結論】トシリズマブは他の生物学的製剤では効果がない高安動脈炎の治療、及び脳卒中を伴う高安動脈炎患者の有望な選択肢である。

- 4) Osman M, Pagnoux C, Dryden DM, Storie D, Yacyshyn E. The role of biological agents in the management of large vessel vasculitis (LVV): A systematic review and meta-analysis. PLoS One. 2014;9(12):e115026. ²⁶⁾

【目的・方法】大型血管炎患者に対する生物学的製剤の有効性と安全性について体系的にレビューするため、5種の電子的データベースで検索され、独立した二人により試験の選択、データの抽出、方法論的な質の評価が行われた。

【結果・結論】25試験〔無作為化比較試験3試験（いずれも抗 TNF α 製剤）と2例以上記載された症例報告22報〕で巨細胞性動脈炎95例、高安動脈炎98例が生物学的製剤を投与されていた。

巨細胞性動脈炎の症例報告では、トシリズマブによる寛解と副腎皮質ステロイドの減量が達成された。寛解の定義は一定ではなく、試験は臨床的に不均一で、これ以上の解析を不可能にしている。

この体系的なレビューでは大型血管炎における生物学的製剤の治療効果を評価するにはエビデンスが乏しいことが示された。トシリズマブは、症例報告からのエビデンスであるものの、巨細胞性動脈炎及び再発性の高安動脈炎のコントロールに効果的かもしれない。これらの所見を確認するために今後解析的な試験が必要とされた。

【高安動脈炎に対するトシリズマブ】高安動脈炎に対するトシリズマブの症例報告は4報11例（Seitz ら，Salvarani ら，Unizony ら，Canas ら）掲載されている。

- 5) Abisror N, Mekinian A, Lavigne C, Vandenhende MA, Soussan M and Fain O. Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review. Autoimmun Rev. 2013;12(12):1143-9. ²⁰⁾

【目的・方法】高安動脈炎（ACR 又は Ishikawa's criteria）患者に対するトシリズマブ投与の有効性及び忍容性がレトロスペクティブに検討された。

対象患者は計44例，うち5例はフランス多施設研究の症例（症例報告の提示あり），39例は文献検索より特定された。

【結果】年齢の中央値は26歳（3～65歳）。トシリズマブ投与開始後の追跡期間の中央値は15カ月（8～33カ月）。疾患活動性はトシリズマブ投与3カ月以内に有意に低下，同様に副腎皮質ステロイド投与量〔ベースライン時：15 mg/日（5～75 mg/日）→6カ月時：10 mg/日（2～30 mg/日）〕，副腎皮質ステロイド依存率も低下した。6カ月時には画像から認められる活動性は低下しなかつたが，動脈での FDG の取込みは有意に減少した。トシリズマブ投与期間の中央値は9カ月（3～180カ月）。最終受診時点で17/32例（53%）がトシリズマブを

継続しており，15例が投与中止していた。投与中止理由の内訳は寛解5例，再発3例，persistent radiological activityが3例，皮疹2例，重度の感染症1例，care welfare systemの失効1例であった。

トシリズマブと関連がある死亡例はなかった。

(3) 日本人での高安動脈炎の有効性に関する文献情報

日本人での高安動脈炎患者に対してトシリズマブが静脈注射によって継続投与された論文報告及び学会抄録を表 2.7.3.7.1-14に示す。なお，複数の論文に同一患者の報告がある場合は，代表的な一報を記載した。

10報26例のトシリズマブを投与した大部分の患者で，副腎皮質ステロイドの減量，高安動脈炎の画像による改善，寛解維持等が認められた。

2.7.3.3.3 部分集団における結果の比較

2.7.3.3.3.1 MRA632JP

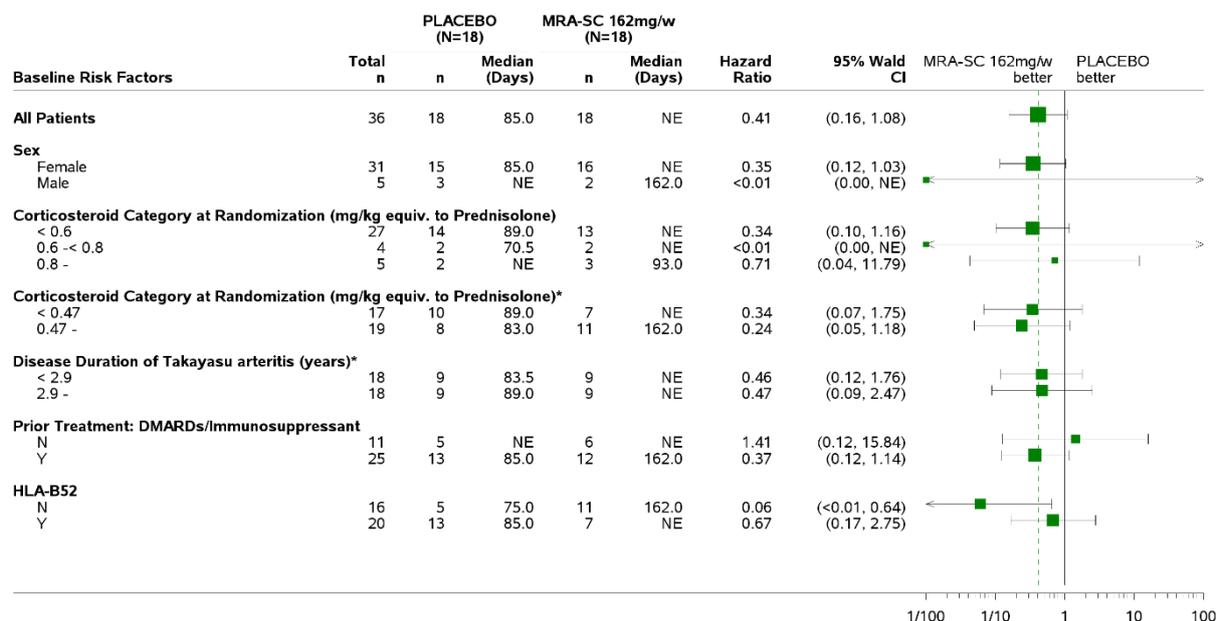
(1) 有効性に及ぼす患者背景の影響

主要評価項目である二重盲検期間の高安動脈炎再発までの期間についての年齢カテゴリ（18歳未満，18歳以上65歳未満，65歳以上）で層化調整したCox回帰分析を，ランダム化時の高安動脈炎に対する副腎皮質ステロイド投与量（0.6 mg/kg未満，0.6 mg/kg以上0.8 mg/kg未満，0.8 mg/kg以上/0.47 mg/kg未満，0.47 mg/kg以上），罹病期間（2.9カ月未満，2.9カ月以上），DMARDs又は免疫抑制剤の前治療歴の有無，HLA-B52抗原判定結果（陽性，陰性），性別の因子で分類した部分集団で解析した結果を図 2.7.3.3.3.1-1に示す。

例数が少ない部分集団もあるが，DMARDs又は免疫抑制剤の前治療歴のない被験者の部分集団を除いたすべてのハザード比の点推定値は1未満であり，MRA-SC群で高安動脈炎の再発のリスクを低下させる傾向が一貫して認められた。特に，HLA-B52抗原陰性の被験者の部分集団では，その傾向がより強く認められた。

図 2.7.3.3.3.1-1 背景因子別の二重盲検期間での再発までの期間（年齢による層別あり）
-19 event (ITT) (MRA632JP 試験)

kmsubgroupfrn_st_itt Relapse Free of Takayasu Arteritis by Subgroup (Stratified, 19 events)
Protocol: MRA632JP
Analysis: ITT



*: Category is defined by median of pooled data.
Program: /opt/BIOSTAT/prod/ctd3489g/gmra632a/kmsubgroupfrn.sas Output: /opt/BIOSTAT/prod/ctd3489g/gmra632a/reports/kmsubgroupfrn_st_itt.png 21DEC2015 21:19

[5.3.5.1-1 図 11.4.3.8-1を再掲]

2.7.3.3.3.2 WA28119試験

(1) 被験者背景因子に基づいて分類した部分集団

主要評価項目である52週時の寛解維持割合について、被験者背景因子で分類した部分集団で解析した結果を表 2.7.3.7.2-6～表 2.7.3.7.2-19に示した。

例数が少ない部分集団もあるが、すべての部分集団でプラセボ+26週群、プラセボ+52週群より、MRA-SC QW 群及び MRA-SC Q2W 群で52週時の寛解維持割合は高い傾向が一貫して認められた。

1) ベースライン時の巨細胞性動脈炎の発症（新規発症、再発）

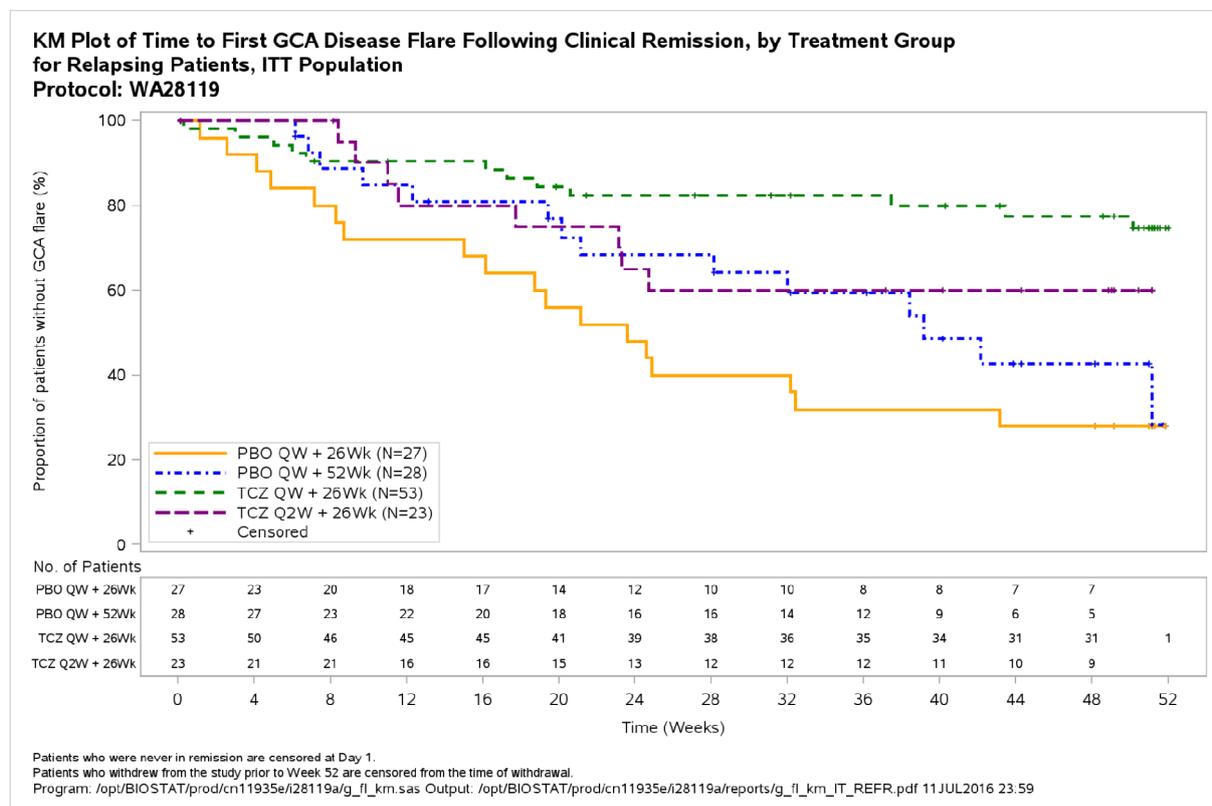
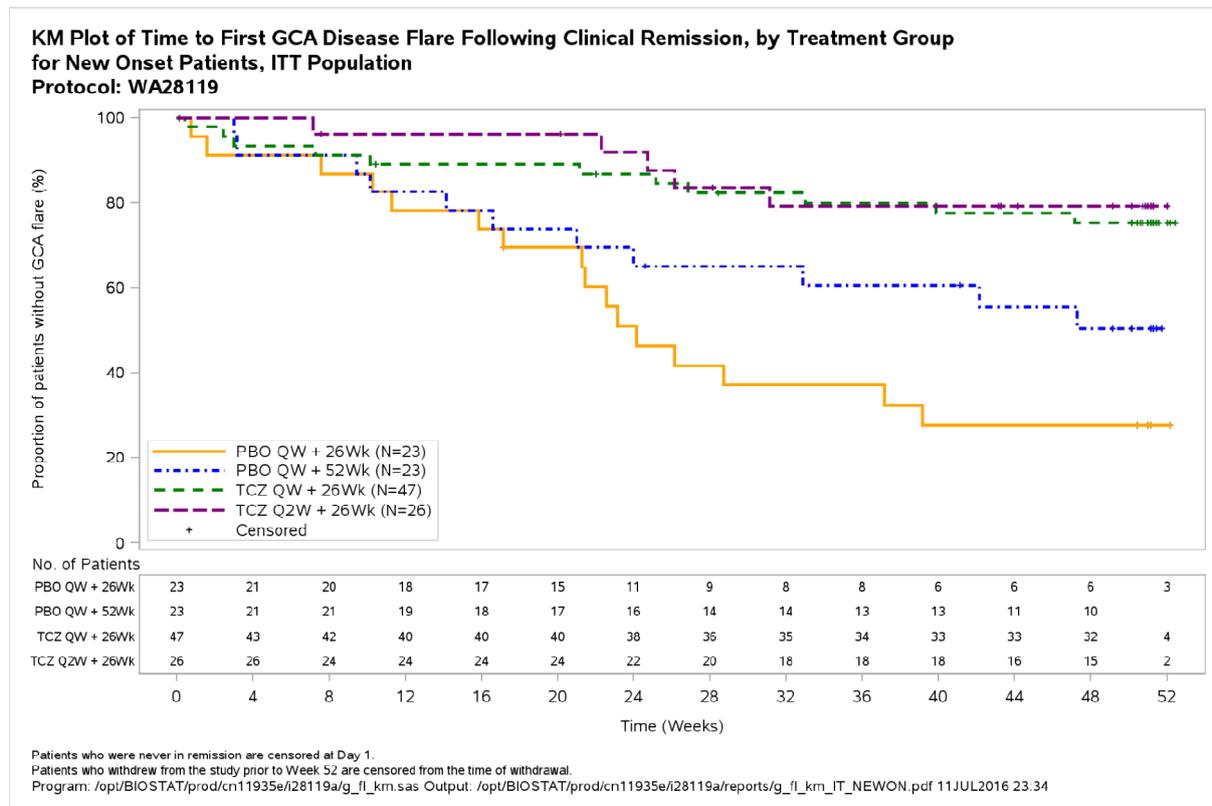
ベースライン時の巨細胞性動脈炎の発症（新規発症、再発）で分けた部分集団のうち、新規発症の患者集団での52週時の寛解維持割合は、プラセボ+26週群で21.7%、プラセボ+52週群で21.7%、MRA-SC QW 群で59.6%、MRA-SC Q2W 群で57.7%であった。再発の患者集団での52週時の寛解維持割合は、プラセボ+26週群で7.4%、プラセボ+52週群で14.3%、MRA-SC QW 群で52.8%、MRA-SC Q2W 群で47.8%であり、新規発症、再発の患者集団ともプラセボ群よりMRA-SC 群で倍以上高かった（表 2.7.3.7.2-6）。

各患者集団での再発までの期間については、試験開始時の副腎皮質ステロイド量（30 mg/日以下、30 mg/日超）を層別因子とした Cox 比例ハザードモデルにより、プラセボ群に対するMRA-SC 群のハザード比及び信頼区間をそれぞれ算出した（表 2.7.3.7.2-20）。新規発症の患者集団の再発までの期間の MRA-SC 群のプラセボ+26週群に対するハザード比は、MRA-SC QW 群で0.25（99%信頼区間：0.09～0.70、P 値：0.0005）、MRA-SC Q2W 群で0.20（99%信頼区間：0.05～0.76）、P 値：0.0019]であった。MRA-SC 群のプラセボ+52週群に対するハザード

ド比は、MRA-SC QW 群で0.44 (99%信頼区間 : 0.14~1.32, P 値 : 0.0541) , MRA-SC Q2W 群で0.35 (99%信頼区間 : 0.09~1.42) , P 値 : 0.0546] であった。一方、再発の患者集団の再発までの期間の MRA-SC 群のプラセボ+26週群に対するハザード比は、 MRA-SC QW 群で0.23 (99%信頼区間 : 0.09~0.61, P 値 : 0.0001) , MRA-SC Q2W 群で0.42 (99%信頼区間 : 0.14~1.28) , P 値 : 0.0459] であった。MRA-SC 群のプラセボ+52週群に対するハザード比は、MRA-SC QW 群で0.36 (99%信頼区間 : 0.13~1.00, P 値 : 0.0100) , MRA-SC Q2W 群で0.67 (99%信頼区間 : 0.21~2.10) , P 値 : 0.3666] であった。

再発までの期間の Kaplan-Meier 曲線は、新規発症の患者では MRA-SC QW 群と MRA-SC Q2W 群が大きく重なっていた (図 2.7.3.3.3.2-1) 。一方、再発の患者では、曲線が MRA-SC Q2W 群とプラセボ+52週群が約38週時まで重なっているが、MRA-SC QW 群は12週時からプラセボ群と重なることなく、MRA-SC Q2W 群よりも上に位置していた。

図 2.7.3.3.2-1 ベースライン時の巨細胞性動脈炎の発症で分けた部分集団での再発までの期間のKaplan-Meier 曲線 (WA28119試験)
(上：新規発症, 下：再発)



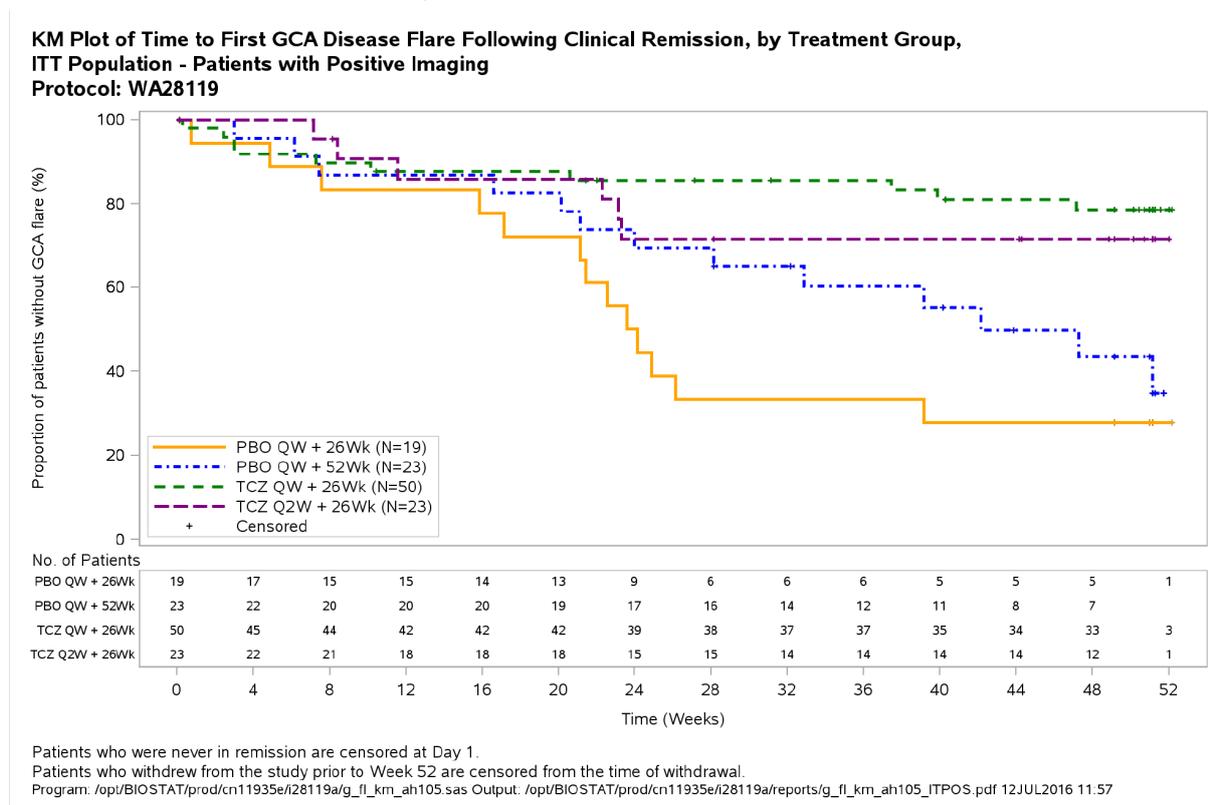
[5.3.5.1-3 Figure 6を再掲]

2) 巨細胞性動脈炎の診断方法（画像判定，側頭動脈生検）

巨細胞性動脈炎の診断方法（画像判定，側頭動脈生検）で分けた部分集団での52週時の寛解維持割合は，いずれの集団でもプラセボ群より MRA-SC 群で高かった（表 2.7.3.7.2-9，表 2.7.3.7.2-10）。画像判定で巨細胞性動脈炎と診断された部分集団での52週時の寛解維持割合は，プラセボ+26週群で21.1%，プラセボ+52週群で17.4%，MRA-SC QW 群で60.0%，MRA-SC Q2W 群で56.5%であった。また，画像判定で巨細胞性動脈炎と診断された患者集団での52週の再発までの期間については，試験開始時の副腎皮質ステロイド量（30 mg/日以下，30 mg/日超）を層別因子とした Cox 比例ハザードモデルにより，プラセボ群に対する MRA-SC 群のハザード比及び信頼区間をそれぞれ算出した（表 2.7.3.7.2-21）。画像判定で巨細胞性動脈炎と診断された患者集団での再発までの期間の MRA-SC 群のプラセボ+26週群に対するハザード比は，MRA-SC QW 群で0.20（99%信頼区間：0.07～0.60，P 値：0.0002），MRA-SC Q2W 群で0.28（99%信頼区間：0.08～1.00），P 値：0.0098] であった。MRA-SC 群のプラセボ+52週群に対するハザード比は，MRA-SC QW 群で0.30（99%信頼区間：0.10～0.91，P 値：0.0049），MRA-SC Q2W 群で0.42（99%信頼区間：0.11～1.52），P 値：0.0825] であった。

画像判定で巨細胞性動脈炎と診断された部分集団の再発までの期間の Kaplan-Meier 曲線は，MRA-SC QW 群と MRA-SC Q2W 群で最初は重なっているが，ITT 対象集団と同様に，盲検化された副腎皮質ステロイド投与量が0 mg/日になり始める20週時から24週時の間でかい離し始めた（図 2.7.3.3.3.2-2）。それ以降は，MRA-SC Q2W 群より MRA-SC QW 群の曲線が上に位置していた。

図 2.7.3.3.3.2-2 画像判定で巨細胞性動脈炎と診断された部分集団の再発までの期間の Kaplan-Meier 曲線（WA28119試験）



(2) 高安動脈炎患者と共通する病変部位を持つ患者集団での有効性

WA28119試験には、以下の①～③の患者集団に高安動脈炎と共通する大血管に病変部位が存在する可能性があると考えられる(2.7.3.3.1.1(2))。そこで、以下の各部分集団を設定し、その有効性に関して評価した。

- ① 画像判定で大血管の血管炎の存在が確認された患者集団
- ② ①で側頭動脈の生検結果で陽性でない患者集団
- ③ ②で頭部の症状のない患者集団

①～③の52週時の寛解維持割合は、表 2.7.3.7.2-9、表 2.7.3.7.2-11、表 2.7.3.7.2-12に示した。52週時の寛解維持割合は、いずれの集団においてもプラセボ群より MRA-SC 群で高く、MRA-SC Q2W 群より MRA-SC QW 群で高い傾向が示された。52週時の寛解維持割合は、①の患者集団から②、③の順に高安動脈炎患者に非特異的な病変や症状を除いた患者集団により絞り込んでも、いずれの患者集団でも ITT 対象の結果と同様に MRA-SC Q2W 群より MRA-SC QW 群の方が高かった。

(3) 結論

巨細胞性動脈炎は、頭蓋型と大血管型に大きく分類され(2.5.1.1項参照)、大血管型は①の画像判定で巨細胞性動脈炎と診断された患者集団に該当する。52週時の寛解維持割合については、ベースライン時の巨細胞性動脈炎の発症(新規発症、再発)で分けた患者、画像判定で大血管の血管炎の存在が確認された患者、側頭動脈生検陽性例を含む患者のいずれの集団においても、プラセボ群より MRA-SC 群で高い有効性が認められた。また、①の患者集団から②、③の順に高安動脈炎患者に非特異的な病変や症状を除いた患者集団により絞り込んでも、大血管型を含む ITT 対象の結果と同様に有効性を示す傾向が認められたことから、巨細胞性動脈炎の大血管型に含まれると考えられる高安動脈炎と共通する病変部位を認める可能性のある患者に対しても、本剤は有効であることが示唆された。

2.7.3.4 推奨用法・用量に関する臨床情報の解析

大型血管炎(高安動脈炎、巨細胞性動脈炎)に対する本剤の推奨用法・用量は、162 mg/週であると考えている。その根拠となった臨床結果を以下に示す。

(1) 薬物動態

MRA632JP 試験では、二重盲検期間に本剤162 mg/週の反復皮下投与した被験者全例の平均血清中トシリズマブトラフ濃度は、ほぼ定常状態に達した初回投与12週後以降、症例数が1例であった初回投与後48週を除き、41.8～56.6 µg/mL で推移した(2.7.2.2.1.2)。血清中トシリズマブトラフ濃度25～50 µg/mL 以上で、血中 sIL-6R 濃度が一定となっていることから、トシリズマブはほとんどの IL-6R と結合していると推測でき、本剤162 mg/週の用法・用量は妥当であると考えられた(2.7.2.2.1.5)。

WA28119試験の MRA-SC QW 群では、血清中トシリズマブトラフ濃度がほぼ定常状態に達した初回投与開始16週後以降の平均トラフ濃度は、63.49～70.46 µg/mL で推移した。また、MRA-SC Q2W 群では、血清中トシリズマブトラフ濃度がほぼ定常状態に達した初回投与開始16週後以降の平均トラフ濃度は、11.57～13.77 µg/mL で推移した。WA28119試験の24週時での MRA-SC QW 群の血清中トシリズマブトラフ濃度は、MRA-SC Q2W 群と比較して、5.47倍と高い結果が得られた(2.7.2.2.2.2)。一方、MRA-SC Q2W 群の血中 sIL-6R 濃度は、MRA-SC QW 群より低かった。トシリズマブは濃度依存的に血中 sIL-6R と免疫複合体を形成することで sIL-6R の消失半減期が延長し、血中 sIL-6R 濃度が上昇すると考えられている。

2週間隔の投与では1週間隔の投与より血中 sIL-6R 濃度が低値を示したことから、トシリズマブの血中濃度が足りず、トシリズマブと sIL-6R との結合が飽和していない可能性が示された (2.7.2.2.5)。

いずれの試験の結果からも本剤162 mg/週の用法・用量は妥当であると考えられた。

(2) 有効性

1) MRA632JP 試験

MRA632JP 試験では、高安動脈炎の再発までの期間の年齢カテゴリを層別因子とした Cox 比例ハザードモデルによるプラセボ群に対する MRA-SC 群のハザード比は0.41で、95.41%信頼区間は0.15~1.10であった。高安動脈炎の再発の大項目での再発までの期間は、すべての項目でハザード比の点推定値は1未満であり、MRA-SC 群で高安動脈炎の再発のリスクを低下させる傾向が一貫して認められた。二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に、「副腎皮質ステロイド量が10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満 (ステロイド減量目標値)」を1回でも達成した被験者は36例中30例 (83.3%) であり、その内25例は2016年11月10日のデータカットオフ時点で再発又は再発の徴候に伴う副腎皮質ステロイドの増量がなく、ステロイド減量目標値を達成している。36例中25例 (69.4%) のステロイド減量目標値達成後の維持期間の中央値は379.0日に及んでおり、25例中22例が少なくとも半年間は副腎皮質ステロイドを低用量で維持した上で再発が抑えられた。また、Maksimowicz-McKinnon らの報告と比較しても、高安動脈炎に対する本剤の有効性は比較的長期間にわたり継続することが認められた。

2) WA28119試験

WA28119試験では、52週時の寛解維持割合についてプラセボ+26週群に対する MRA-SC QW 群と MRA-SC Q2W 群の優越性と、プラセボ+52週群に対する MRA-SC QW 群と MRA-SC Q2W 群の非劣性と優越性が示された。主要評価項目である52週時の寛解維持割合は MRA-SC QW 群で56.0%、MRA-SC Q2W 群で53.1%であった。ベースライン時の副腎皮質ステロイド投与量を層別因子とした MRA-SC Q2W 群と MRA-SC QW 群の寛解維持割合の差は-2.94% (99.5%信頼区間：-19.94~14.06) であった (表 2.7.3.7.2-22)。また、副次的評価項目である再発までの期間のベースライン時の副腎皮質ステロイド投与量を層別因子とした MRA-SC QW 群に対する MRA-SC Q2W 群のハザード比は1.24 (99%信頼区間：0.63~2.44) であった (表 2.7.3.7.2-23)。再発までの期間の Kaplan-Meier 曲線は、MRA-SC QW 群と MRA-SC Q2W 群が最初は重なっているが、副腎皮質ステロイド投与量が減量で0 mg/日に達する20週時から24週時に離れ始め、それ以降は MRA-SC Q2W 群より MRA-SC QW 群の曲線が上に位置していた (図 2.7.3.3.2.2-1)。これらのことから、52週時の寛解維持割合及び再発までの期間で、MRA-SC QW 群は MRA-SC Q2W 群と比べて高い有効性が認められることが示唆された。

被験者背景因子に基づいて分類したすべての部分集団での52週時の寛解維持割合は、例数が少ない部分集団もあるが、MRA-SC 群の方がプラセボ群よりも高い傾向が一貫して認められた。それらの部分集団のうち、52週時の寛解維持割合と再発までの期間について MRA-SC 群 QW 群及び MRA-SC Q2W 群で差が認められた部分集団について以下に示す。

ベースライン時の巨細胞性動脈炎の発症 (新規発症119例、再発131例) で分けた部分集団での52週時の寛解維持割合は、新規発症、再発の患者ともプラセボ群より MRA-SC 群で倍以上高かった (表 2.7.3.7.2-6)。再発までの期間の Kaplan-Meier 曲線は、新規発症の患者では MRA-SC 群 QW 群及び MRA-SC Q2W 群が大部分で重なっていた。一方、再発の患者では、曲線が MRA-SC Q2W 群とプラセボ+52週群が約38週時まで重なっているが、MRA-SC QW 群は12週時からプラセボ群と重なることなく、MRA-SC Q2W 群よりも上に位置していた (図 2.7.3.3.3.2-1)。

画像判定で大血管炎の血管炎の存在が確認された部分集団115例 (2.7.3.3.3.2(2)①) での52週時の寛解維持割合は、ITT 対象の結果と類似しており、MRA-SC Q2W 群の56.5%に比べMRA-SC QW 群は60.0%とやや高かった (表 2.7.3.7.2-9)。再発までの期間のプラセボ+26週群に対するMRA-SC QW 群及びMRA-SC Q2W 群のハザード比は、それぞれ0.20 (99%信頼区間：0.07～0.60)，0.28 (99%信頼区間：0.08～1.00) で、プラセボ+52週群に対するハザード比は、それぞれ0.30 (99%信頼区間：0.10～0.91)，0.42 (99%信頼区間：0.11～1.52) であった (表 2.7.3.7.2-21)。再発までの期間の Kaplan-Meier 曲線は、ITT 対象 (図 2.7.3.3.2.2-1) とほぼ同様の推移を示した。MRA-SC QW 群と MRA-SC Q2W 群の Kaplan-Meier 曲線は、最初は重なっているが、ITT 対象集団と同様に副腎皮質ステロイド投与量が減量により0 mg/日に達する20週時から24週時の間で離れ始め、それ以降は、MRA-SC Q2W 群より MRA-SC QW 群の曲線が上に位置していた (図 2.7.3.3.3.2-2)。

いずれの試験の結果からも本剤162 mg/週の用法・用量は妥当であると考えられた。

(3) 安全性

MRA632JP 試験及び WA28119試験の安全性プロファイルは、これまでにトシリズマブにおいて確認されているものと変わらなかった。WA28119試験の MRA-SC QW 群と MRA-SC Q2W 群とで有害事象，副作用，重篤な有害事象等の発現頻度，臨床検査，バイタルサイン及び本剤の免疫原性に大きな違いは認められなかった。よって，MRA632JP 試験と WA28119試験の安全性の結果から，162 mg/週での安全性上の新たな問題点は認められなかった。

以上より，MRA632JP 試験及び WA28119試験の薬物動態・薬力学，有効性及び安全性の結果から大型血管炎に対する本剤の臨床推奨用法・用量は162 mg/週と考えられた。

2.7.3.5 効果の持続，耐薬性

MRA632JP 試験では，二重盲検期間と非盲検期間の本剤投与状況は表 2.7.3.3.1.2-1に示した。二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に，ステロイド減量目標値を一回でも達成した被験者数は30例であり，未達は6例であった (表 2.7.3.7.1-8)。ステロイド減量目標値を達成した30例中25例は，2016年11月10日のデータカットオフ時点で再発又は再発の徴候に伴う副腎皮質ステロイドの増量がなくステロイド減量目標値を達成している。この25例のステロイド減量目標値達成後の維持期間の中央値は379.0日であり，25例中22例 (88.0%) が少なくとも半年間は副腎皮質ステロイドを低用量で維持した上で再発抑制効果を示した。以上より，MRA632JP 試験では0.2 mg/kg/日以上副腎皮質ステロイド投与量で再発した被験者を対象としたが，本剤投与によって副腎皮質ステロイド減量目標値を維持した上で，高安動脈炎の再発を認めなかった被験者は36例中25例 (69.4%) であり，副腎皮質ステロイドを低用量で維持した上で再発抑制効果を示した。

WA28119試験では，二重盲検期間の52週まで本剤投与が完了した被験者数は表 2.7.4.1.2.1-2，本剤の投与期間は表 2.7.4.1.2.2-4に示した。本剤の52週の有効性の結果を2.7.3.2.2項に示した通り，効果減弱は認められなかった。再発までの期間の Kaplan-Meier 曲線 (図 2.7.3.3.2.2-1) は，12週時以降はプラセボ群より MRA-SC 群が上に位置していた。副腎皮質ステロイド投与量が0 mg/日になり始める20週時から24週時の間にかい離し，MRA-SC Q2W 群より MRA-SC QW 群の曲線が上に位置していた。52週までの副腎皮質ステロイド累積投与量は，プラセボ群は MRA-SC 群の約2倍であった (図 2.7.3.3.2.2-2)。副腎皮質ステロイド累積投与量の推移は，22週時位まで全群同様であったが，それ以降は副腎皮質ステロイド投与量が増加しないと考えられる MRA-SC QW 群と MRA-SC Q2W 群では上昇せず，プラセボの2群では上昇した。いず

れの有効性評価項目においても、52週時にプラセボ群に対する MRA-SC 群の有効性が認められた。

以上より、WA28119試験と MRA632JP 試験の52週までの有効性の結果から、大型血管炎での長期投与における効果減弱は認められず、耐薬性は現在までのところ示されていない。

2.7.3.6 参考文献

- 1) Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med.* 1994;120(11):919-29.
- 2) Misra R, Danda D, Rajappa SM, Ghosh A, Gupta R, Mahendranath KM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). *Rheumatology (Oxford).* 2013;52(10):1795-801.
- 3) 尾崎承一, 安藤太三, 居石克夫, 磯部光章, 太田敬, 小林茂人, et al. 血管炎症候群の診療ガイドライン [循環器病の診断と治療に関するガイドライン (2006-2007年度合同研究班報告)]. *Circ J* 2008;72(Suppl.IV): 1253-318.
- 4) 公益財団法人 難病医学研究財団/難病情報センター/診断・治療指針 (医療従事者向け)/高安動脈炎 (大動脈炎症候群). <http://www.nanbyou.or.jp/entry/290>. (Accessed date:2015年12月)
- 5) 平成26年国民健康・栄養調査報告. <http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h26-houkoku.pdf>. (Accessed date:2016年7月)
- 6) O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35(3):549-56.
- 7) Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheum.* 2007;56(3):1000-9.
- 8) Nishimoto N, Nakahara H, Yoshio-Hoshino N, Mima T. Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum* 2008;58(4):1197-200.
- 9) Salvarani C, Magnani L, Catanoso M, Pipitone N, Versari A, Dardani L, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology (Oxford).* 2012;51(1):151-6.
- 10) Bredemeier M, Rocha CM, Barbosa MV, Pitrez EH. One-year clinical and radiological evolution of a patient with refractory Takayasu's arteritis under treatment with tocilizumab. *Clin Exp Rheumatol* 2012;30(1 Suppl 70):S98-100.
- 11) Unizony S, Arias-Urdaneta L, Miloslavsky E, Arvikar S, Khosroshahi A, Keroack B, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, takayasu arteritis) and polymyalgia rheumatica. *Arthritis Care Res (Hoboken).* 2012;64(11):1720-9.
- 12) Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med Wkly.* 2011;141:w13156.
- 13) Salvarani C, Magnani L, Catanoso MG, Pipitone N, Versari A, Dardani L, et al. Rescue treatment with tocilizumab for Takayasu arteritis resistant to TNF- α blockers. *Clin Exp Rheumatol* 2012;30(1 Suppl 70):S90-3.
- 14) Xenitidis T, Horger M, Zeh G, Kanz L, Henes JC. Sustained inflammation of the aortic wall despite tocilizumab treatment in two cases of Takayasu arteritis. *Rheumatology (Oxford).* 2013;52(9):1729-31.
- 15) Bravo Mancheno B, Perin F, Guez Vázquez Del Rey Mdel M, García Sánchez A, Alcázar Romero PP. Successful tocilizumab treatment in a child with refractory Takayasu arteritis. *Pediatrics*

- 2012;130(6):e1720-4.
- 16) Tombetti E, Franchini S, Papa M, Sabbadini M, Baldissera E. Treatment of refractory Takayasu arteritis with tocilizumab: 7 Italian patients from a single referral center. *J Rheumatol.* 2013;40(12):2047-51.
 - 17) Nakaoka Y, Higuchi K, Arita Y, Otsuki M, Yamamoto K, Hashimoto-Kataoka T, et al. Tocilizumab for the treatment of patients with refractory Takayasu arteritis. *Int Heart J.* 2013;54:405-11.
 - 18) Gunnarsson R, Midtvedt O, Palm O, Guobrandsson B, Merckoll E, Johnsrud K. Severe relapse of Takayasu arteritis ongoing treatment with Tocilizumab. *Anca Workshop; 2013* [poster].
 - 19) Goel R, Danda D, Joseph G. Rapid control of disease activity by tocilizumab in ten “difficult to treat” cases of Takayasu arteritis. *Indian J Rheumatol.* 2012;7:S7-S56 [abstract].
 - 20) Abisror N, Mekinian A, Lavigne C, Vandenhende MA, Soussan M and Fain O. Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review. *Autoimmun Rev.* 2013;12(12):1143-9.
 - 21) Youngstein T, Peters JE, Hamdulay SS, Mewar D, Price-Forbes A, Lloyd M, et al., Serial analysis of clinical and imaging indices reveals prolonged efficacy of TNF- α and IL-6 receptor targeted therapies in refractory Takayasu arteritis. *Clin Exp Rheumatol.* 2014;32(3 Suppl 82):S11-8.
 - 22) Loricera J, Blanco R, Castaneda S, Humbría A, Melchor S, Calvo-Alen J, et al., Tocilizumab in refractory aortitis: a multicenter study of 13 patients. *Arthritis Rheum* 2013;65(10):S714-5.
 - 23) Koster MJ, Matteson EL, Warrington KJ. Recent advances in the clinical management of giant cell arteritis and Takayasu arteritis. *Curr Opin Rheumatol.* 2016;28(3):211-7.
 - 24) Mekinian A, Comarmond C, Resche-Rigon M, Mirault T, Kahn JE, Lambert M, et al. Efficacy of Biological-Targeted Treatments in Takayasu Arteritis: Multicenter, Retrospective Study of 49 Patients. *Circulation.* 2015;132(18):1693-700.
 - 25) Osman M, Emery D, Yacyshyn E. Tocilizumab for treating takayasu's arteritis and associated stroke: A case series and updated review of the literature. *J Stroke Cerebrovasc Dis.* 2015;24(6):1291-8.
 - 26) Osman M, Pagnoux C, Dryden DM, Storie D, Yacyshyn E. The role of biological agents in the management of large vessel vasculitis (LVV): A systematic review and meta-analysis. *PLoS One.* 2014;9(12):e115026.
 - 27) 中岡良和. 大型血管炎の診断・治療の最前線 難治性高安動脈炎に対する tocilizumab による IL-6阻害療法の有効性と安全性. *脈管学.* 2015;55(Suppl.):S97.
 - 28) Arita Y, Nakaoka Y, Otsuki M, Higuchi K, Hashimoto-Kataoka T, Yasui T, et al. Cytokine storm after cessation of tocilizumab in a patient with refractory Takayasu arteritis. *Int J Cardiol* 2015;187:319-21.
 - 29) 野本英嗣, 吉川俊治, 田中泰章, 篠岡太郎, 栗原顕, 足利貴志, et al. 抗 IL-6レセプター抗体トシリズマブ投与により寛解導入・維持が可能となった難治性高安動脈炎の1例. *心臓.* 2014;46(12):1585-91.
 - 30) 西村謙一, 桃井貴裕, 櫻井のどか, 野澤智, 菊地雅子, 原良紀. トシリズマブを導入した高安動脈炎における, バイオマーカーの検討と画像評価の重要性. *日本小児リウマチ学会総会・学術集会プログラム・抄録集.* 24回; 2014年10月:118.
 - 31) 末松梨絵, 貞永裕梨, 永尾奈津美, 田代知子, 小荒田秀一, 澤部琢哉等. 血管炎 高安病難治性症例に対する生物学的製剤の有用性. *日本リウマチ学会総会・学術集会・国際リウマチシンポジウムプログラム・抄録集.* 58回; 2014年3月:413.
 - 32) 小林達雄, 押川英仁, 滝澤直歩, 徳永健一郎, 蓑田正祐, 仲野寛人, et al. TNF α 阻害剤にても治療抵抗性高安動脈炎に対し, トシリズマブにて良好な経過を示した1例. *日本リウマチ学会総会・学術集会・国際リウマチシンポジウムプログラム・抄録集.* 58回; 2014年3月:713.
 - 33) 土田哲也, 池川健, 西村謙一, 野澤智, 佐藤知実, 金高太一, et al. 異なる入院時臨床所見を呈した小児高安動脈炎の2症例 トシリズマブの治療効果. *日本小児リウマチ学会総会・学術集会プログラム・抄録集.* 23回; 2013年10月:87.

- 34) 山崎和子, 野澤智, 金高太一, 菊地雅子, 西村謙一, 櫻井のどか, et al. 治療抵抗性高安動脈炎に対するトシリズマブの効果. 日本小児リウマチ学会総会・学術集会プログラム・抄録集. 23回; 2013年10月:87.

2.7.3.7 付録

表 2.7.3.7.1-1 人口統計学的特性及びベースライン時特性 (MRA632JP 試験) 51

表 2.7.3.7.1-2 二重盲検期間での高安動脈炎の再発率-20 events (MRA632JP 試験, ITT) 54

表 2.7.3.7.1-3 非盲検期間での高安動脈炎の再発率 (MRA632JP 試験) 54

表 2.7.3.7.1-4 非盲検期間での副腎皮質ステロイド投与量の推移 (MRA632JP 試験) 55

表 2.7.3.7.1-5 非盲検期間の副腎皮質ステロイド最終投与量 (MRA632JP 試験) 65

表 2.7.3.7.1-6 非盲検期間の副腎皮質ステロイド最終投与量が基準値以下になった期間 (MRA632JP 試験) 65

表 2.7.3.7.1-7 再発一覧 (MRA632JP 試験) 67

表 2.7.3.7.1-8 副腎皮質ステロイド一覧 (MRA632JP 試験) 71

表 2.7.3.7.1-9 高安動脈炎の再発の定義 (同意取得前/選択基準) 74

表 2.7.3.7.1-10 高安動脈炎の寛解の定義 (スクリーニング期間) 75

表 2.7.3.7.1-11 高安動脈炎の再発の定義 (二重盲検期間, 非盲検期間/有効性評価) 76

表 2.7.3.7.1-12 高安動脈炎症状・徴候に関連する CTCAE の Grade 一覧..... 77

表 2.7.3.7.1-13 大動脈弁閉鎖不全症の重症度評価 (左室内マッピング法) 78

表 2.7.3.7.1-14 日本人での高安動脈炎の有効性に関する文献一覧 79

表 2.7.3.7.2-1 副腎皮質ステロイド漸減投与スケジュール (WA28119試験) 83

表 2.7.3.7.2-2 人口統計学的特性及びベースライン時特性1 (WA28119試験) 85

表 2.7.3.7.2-3 人口統計学的特性及びベースライン時特性2 (WA28119試験) 87

表 2.7.3.7.2-4 人口統計学的特性及びベースライン時特性3 (WA28119試験) 90

表 2.7.3.7.2-5 巨細胞性動脈炎の再発率 (1人年あたりの再発回数) (WA28119試験) 94

表 2.7.3.7.2-6 ベースライン時の巨細胞性動脈炎の発症 (新規発症, 再発) で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 95

表 2.7.3.7.2-7 試験開始時の副腎皮質ステロイド (30 mg/日以下, 30 mg/日超) で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 96

表 2.7.3.7.2-8 巨細胞性動脈炎の寛解歴の有無で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 97

表 2.7.3.7.2-9 画像判定で巨細胞性動脈炎と診断された部分集団での52週時の寛解維持割合 (WA28119試験) 98

表 2.7.3.7.2-10 側頭動脈生検で巨細胞性動脈炎と診断された部分集団での52週時の寛解維持割合 (WA28119試験) 99

表 2.7.3.7.2-11 画像判定で巨細胞性動脈炎と診断され, 側頭動脈の生検結果が陽性でない部分集団での 52週時の寛解維持割合 (WA28119試験) 100

表 2.7.3.7.2-12 画像判定で巨細胞性動脈炎と診断され, 側頭動脈の生検結果が陽性ではなく, 頭部の症状のない部分集団での52週時の寛解維持割合 (WA28119試験) 101

表 2.7.3.7.2-13 ACR の基準に合致した巨細胞性動脈炎の判定の有無で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 102

表 2.7.3.7.2-14 年齢 (65歳未満, 65歳以上) で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 103

表 2.7.3.7.2-15 体重 (60 kg 未満, 60 kg 以上~100 kg 以下, 100 kg 超) で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 104

表 2.7.3.7.2-16 性別で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 105

表 2.7.3.7.2-17 人種で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 106

表 2.7.3.7.2-18 地域で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 107

表 2.7.3.7.2-19 血清中トシリズマブ濃度 (四分位) で分けた部分集団での52週時の寛解維持割合 (WA28119試験) 108

表 2.7.3.7.2-20	ベースライン時の巨細胞性動脈炎の発症（新規発症，再発）で分けた部分集団での再発までの期間（WA28119試験）	109
表 2.7.3.7.2-21	画像判定で巨細胞性動脈炎と診断された部分集団での再発までの期間（WA28119試験）	111
表 2.7.3.7.2-22	52週時の寛解維持割合における MRA-SC QW 群と MRA-SC Q2W 群の差（WA28119試験）	112
表 2.7.3.7.2-23	再発までの期間における MRA-SC Q2W 群と MRA-SC QW 群の差（WA28119試験）	113
表 2.7.3.7.3-1	MRA632JP 試験と WA28119試験の主な試験デザインの比較	114

2.7.3.7.1 MRA632JP 試験

表 2.7.3.7.1-1 人口統計学的特性及びベースライン時特性 (MRA632JP 試験)

dmt01_itt Demographic Data
 Protocol: MRA632JP
 Analysis: ITT

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Sex		
n	18	18
Male	3 (16.7%)	2 (11.1%)
Female	15 (83.3%)	16 (88.9%)
Age (years)		
n	18	18
mean	30.8	31.1
std	13.1	18.1
min	17	13
median	27.0	26.5
max	68	66
Age (years) Category		
n	18	18
< 18	2 (11.1%)	4 (22.2%)
18 -< 65	15 (83.3%)	12 (66.7%)
65 -	1 (5.6%)	2 (11.1%)
Weight (kg) at Randomized		
n	18	18
mean	59.73	55.04
std	14.67	15.87
min	39.4	32.9
median	57.90	53.05
max	99.7	97.4
Height (cm) at Screening		
n	18	18
mean	162.8	157.9
std	6.8	8.1
min	152	139
median	161.0	160.0
max	177	169
BMI (kg/m**2) at Randomized		
n	18	18
mean	22.58	21.79
std	5.64	4.69
min	15.4	15.2
median	21.26	20.80
max	39.0	34.1
HLA-B39		
n	18	18
NO	18 (100.0%)	18 (100.0%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_itt.out
 21DEC2015 21:14

dmt01_itt Demographic Data
 Protocol: MRA632JP
 Analysis: ITT

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
HLA-B52		
n	18	18
YES	13 (72.2%)	7 (38.9%)
NO	5 (27.8%)	11 (61.1%)
Exposure to Corticosteroids (mg/kg Equivalent to Prednisolone) at Randomization		
n	18	18
mean	0.52	0.57
std	0.16	0.19
min	0.4	0.4
median	0.45	0.50
max	0.9	1.0
Exposure to Corticosteroids Category (mg/kg Equivalent to Prednisolone) at Randomization		
n	18	18
< 0.6	14 (77.8%)	13 (72.2%)
0.6 -< 0.8	2 (11.1%)	2 (11.1%)
0.8 -	2 (11.1%)	3 (16.7%)
Pregnancy Test		
n	14	12
NEGATIVE	14 (100.0%)	12 (100.0%)
Takayasu Arteritis Classification		
n	18	18
I	2 (11.1%)	2 (11.1%)
IIA	3 (16.7%)	2 (11.1%)
IIB	5 (27.8%)	3 (16.7%)
III	1 (5.6%)	3 (16.7%)
V	7 (38.9%)	8 (44.4%)
Disease Duration of Takayasu arteritis (years)		
n	18	18
mean	3.57	6.46
std	4.03	7.37
min	0.1	0.4
median	2.89	3.33
max	16.5	22.8
Prior Treatment: Surgery		
n	18	18
YES	1 (5.6%)	5 (27.8%)
NO	17 (94.4%)	13 (72.2%)
Prior Treatment: Biologics		
n	18	18
YES	2 (11.1%)	0
NO	16 (88.9%)	18 (100.0%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_itt.out
 21DEC2015 21:14

dmt01_itt Demographic Data
 Protocol: MRA632JP
 Analysis: ITT

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Prior Treatment: DMARDs/Immunosuppressant		
n	18	18
YES	13 (72.2%)	12 (66.7%)
NO	5 (27.8%)	6 (33.3%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_itt.out
 21DEC2015 21:14

Page 3 of 3

[5.3.5.1-1 表 11.2-1を再掲]

表 2.7.3.7.1-2 二重盲検期間での高安動脈炎の再発率-20 events (MRA632JP 試験, ITT)

rlpsrateB_itt Relapse Rate -Double Blind Period
 Protocol: MRA LVV
 Analysis: ITT

	Placebo N = 18 Event (E/100PY)	MRA-SC 162mg/W N = 18 Event (E/100PY)
Total Observation Period (Patient-years)	5.9	7.9
Total Pts with at Least one Relapse	12	8
Total Number of Relapse	12 (203.1)	8 (101.1)
95% CI for Rate	[115.3:357.6]	[50.6:202.2]

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/rlpsrateB.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/rlpsrateB_itt.out
 21JUN2016 11:56

Page 1 of 1

[5.3.5.3-1 表 2.1.1-1を再掲]

表 2.7.3.7.1-3 非盲検期間での高安動脈炎の再発率 (MRA632JP 試験)

rlpsrate0_mt_itt Relapse Rate -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

	MRA-SC 162mg/W N = 36 Event (E/100PY)
Total Observation Period (Patient-years)	38.2
Total Pts with at Least one Relapse	8
Total Number of Relapse	9 (23.6)
95% CI for Rate	[12.3: 45.3]

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/rlpsrate0.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/rlpsrate0_mt_itt.out
 12JAN2017 17:15

Page 1 of 1

[5.3.5.1-7 表 11.2-1を再掲]

表 2.7.3.7.1-4 非盲検期間での副腎皮質ステロイド投与量の推移 (MRA632JP 試験)

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Average Steroid dose (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 0 -< Week 4	
n	36
mean	14.66
std	7.88
min	4.0
median	14.93
max	34.0
Week 4 -< Week 8	
n	36
mean	13.65
std	7.38
min	4.0
median	12.90
max	30.7
Week 8 -< Week 12	
n	36
mean	12.20
std	6.37
min	4.0
median	11.25
max	28.8
Week 12 -< Week 16	
n	34
mean	11.43
std	5.60
min	4.0
median	11.00
max	26.4
Week 16 -< Week 20	
n	33
mean	10.63
std	5.65
min	3.0
median	10.00
max	29.8
Week 20 -< Week 24	
n	33
mean	10.23
std	5.59
min	2.1
median	10.00
max	29.5

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Average Steroid dose (mg/day Equivalent to Prednisolone)

Visit MRA-SC 162mg/W Total
 (N=36)

Week 24 -< Week 28

n 32
 mean 9.65
 std 5.44
 min 2.0
 median 10.00
 max 27.5

Week 28 -< Week 32

n 32
 mean 9.19
 std 5.06
 min 1.1
 median 9.64
 max 24.7

Week 32 -< Week 36

n 32
 mean 8.74
 std 4.90
 min 0.1
 median 8.66
 max 22.1

Week 36 -< Week 40

n 32
 mean 8.31
 std 4.58
 min 0.0
 median 8.04
 max 20.0

Week 40 -< Week 44

n 32
 mean 8.02
 std 4.47
 min 0.0
 median 7.05
 max 18.1

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Average Steroid dose (mg/day Equivalent to Prednisolone)

Visit MRA-SC 162mg/W Total
 (N=36)

Week 44 -< Week 48

n 31
 mean 7.87
 std 4.67
 min 0.0
 median 7.00
 max 18.2

Week 48 -< Week 52

n 30
 mean 7.83
 std 5.29
 min 0.0
 median 7.00
 max 23.9

Week 52 -< Week 56

n 30
 mean 8.06
 std 6.90
 min 0.0
 median 7.00
 max 36.6

Week 56 -< Week 60

n 14
 mean 8.51
 std 2.82
 min 4.0
 median 8.52
 max 13.0

Week 60 -< Week 64

n 12
 mean 8.91
 std 3.04
 min 3.0
 median 8.50
 max 13.0

Week 64 -< Week 68

n 9
 mean 9.65
 std 4.69
 min 3.0
 median 9.00
 max 19.6

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Average Steroid dose (mg/day Equivalent to Prednisolone)

Visit MRA-SC 162mg/W Total
 (N=36)

Week 68 -< Week 72

n	8
mean	7.90
std	2.95
min	3.0
median	8.00
max	12.0

Week 72 -< Week 76

n	7
mean	7.15
std	2.42
min	3.0
median	8.00
max	10.0

Week 76 -< Week 80

n	4
mean	7.35
std	2.28
min	4.1
median	8.00
max	9.3

Week 80 -< Week 84

n	3
mean	6.42
std	2.74
min	3.3
median	8.00
max	8.0

Week 84 -< Week 88

n	1
mean	2.29
std	NE
min	2.3
median	2.29
max	2.3

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Average Steroid dose (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
-------	--------------------------------

Week 88 -< Week 92

n	1
mean	2.00
std	NE
min	2.0
median	2.00
max	2.0

Week 92 -< Week 96

n	1
mean	2.00
std	NE
min	2.0
median	2.00
max	2.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Corticosteroids (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 0	
n	36
mean	11.83
std	6.11
min	4.0
median	10.45
max	32.0
Week 4	
n	36
mean	14.77
std	8.12
min	4.0
median	15.00
max	35.0
Week 8	
n	36
mean	12.63
std	6.43
min	4.0
median	11.75
max	30.0
Week 12	
n	34
mean	11.67
std	5.60
min	4.0
median	11.00
max	27.5
Week 16	
n	33
mean	10.71
std	5.26
min	3.0
median	10.00
max	25.0
Week 20	
n	33
mean	10.53
std	5.61
min	2.7
median	10.00
max	30.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter: Corticosteroids (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 24	
n	32
mean	9.84
std	5.38
min	2.0
median	10.00
max	27.5
Week 28	
n	32
mean	9.50
std	5.40
min	1.8
median	10.00
max	27.5
Week 32	
n	32
mean	8.93
std	4.77
min	1.0
median	9.50
max	22.5
Week 36	
n	32
mean	8.42
std	4.58
min	0.0
median	8.50
max	20.0
Week 40	
n	32
mean	8.16
std	4.57
min	0.0
median	8.00
max	20.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter:Corticosteroids (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 44	
n	31
mean	8.12
std	4.82
min	0.0
median	7.00
max	18.2
Week 48	
n	30
mean	7.55
std	4.55
min	0.0
median	7.00
max	16.4
Week 52	
n	30
mean	8.36
std	7.45
min	0.0
median	7.00
max	40.0
Week 56	
n	14
mean	8.93
std	2.64
min	4.0
median	9.00
max	13.0
Week 60	
n	12
mean	8.67
std	2.61
min	4.0
median	8.50
max	13.0
Week 64	
n	9
mean	9.11
std	3.33
min	3.0
median	9.00
max	13.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter:Corticosteroids (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 68	
n	8
mean	8.25
std	3.06
min	3.0
median	8.00
max	12.0
Week 72	
n	7
mean	7.29
std	2.63
min	3.0
median	8.00
max	11.0
Week 76	
n	4
mean	7.75
std	2.06
min	5.0
median	8.00
max	10.0
Week 80	
n	3
mean	6.67
std	2.31
min	4.0
median	8.00
max	8.0
Week 84	
n	1
mean	3.00
std	NE
min	3.0
median	3.00
max	3.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

sumcs_mt_itt Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

Parameter:Corticosteroids (mg/day Equivalent to Prednisolone)

Visit	MRA-SC 162mg/W Total (N=36)
Week 88	
n	1
mean	2.00
std	NE
min	2.0
median	2.00
max	2.0
Week 92	
n	1
mean	2.00
std	NE
min	2.0
median	2.00
max	2.0
Last Obs	
n	36
mean	8.55
std	6.94
min	0.0
median	7.00
max	30.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/sumcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumcs_mt_itt.out
 23JAN2017 19:02

[5.3.5.3-7 表 11.2-9を再掲]

表 2.7.3.7.1-5 非盲検期間の副腎皮質ステロイド最終投与量 (MRA632JP 試験)

csprp_mt_itt Corticosteroid Status at Last Obs -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

	MRA-SC 162mg/W Total (N=36)
<= 0.1 mg/kg	13 (36.1%)
<= 0.2 mg/kg	30 (83.3%)
<= 5 mg	14 (38.9%)
<= 10 mg	26 (72.2%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/csprp.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/csprp_mt_itt.out
 12JAN2017 17:07

[5.3.5.1-7 表 11.2-10を再掲]

表 2.7.3.7.1-6 非盲検期間の副腎皮質ステロイド最終投与量が基準値以下になった期間 (MRA632JP 試験)

durcs_mt_itt Duration below Reference of Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

	MRA-SC 162mg/W Total (N=36)
Duration from the first date of Corticosteroid <= 0.1 mg/kg to censored date (day)	
n	16
Mean (SD)	266.3 (150.4)
Min - Max	15 - 583
Median	277.5
Duration from the first date of Corticosteroid <= 0.2 mg/kg to censored date (day)	
n	35
Mean (SD)	316.8 (163.0)
Min - Max	10 - 646
Median	367.0
Duration from the first date of Corticosteroid <= 5 mg to censored date (day)	
n	16
Mean (SD)	239.9 (148.4)
Min - Max	42 - 583
Median	252.0
Duration from the first date of Corticosteroid <= 10 mg to censored date (day)	
n	33
Mean (SD)	340.1 (126.2)
Min - Max	58 - 588
Median	373.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/durcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/durcs_mt_itt.out
 12JAN2017 17:10

durcs_mt_itt Duration below Reference of Corticosteroid -Open Period
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: ITT

MRA-SC 162mg/W Total
(N=36)

Duration of Corticosteroid <= 0.1 mg/kg (day)
 n 16
 Mean (SD) 214.5 (154.9)
 Min - Max 1 - 382
 Median 259.5

Duration of Corticosteroid <= 0.2 mg/kg (day)
 n 35
 Mean (SD) 272.1 (152.5)
 Min - Max 3 - 602
 Median 321.0

Duration of Corticosteroid <= 5 mg (day)
 n 16
 Mean (SD) 199.5 (134.1)
 Min - Max 1 - 379
 Median 208.0

Duration of Corticosteroid <= 10 mg (day)
 n 33
 Mean (SD) 274.9 (152.0)
 Min - Max 14 - 587
 Median 349.0

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/durcs.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/durcs_mt_itt.out
 12JAN2017 17:10

表 2.7.3.7.1-7 再発一覧 (MRA632JP 試験)

Istrelaps_ap Listing of Relapse
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: PLACEBO (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Before randomization	Blind Period				Open Period						
				Cortico-steroids (mg) at Relapse	Cortico-steroids (mg)	Relapse	Time to First Relapse (Weeks)	Cortico-steroids (mg) at Relapse	Cortico-steroids (mg) at Last Observation	Cortico-steroids (mg)	Relapse	Cortico-steroids (mg) at Last Observation	Relapse No.	Time to Relapse (Weeks)	Cortico-steroids (mg) at Relapse
1265/60105	56	F	63.0	13.0	30.0	N			10.0	10.0	N	7.0			
1265/60106	26	M	61.2	15.0	30.0	Y	8.1	20.0	20.0	20.0	N	8.0			
1267/60301	17	F	53.1	12.0	24.0	N			13.0	13.0	N	30.0			
1268/60401	23	F	45.7	11.0	22.0	Y	8.3	14.0	13.0	13.0	N	9.0			
1268/60402	26	F	72.9	20.0	45.0	Y	12.0	19.0	17.0	17.0	Y	18.3	1	43.0	12.5
1269/60501	36	F	44.1	17.5	40.0	Y	11.9	17.0	14.0	14.0	N	8.0			
1269/60502	21	F	55.5	12.0	25.0	Y	12.1	11.0	10.0	10.0	Y	20.0	1	64.1	13.0
1269/60504	37	F	48.3	10.0	25.0	N			8.0	8.0	N	5.0			
1274/60901	28	F	99.7	20.0	40.9	Y	16.0	11.8	10.9	10.9	N	13.6			
1274/60902	23	F	39.4	8.0	35.0	N			4.0	4.0	N	0.0			
1274/60904	68	M	56.8	12.0	24.0	N			6.0	6.0	Y	5.0	1	8.3	5.0

CRTN = Clinical Research Task Number (center no.)
 Time to First Relapse in DB Period : from the day of Randomization.
 Time to Relapse in OPEN Period : from the day of first MRA-SC injection.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/istrelaps.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/istrelaps_ap.out
 12JAN2017 17:11

Istrelaps_ap Listing of Relapse
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: PLACEBO (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Before randomization	Blind Period				Open Period						
				Cortico-steroids (mg) at Relapse	Cortico-steroids (mg)	Relapse	Time to First Relapse (Weeks)	Cortico-steroids (mg) at Last Observation	Cortico-steroids (mg)	Relapse	Cortico-steroids (mg) at Last Observation	Relapse No.	Time to Relapse (Weeks)	Cortico-steroids (mg) at Relapse	
1275/61002	30	F	74.1	15.0	30.0	Y	14.0	10.0	10.0	10.0	Y	12.0	1	12.1	10.0
1276/61101	17	M	66.1	15.0	30.0	Y	10.3	14.0	13.0	13.0	Y	9.0	1 2	28.1 60.1	10.0 9.0
1280/61201	36	F	73.2	15.0	30.0	N			7.0	7.0	N	0.0			
1280/61202	29	F	43.3	10.0	30.0	Y	8.1	20.0	14.0	25.0	Y	15.0	1	12.1	15.0
1280/61204	35	F	67.7	12.0	30.0	Y	12.7	12.0	12.0	12.0	N	2.0			
1285/61601	22	F	52.1	10.0	20.0	Y	10.7	10.0	15.0	15.0	N	13.0			
1286/61701	24	F	59.0	12.0	24.0	Y	10.1	13.0	11.0	11.0	Y	8.0	1	54.4	6.0

CRTN = Clinical Research Task Number (center no.)
 Time to First Relapse in DB Period : from the day of Randomization.
 Time to Relapse in OPEN Period : from the day of first MRA-SC injection in OPEN Period.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/istrelaps.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/istrelaps_ap.out
 12JAN2017 17:11

Istrelaps_ap Listing of Relapse
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: MRA-SC 162mg/w (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Before randomization			Blind Period				Open Period				
				Cortico-steroids (mg) at Relapse	Cortico-steroids (mg)	Relapse	Time to First Relapse (Weeks)	Cortico-steroids (mg) at Relapse	Cortico-steroids (mg) at Last Observation	Cortico-steroids (mg)	Relapse	Cortico-steroids (mg) at Last Observation	Relapse No.	Time to Relapse (Weeks)	Cortico-steroids (mg) at Relapse
1265/60101	36	F	70.9	15.0	30.0	N			7.0	7.0	N	7.0			
1265/60102	27	F	40.3	10.0	25.0	N			4.0	4.0	N	2.0			
1265/60103	18	F	76.1	17.5	35.0	N			8.0	8.0	N	3.0			
1265/60104	13	F	43.2	9.0	20.0	N			13.0	13.0	N	4.0			
1269/60503	37	F	69.1	16.0	40.0	N			8.0	8.0	N	5.0			
1271/60601	14	F	32.9	8.0	20.0	Y	8.1	13.0	17.0	17.0	N	4.0			
1272/60701	20	F	54.4	12.0	30.0	Y	13.3	10.0	20.0	20.0	N	7.0			
1272/60702	65	F	51.7	11.0	22.0	Y	12.0	9.0	10.0	10.0	N	3.0			
1273/60801	66	F	64.4	15.0	30.0	N			6.0	6.0	N	0.0			
1273/60802	22	F	56.1	15.0	50.0	Y	13.3	17.0	16.0	16.0	N	11.0			
1274/60903	57	F	52.1	11.4	22.7	N			9.1	9.1	N	4.5			

CRTN = Clinical Research Task Number (center no.)
 Time to First Relapse in DB Period : from the day of Randomization.
 Time to Relapse in OPEN Period : from the day of first MRA-SC injection in OPEN Period.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/istrelaps.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/istrelaps_ap.out
 12JAN2017 17:11

Istrelaps_ap Listing of Relapse
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: MRA-SC 162mg/w (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Before randomization	Blind Period				Open Period						
				Cortico-steroids (mg) at Relapse	Cortico-steroids (mg)	Relapse	Time to First Relapse (Weeks)	Cortico-steroids (mg) at Relapse	Cortico-steroids (mg) at Last Observation	Cortico-steroids (mg)	Relapse	Cortico-steroids (mg) at Last Observation	Relapse No.	Time to Relapse (Weeks)	Cortico-steroids (mg) at Relapse
1275/61001	57	F	55.5	12.5	25.0	N			6.0	6.0	N	6.0			
1275/61003	19	M	97.4	22.5	100.0	N			19.0	19.0	N	14.0			
1276/61102	26	F	54.0	14.0	28.0	N			5.0	5.0	N	4.0			
1281/61301	13	M	42.5	10.0	20.0	Y	23.1	4.0	4.0	4.0	N	8.0			
1282/61401	16	F	36.7	15.0	35.0	Y	5.1	32.0	32.0	32.0	N	27.5			
1286/61702	27	F	48.3	10.0	25.0	Y	12.1	11.0	10.0	10.0	Y	9.0	1	26.9	10.0
1287/61801	27	F	45.2	9.0	20.0	Y	8.1	13.0	13.0	13.0	N	6.0			

CRTN = Clinical Research Task Number (center no.)
 Time to First Relapse in DB Period : from the day of Randomization.
 Time to Relapse in OPEN Period : from the day of first MRA-SC injection in OPEN Period.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632f/istrelaps.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/istrelaps_ap.out
 12JAN2017 17:11

Page 4 of 4

[5.3.5.1-7 表 11.4-6を再掲]

表 2.7.3.7.1-8 副腎皮質ステロイド一覧 (MRA632JP 試験)

投与群	症例番号	体重 (kg)	副腎皮質ステロイド							非盲検期間		副腎皮質ステロイド目標値以下の延べ日数 ^a
			登録前		二重盲検期間		非盲検期間			再発回数	再発までの期間(週)	
			再発時		最終観察時		中止時又はデータカットオフ時点		再発時			
(mg)	(mg/kg)	(mg)	(mg/kg)	(mg)	(mg/kg)	(mg)	(mg/kg)	(mg)				
PLACEBO	60105	63.0	13.0	0.21	10.0	0.16	7.0	0.11				373
PLACEBO	60106	61.2	15.0	0.25	20.0	0.33	8.0	0.13				266
PLACEBO	60301 ^b	53.1	12.0	0.23	13.0	0.24	30.0	0.56				321
PLACEBO	60401	45.7	11.0	0.24	13.0	0.28	9.0	0.20				96
PLACEBO	60402 ^b	72.9	20.0	0.27	17.0	0.23	18.3	0.25	12.5	1	43.0	27
PLACEBO	60501	44.1	17.5	0.40	14.0	0.32	8.0	0.18				302
PLACEBO	60502 ^c	55.5	12.0	0.22	10.0	0.18	20.0	0.36	13.0	1	64.1	-
PLACEBO	60504	48.3	10.0	0.21	8.0	0.17	5.0	0.10				373
PLACEBO	60901	99.7	20.0	0.20	10.9	0.11	13.6	0.14				-
PLACEBO	60902	39.4	8.0	0.20	4.0	0.10	0.0	0.00				379
PLACEBO	60904 ^{b,d}	56.8	12.0	0.21	6.0	0.11	5.0	0.09	5.0	1	8.3	58
PLACEBO	61002 ^b	74.1	15.0	0.20	10.0	0.13	12.0	0.16	10.0	1	12.1	29
PLACEBO	61101 ^h	66.1	15.0	0.23	13.0	0.20	9.0	0.14	10.0	1	28.1	202
PLACEBO									9.0	2	60.1	
PLACEBO	61201	73.2	15.0	0.20	7.0	0.10	0.0	0.00				380
PLACEBO	61202 ^e	43.3	10.0	0.23	14.0	0.32	15.0	0.35	15.0	1	12.1	-
PLACEBO	61204 ^f	67.7	12.0	0.18	12.0	0.18	2.0	0.03				587
PLACEBO	61601	52.1	10.0	0.19	15.0	0.29	13.0	0.25				-
PLACEBO	61701 ^h	59.0	12.0	0.20	11.0	0.19	8.0	0.14	6.0	1	54.4	245
MRA-SC	60101	70.9	15.0	0.21	7.0	0.10	7.0	0.10				567
MRA-SC	60102	40.3	10.0	0.25	4.0	0.10	2.0	0.05				622
MRA-SC	60103	76.1	17.5	0.23	8.0	0.11	3.0	0.04				507
MRA-SC	60104	43.2	9.0	0.21	13.0	0.30	4.0	0.09				297
MRA-SC	60503	69.1	16.0	0.23	8.0	0.12	5.0	0.07				387
MRA-SC	60601	32.9	8.0	0.24	17.0	0.52	4.0	0.12				127
MRA-SC	60701 ^g	54.4	12.0	0.22	20.0	0.37	7.0	0.13				361
MRA-SC	60702 ^g	51.7	11.0	0.21	10.0	0.19	3.0	0.06				518
MRA-SC	60801	64.4	15.0	0.23	6.0	0.09	0.0	0.00				486
MRA-SC	60802	56.1	15.0	0.27	16.0	0.29	11.0	0.20				-
MRA-SC	60903	52.1	11.4	0.22	9.1	0.17	4.5	0.09				511
MRA-SC	61001	55.5	12.5	0.23	6.0	0.11	6.0	0.11				630
MRA-SC	61003 ^b	97.4	22.5	0.23	19.0	0.20	14.0	0.14				28
MRA-SC	61102	54.0	14.0	0.26	5.0	0.09	4.0	0.07				450
MRA-SC	61301 ^g	42.5	10.0	0.24	4.0	0.09	8.0	0.19				391
MRA-SC	61401	36.7	15.0	0.41	32.0	0.87	27.5	0.75				-
MRA-SC	61702 ^h	48.3	10.0	0.21	10.0	0.21	9.0	0.19	10.0	1	26.9	84
MRA-SC	61801	45.2	9.0	0.20	13.0	0.29	6.0	0.13				307
		n	36	36	36	36	36	36				25 ⁱ
		Median	12.0	0.22	10.5	0.18	7.0	0.13				379.0 ⁱ
		Max	22.5	0.41	32.0	0.87	30.0	0.75				630 ⁱ
		Min	8.0	0.18	4.0	0.09	0.0	0.00				84 ⁱ

a : 二重盲検期間又は非盲検期間のいずれかの本剤投与開始時以降に、副腎皮質ステロイド量が10 mg/日以下かつ登録前再発時の副腎皮質ステロイド量未満 (ステロイド減量目標値) を達成した延べ日数。「-」は、ステロイド減量目標値の未達成6例 (表 2.7.3.3.2.1-4参照)。

b : ステロイド減量目標値以下を達成した後に、データカットオフ時点で再発又は再発の徴候によりステロイド減量目標値を超える副腎皮質ステロイドの増量のある症例。

- c : 本剤投与開始時以降, ステロイド減量目標値以下を14日間達成したが, 本剤投与による減量効果ではないため対象外とした症例。
- d : 中止時検査で再発が認められ, 副腎皮質ステロイドの増量のない症例。
- e : 副腎皮質ステロイドの投与が行われなかった非盲検期間の Day 26~28は対象外とした症例。
- f : 非盲検期間の Day 97に副腎皮質ステロイドを増量したが再発の徴候はなく, 「再発の徴候によるステロイド増量あり」に該当しない症例。
- g : 二重盲検期間でステロイド減量目標値以下を達成した後に再発が認められ, 非盲検期間でステロイド減量目標値以下を達成した症例。
- h : 非盲検期間で再発が認められ, 副腎皮質ステロイドを増量をした後にステロイド減量目標値以下を達成した症例。
- i : 全例からステロイド減量目標値の未達成6例と, ステロイド減量目標値を達成し, データカットオフ時点で再発又は再発の徴候による副腎皮質ステロイドの増量のある5例を除いた。

[表 2.7.3.7.1-7, 5.3.5.1-7 表 11.4-1, 表 11.4-5, 表 11.4-7を改変]

高安動脈炎の再発及び寛解の定義（MRA632JP 試験）

(1) 高安動脈炎の再発の定義（同意取得前／選択基準）

以下、5つの大項目のうち2項目以上で再発の徴候ありと判定された場合を高安動脈炎の再発と定義する。いずれの項目も高安動脈炎以外の原因（特に感染症、アレルギー疾患及び不定愁訴等）を除外し、高安動脈炎が原因であることが医学的に判断できる場合に限る。各項目の細項目を表 2.7.3.7.1-9に、CTCAE の Grade 一覧及び大動脈弁閉鎖不全症の重症度評価をそれぞれ表 2.7.3.7.1-12及び表 2.7.3.7.1-13に記載する。

- ① 客観的評価での全身症状
- ② 主観的評価での全身症状
- ③ 炎症マーカーの上昇
- ④ 血管病変
- ⑤ 臓器病変を伴う虚血症状

(2) 高安動脈炎の寛解の定義（スクリーニング期間）

以下、5つの大項目のうちすべての症状・徴候が認められない場合を高安動脈炎の寛解と定義する。各項目の細項目を表 2.7.3.7.1-10に、CTCAE の Grade 一覧を表 2.7.3.7.1-12に記載する。

- ① 客観的評価での全身症状
- ② 主観的評価での全身症状
- ③ 炎症マーカーの上昇
- ④ 血管病変
- ⑤ 臓器病変を伴う虚血症状

(3) 高安動脈炎の再発の定義（二重盲検期間，非盲検期間／有効性評価）

以下、5つの大項目のうち2項目以上で再発の徴候ありと判定された場合、高安動脈炎の再発と定義する。ただし、「④血管病変」にて心不全症状を伴う重度の大動脈弁閉鎖不全症が発現した場合、又は、「⑤臓器病変を伴う虚血症状」で1項目でも Grade 2以上（心筋梗塞は Grade 3以上）の症状を認めた場合は、他の項目を満たさなくても高安動脈炎の再発と判定する。いずれの項目も高安動脈炎以外の原因（特に感染症、アレルギー疾患及び不定愁訴等）を除外し、高安動脈炎が原因であることが医学的に判断できる場合に限る。

各項目の細項目を表 2.7.3.7.1-11に、CTCAE の Grade 一覧及び大動脈弁閉鎖不全症の重症度評価をそれぞれ表 2.7.3.7.1-12及び表 2.7.3.7.1-13に記載する。

- ① 客観的評価での全身症状
- ② 主観的評価での全身症状
- ③ 炎症マーカーの上昇
- ④ 血管病変
- ⑤ 臓器病変を伴う虚血症状

表 2.7.3.7.1-9 高安動脈炎の再発の定義（同意取得前／選択基準）

大項目	細項目(定義)
① 客観的評価での全身症状	<p>下記のいずれかが認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 発熱：38.0°C以上の発熱 ● 体重減少：4週間以内に2 kgを超える体重減少 ● 関節炎：2関節以上の腫脹及び熱感を伴う関節炎
② 主観的評価での全身症状	<p>下記のいずれかについて、CTCAE Grade2以上の症状が認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 倦怠感 ● 筋肉痛 ● 自発的関節痛 ● 頭痛 ● めまい
③ 炎症マーカーの上昇	<p>下記のいずれかが認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● CRP 1.0 mg/dL 以上及び ESR 30 mm/h 以上 ● SAA 20 µg/mL 以上及び ESR 30 mm/h 以上 ● 白血球数 10,000/µL 以上
④ 血管病変	<p>下記のいずれかが認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 腎血管性高血圧 通常血圧が120/80 mmHg未満：140/90 mmHg以上への上昇 通常血圧が120/80 mmHg以上140/90 mmHg未満だった場合、拡張期血圧20 mmHg以上の上昇 ● 新たな血管雑音（頸動脈、鎖骨下動脈、腎動脈） ● 新たな脈拍の消失（頸動脈、鎖骨下動脈、上腕動脈、橈骨動脈、大腿動脈、膝窩動脈、後脛骨動脈、足背動脈） ● 新たな血圧の左右差：新たに拡張期血圧の左右差が10 mmHg以上開いた場合 ● 頸動脈の圧痛：CTCAE Grade 2以上の症状 ● 胸部及び背部の自発痛：CTCAE Grade 2以上の症状 ● 大動脈弁閉鎖不全症（中等度又は重度）の発現
⑤ 臓器病変を伴う虚血症状	<p>下記のいずれかについて、CTCAE Grade 2以上の症状が認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 腹痛 ● 癲癇発作 ● 失神 ● 間欠性跛行 ● 虚血性心痛

表 2.7.3.7.1-10 高安動脈炎の寛解の定義（スクリーニング期間）

大項目	細項目(定義)
⑥ 客観的評価での全身症状	<p>下記のいずれかが認められた場合、本項目は症状ありと判定する。</p> <ul style="list-style-type: none"> ● 発熱：38.0℃以上の発熱 ● 体重減少：4週間以内に2 kg を超える体重減少 ● 関節炎：2関節以上の腫脹及び熱感を伴う関節炎
⑦ 主観的評価での全身症状	<p>下記のいずれかについて、CTCAE Grade 2以上の症状が認められた場合、本項目は症状ありと判定する。</p> <ul style="list-style-type: none"> ● 倦怠感 ● 筋肉痛 ● 自発的関節痛 ● 頭痛 ● めまい
⑧ 炎症マーカーの上昇	<p>下記のいずれかが認められた場合、本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● CRP 1.0 mg/dL 以上及び ESR 30 mm/h 以上 ● SAA 20 µg/mL 以上及び ESR 30 mm/h 以上
⑨ 血管病変	<p>下記のいずれかについて、CTCAE Grade 2以上の症状が認められた場合、本項目は症状ありと判定する。</p> <ul style="list-style-type: none"> ● 頰動脈の圧痛 ● 胸部及び背部の自発痛
⑩ 臓器病変を伴う虚血症状	<p>下記のいずれかについて、CTCAE Grade 2以上の症状が認められた場合、本項目は症状ありと判定する。</p> <ul style="list-style-type: none"> ● 腹痛 ● 癲癇発作 ● 失神 ● 間欠性跛行 ● 虚血性心痛

表 2.7.3.7.1-11 高安動脈炎の再発の定義（二重盲検期間，非盲検期間／有効性評価）

大項目	細項目(定義)
⑪ 客観的評価での全身症状	<p>下記のいずれかが認められた場合，本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 発熱：38.0°C 以上の発熱 ● 体重減少：前回測定時から2 kg を超える体重減少 ● 関節炎：2関節以上の腫脹及び熱感を伴う関節炎
⑫ 主観的評価での全身症状	<p>下記のいずれかについて，ベースラインと比較して CTCAE Grade の上昇が認められた場合，本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● 倦怠感 ● 筋肉痛 ● 自発的関節痛 ● 頭痛 ● めまい
⑬ 炎症マーカーの上昇	<p>下記のいずれかが認められた場合，本項目は再発の徴候ありと判定する。</p> <ul style="list-style-type: none"> ● CRP 1.0 mg/dL 以上及び ESR 30 mm/h 以上 ● SAA 20 µg/mL 以上及び ESR 30 mm/h 以上 ● 白血球数 10,000/µL 以上かつベースラインの1.3倍以上への上昇
⑭ 血管病変	<p>下記のいずれかが認められた場合，本項目は再発の徴候ありと判定する。心不全症状を伴う重度の大動脈弁閉鎖不全症が発現した場合，大項目⑪から⑬，及び⑮が認められない場合でも，高安動脈炎の再発と定義する。</p> <ul style="list-style-type: none"> ● 腎血管性高血圧 <ul style="list-style-type: none"> ○ ベースラインが120/80 mmHg 未満：140/90 mmHg 以上への上昇 ○ ベースラインが120/80 mmHg 以上：拡張期血圧20 mmHg 以上の上昇 ● 新たな血管雑音（頸動脈，鎖骨下動脈，腎動脈） ● 新たな脈拍の消失（頸動脈，鎖骨下動脈，上腕動脈，橈骨動脈，大腿動脈，膝窩動脈，後脛骨動脈，足背動脈） ● 新たな血圧の左右差：新たに拡張期血圧の左右差が10 mmHg 以上開いた場合 ● 頸動脈の圧痛：ベースラインと比較した CTCAE Grade の上昇 ● 胸部及び背部の自発痛：ベースラインと比較した CTCAE Grade の上昇 ● 大動脈弁閉鎖不全症（症状なし又は軽度から中等度以上への悪化，又は中等度から重度への悪化）
⑮ 臓器病変を伴う虚血症状	<p>下記の事象について，ベースラインと比較して CTCAE Grade の上昇が認められた場合，本項目は再発の徴候ありと判定する。Grade 2以上（心筋梗塞は Grade 3以上）の症状が認められた場合，大項目⑪から⑭が認められない場合でも高安動脈炎の再発と定義する。</p> <ul style="list-style-type: none"> ● 腹痛 ● 脳卒中 ● 癲癇発作 ● 失神 ● 間欠性跛行 ● 虚血性心痛 ● 心筋梗塞

表 2.7.3.7.1-12 高安動脈炎症状・徴候に関連する CTCAE の Grade 一覧

	CTCAE v4.03 Term 日本語	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
主観的評価での 全身症状	倦怠感	だるさ、又は元気がない	だるさ、又は元気がない； 身の回り以外の日常生活動作の制限	-	-	-
	筋肉痛	軽度の疼痛	中等度の疼痛；身の回り以外 の日常生活動作の制限	高度の疼痛；身の回りの日 常生活動作の制限	-	-
	関節痛 (自発的関節痛)	軽度の疼痛	中等度の疼痛；身の回り以外 の日常生活動作の制限	高度の疼痛；身の回りの日 常生活動作の制限	-	-
	頭痛	軽度の疼痛	中等度の疼痛；身の回り以外 の日常生活動作の制限	高度の疼痛；身の回りの日 常生活動作の制限	-	-
	浮動性めまい*1	軽度の浮遊感又は身体が動 く感覚がある	中等度の浮遊感又は身体が動 く感覚がある；身の回り 以外の日常生活動作の制限	高度の浮遊感又は身体が動 く感覚がある；身の回りの 日常生活動作が制限される	-	-
	回転性めまい*1	軽度の症状がある	中等度の症状がある；身の 回り以外の日常生活動作の 制限	高度の症状がある；身の回 りの日常生活動作の制限	-	-
血管病変	頰動脈圧痛*2	症状がない、又は軽度の症 状がある；臨床所見又は検 査所見のみ；治療を要さな い	中等症；最小限/局所的/非 侵襲的治療を要する；年齢 相応の身の回り以外の日常 生活動作の制限	重症又は医学的に重大であ るが、直ちに生命を脅かす ものではない；入院又は入 院期間の延長を要する；活 動不能/動作不能；身の回り の日常生活動作の制限	生命を脅かす；緊急処置を 要する	死亡
	胸部及び背部の自発痛 *2	症状がない、又は軽度の症 状がある；臨床所見又は検 査所見のみ；治療を要さな い	中等症；最小限/局所的/非 侵襲的治療を要する；年齢 相応の身の回り以外の日常 生活動作の制限	重症又は医学的に重大であ るが、直ちに生命を脅かす ものではない；入院又は入 院期間の延長を要する；活 動不能/動作不能；身の回り の日常生活動作の制限	生命を脅かす；緊急処置を 要する	死亡

	CTCAE v4.03 Term 日本語	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
臓器病変を伴う 虚血症状	腹痛	軽度の疼痛	中等度の疼痛; 身の回り以外 の日常生活動作の制限	高度の疼痛; 身の回りの日 常生活動作の制限	-	-
	脳卒中	症状がない, 又は軽度の神 経障害がある; 画像所見の み	中等度の神経障害がある	高度の神経障害がある	生命を脅かす; 緊急処置を 要する	死亡
	癲癇発作 (発作)	部分痙攣発作; 意識障害は ない	短い全身性痙攣発作	内科的治療を行っているに もかかわらず繰り返し起こ る痙攣発作	生命を脅かす; 遷延する痙 攣発作の重積状態	死亡
	失神	-	-	失神; 起立性の卒倒	-	-
	間欠性跛行 ^{*2}	症状がない, 又は軽度の症 状がある; 臨床所見又は検 査所見のみ; 治療を要さな い	中等症; 最小限/局所的/非 侵襲的治療を要する; 年齢 相応の身の回り以外の日常 生活動作の制限	重症又は医学的に重大であ るが, 直ちに生命を脅かす ものではない; 入院又は入 院期間の延長を要する; 活 動不能/動作不能; 身の回り の日常生活動作の制限	生命を脅かす; 緊急処置を 要する	死亡
	虚血性心痛 ^{*2}	症状がない, 又は軽度の症 状がある; 臨床所見又は検 査所見のみ; 治療を要さな い	中等症; 最小限/局所的/非 侵襲的治療を要する; 年齢 相応の身の回り以外の日常 生活動作の制限	重症又は医学的に重大であ るが, 直ちに生命を脅かす ものではない; 入院又は入 院期間の延長を要する; 活 動不能/動作不能; 身の回り の日常生活動作の制限	生命を脅かす; 緊急処置を 要する	死亡
心筋梗塞	-	症状がなく, 心筋酵素のわ ずかな異常があるが, 心電 図上の虚血性変化はない	高度の症状がある; 心筋酵 素の異常がある; 循環動態 は安定; 心電図変化は梗塞 を示す	生命を脅かす; 緊急処置を 要する (例: 持続的静注療 法や機械的な循環動態の補 助)	死亡	

*1; 浮動性めまい及び回転性めまいのどちらかの症状が認められた場合に Grading する。

*2; CTCAE には項目が設けられていないが「その他」の項目に準じて設定した

表 2.7.3.7.1-13 大動脈弁閉鎖不全症の重症度評価 (左室内マッピング法)

軽度	中等度	重度
逆流が僧帽弁前尖先端まで	逆流が乳頭筋まで	乳頭筋を超える

表 2.7.3.7.1-14 日本人での高安動脈炎の有効性に関する文献一覧

参考文献	患者数	年齢	性別	前治療	用法・用量	有効性に関する情報	安全性に関する情報
27)	9	不明	不明	ステロイド	8 mg/kg/4週で1年以上投与 (投与回数：12~88回)	ステロイド治療抵抗性を示す難治性の全患者に対して TCZ 投与した。臨床症状、血清中 CRP, SAA, IL-6濃度、寛解維持に必要なステロイド投与量と画像診断（造影 CT, MRI）で評価したところ、継続投与し得た全患者で良好な臨床的反応がみられた。急速に CRP と SAA は正常化し、平均 PSL 投与量は、17.2 mg/日から4.8 mg/日へ減量し得た。血清 IL-6値は全例で TCZ 治療開始後に一過性に上昇した後には低下する傾向がみられ、この低下時期に一致して4例に画像上の肥厚血管の退縮がみられた。	報告なし
28)	1	27	女	ステロイド	8 mg/kg/4週で26カ月間投与	高安動脈炎と診断されてまず最初に PSL (40 mg/日) を投与された。PSL の減量により CRP の上昇が認められたため TCZ 投与に至った。単回投与で CRP と SAA は正常化した。TCZ 投与中に PSL を18.75 mg/日から3 mg/日に漸減し、再発の徴候は認められなかった。TCZ を20回投与後に終了し、PSL を5 mg/日に増量した。しかし、TCZ 終了9週間後、CRP と SAA 上昇を伴う乾性咳嗽を発症した。PSL を10 mg/日まで増量するも症状は改善しなかった。そこで、TCZ を再開した。1カ月以内に乾性咳嗽は消失し、CRP と SAA は再び正常化した。PSL を5 mg/日に漸減後、MTX を加療して再燃なく TCZ を終了した。2年の追跡期間中に再燃の徴候は認められなかった。	報告なし

参考文献	患者数	年齢	性別	前治療	用法・用量	有効性に関する情報	安全性に関する情報
29)	1	29	女	ステロイド, 免疫抑制剤, 生物製剤	8 mg/kg/4週→ 8 mg/kg/2週で6 カ月投与 → 8 mg/kg/4~5週 で約1年投与	副腎皮質ステロイド, 免疫抑制剤, 生物学的製剤を多様な組み合わせで投与されたが, 再燃を繰り返した。TCZ 8 mg/kg/4週で投与を開始し, 一時的に症状改善が認められたが, メチルプレドニゾン8 mg/日まで減量に伴い発熱, 胸背部痛が再燃した。上行大動脈径の拡大傾向と, 同部位の炎症が示唆された。メチルプレドニゾン24 mg/日, MTX 12 mg/週の併用に加え, TCZ 8 mg/kg/2週で投与間隔を短縮して投与したところ, 自覚症状, FDG-PET 所見の改善を認めた。以後はステロイド減量が可能となり, 上行大動脈径は拡大なく経過している。TCZ の2週間隔投与を6カ月間継続し, その後4~5週ごとに投与間隔を延長し, 投与を継続中である。TCZ 投与間隔を短縮することで臨床上, 画像上の改善を認め, 再発後の寛解導入と維持に成功した。	TCZ 投与中に感染症などの合併症は認められなかった。
30)	2	20 15	女 2	ステロイド	不明	1例: 全身症状は認めないが, 赤沈亢進と血管壁の肥厚を認めた。PSL 25 mg/日に増量して TCZ 投与開始した。PSL 8.5 mg/日まで減量した。IL-6は30~40 pg/mL で経過しており, 治療開始2年目には, FDG-PET による両側総頸動脈に異常集積, 造影 CT による右総頸動脈狭窄の増悪を認めた。 1例: ステロイドパルス療法を1クール行って投与開始した。PSL 15 mg/日まで減量した。投与開始から4カ月の時点でそれまで1桁であった IL-6が21.1 pg/mL となり, 6カ月の FDG-PET では上行~弓部大動脈, 両側総頸動脈, 左鎖骨下動脈に集積が残存し, 造影 CT で両側総頸動脈狭窄の増悪と範囲の拡大を認めた。	報告なし
31)	9	中央値 19	不明	生物学的製剤	不明	生物製剤初回投与までの罹病期間の中央値は15カ月であった。TCZ 4例 (重複あり) であった。IFX は全例で第1選択薬として使用されており, 全例で寛解導入したが, 4例が二次無効で多剤へ変更された。TCZ は第2選択以降で使用されており, 4例中3例で寛解を達成した。寛解による中止はなかった。また, TCZ では有意にステロイドの減量効果を認めた。	副作用による中止はなかった。

参考文献	患者数	年齢	性別	前治療	用法・用量	有効性に関する情報	安全性に関する情報
32)	1	25	女	ステロイド, 免疫抑制剤, 生物学的製剤	投与量, 期間不明 →8 mg/kg を4週ごとに投与	高安動脈炎に対してステロイド, MTX 25 mg/週, シクロホスファミド, タクロリムス5 mg/日などの免疫抑制剤を単剤又は併用療法で加療しても, PSL 10 mg/日以下に減量することができず, 再燃を繰り返した。インフリキシマブ導入したが, 十分なステロイド減量に至らず, エタネルセプトに変更するも同様の結果であった。高安動脈炎発症から3年後に TCZ 単剤で投与したが, 同時期に壊疽性膿皮症を発症して中止した。2013年3月の再燃をきっかけに, MTX 併用下で TCZ 8 mg/kg を4週ごとに再度投与した。右踵皮下腫瘍を併発したが, 抗生剤加療後も TCZ 投与を継続した。更に, タクロリムスも併用し, ステロイド減量は順調に行われ, 現在再燃なく経過している。	報告なし
17)	4	20 22 29 44	女 3 男 1	ステロイド, 免疫抑制剤	8 mg/kg/4週で 24~51回投与	4例中2例は, TCZ 投与前に PSL のみ, 他の2例は免疫抑制剤と PSL の投与歴があった。TCZ 投与により臨床症状と IL-6, CRP, SAA が速やかに正常化し, PSL の平均値は 21.3 mg/日から1.5 mg/日に低下した。TCZ を複数回投与後, 全例でsIL-6が一時的に上昇したが, 徐々に最初の値に戻った。内2例には, 血清 IL-6の減少とともに, 動脈肥厚の減少が認められた。難治性の患者で TCZ の有効性が認められた。	忍容性が認められた。新たな副作用は認められなかった。
33)	2	14 14	女 2	ステロイド	不明	1例: ステロイドパルス療法を2クール行い, 投与開始した。頸部血管雑音及び炎症反応の改善を認め, 炎症マーカーの上昇なく経過している。 1例: ステロイドパルス療法を1クール行い, 投与開始した。炎症反応の改善を認めた。炎症反応の再燃は認められていない。	報告なし

参考文献	患者数	年齢	性別	前治療	用法・用量	有効性に関する情報	安全性に関する情報
34)	6	平均値 12.5 (7～17)	女 6	ステロイド, 免疫抑制剤, 生物製剤	8～10 mg/kg/2週で24カ月 (6～58カ月) 投与	TCZ 投与前の治療は, PSL (6/6), エンドキサソパルス療法 (5/6), アザチオプリン (3/6), ミコフェノール酸モフェチル (2/6), MTX (2/6), IFX (2/6) であった。TCZ 投与開始前には発熱, 筋痛, 頭痛, 高血圧, 腹痛などの症状を認めたが, 投与開始後に改善した。ESR は TCZ 前後で 36.1 mm/h (11～58 mm/h) が 3.2 mm/h (1～6 mm/h) に減少した。PSL 使用量 (平均値) は, TCZ 前後で 24.3 mg/日 (11～45 mg/日) から投与24カ月後には 5.7 mg/日 (5～6.5 mg/日) に減量できた。血清 IL-6 値は投与開始後 2～3カ月に 166.7 pg/mL (20.7～548.1 pg/mL) と頂値を認め, 6カ月後には 33.3 pg/mL (7.1～54.8 pg/mL) に低下した。TCZ 治療 (6～48カ月) によって3例で画像上血管の肥厚, 狭窄の改善を認めた。	報告なし
8)	1	20	女	ステロイド, 免疫抑制剤	4 mg/kg/週で6回投与 →4 mg/kg/2週 →投与開始から46週後に8 mg/kg/3週に変更。 45カ月間以上投与	TCZ 投与前の治療は, PSL とシクロスポリン, シクロホスファミドなどであった。TCZ 投与開始から3週間以内に CRP が完全に正常化し, 投与から1カ月後にはフィブリノゲン及び SAA が正常化した。頸部痛, 胸痛, 失神の発現はなくなった。再発はなかった。PSL は, 他剤との併用のない投与開始時の 60 mg/日から, TCZ 併用投与によって最終観察時には 7.5 mg/日に減量されていた。	ウイルス感染による腸炎以外に副作用なし。 5年を超える期間の間, 抗 TCZ 抗体は検出されなかった。

SAA : 血清アミロイド A PSL : プレドニゾロン TCZ : トシリズマブ PET/CT : positron emission/computerized tomography MTX : メトトレキサート

2.7.3.7.2 WA28119試験

表 2.7.3.7.2-1 副腎皮質ステロイド漸減投与スケジュール (WA28119試験)

Prednisone Short Taper (26 weeks N=200)							Prednisone Long Taper (52 weeks N=50)					
Taper Week	mg/d	5 mg	2.5 mg	1 mg	Placebo		Taper Week	mg/d	5 mg	2.5 mg	1 mg	Placebo
1	60	Open label supplied by Sponsor Patient starts at any of these incremental dosages				OPEN LABEL	1	60	Open label supplied by Sponsor Patient starts at any of these incremental dosages			
2	50											
3	40											
4	35											
5	30											
6	25											
7	20											
8	15	3			1	BLINDED	8	17.5	3	1		
9	12.5	2	1		1		9	17.5	3	1		
10	12.5	2	1				10	15	3			
11	10	2			1		11	15	3			
12	9	1		4			12	12.5	2	1		2
13	8	1		3			13	10	2			2
14	7	1		2			14	10	2			1
15	6	1		1			15	10	2			
16	6	1		1			16	10	2			
17	5	1			4		17	9	1		4	
18	5	1			4		18	9	1		4	
19	4			4	1		19	9	1		4	
20	4			4	1		20	9	1		4	
21	3			3	1		21	8	1		3	
22	3			3	1		22	8	1		3	
23	2			2	2		23	8	1		3	
24	2			2	2		24	8	1		3	
25	1			1	2		25	7	1		2	
26	1			1	2		26	7	1		2	
27	0				3		27	7	1		2	
28	0				3		28	7	1		2	
29	0				2		29	6	1		1	
30	0				2		30	6	1		1	
31	0				2		31	6	1		1	
32	0				2		32	6	1		1	
33	0				1		33	5	1			
34	0				1		34	5	1			

Prednisone Short Taper (26 weeks N=200)						Prednisone Long Taper (52 weeks N=50)					
Taper Week	mg/d	5 mg	2.5 mg	1 mg	Placebo	Taper Week	mg/d	5 mg	2.5 mg	1 mg	Placebo
35	0				1	35	5	1			
36	0				1	36	5	1			
37	0				4	37	4			4	
38	0				4	38	4			4	
39	0				4	39	4			4	
40	0				4	40	4			4	
41	0				3	41	3			3	
42	0				3	42	3			3	
43	0				3	43	3			3	
44	0				3	44	3			3	
45	0				2	45	2			2	
46	0				2	46	2			2	
47	0				2	47	2			2	
48	0				2	48	2			2	
49	0				1	49	1			1	
50	0				1	50	1			1	
51	0				1	51	1			1	
52	0				1	52	1			1	
53	0				1	53	0				1
54	0				1	54	0				1
55	0				1	55	0				1
56	0				1	56	0				1
57	0				1	57	0				1
58	0				1	58	0				1

[5.3.5.1-3 Appendix 3を再掲]

表 2.7.3.7.2-2 人口統計学的特性及びベースライン時特性1 (WA28119試験)

Summary of Demographic Characteristics, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age (years)				
n	50	51	100	50
Mean (SD)	69.3 (8.1)	67.8 (7.7)	69.5 (8.5)	69.4 (8.2)
Median	70.5	68.0	71.0	71.0
Min - Max	52 - 83	52 - 84	51 - 85	53 - 91
Age group (years)				
n	50	51	100	50
< 65 years	16 (32.0%)	17 (33.3%)	32 (32.0%)	17 (34.0%)
>= 65 years	34 (68.0%)	34 (66.7%)	68 (68.0%)	33 (66.0%)
Sex				
n	50	51	100	50
Male	12 (24.0%)	14 (27.5%)	22 (22.0%)	15 (30.0%)
Female	38 (76.0%)	37 (72.5%)	78 (78.0%)	35 (70.0%)
Ethnicity				
n	50	51	100	50
Hispanic or Latino	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
Not Hispanic or Latino	49 (98.0%)	49 (96.1%)	96 (96.0%)	46 (92.0%)
Not Reported	0	1 (2.0%)	2 (2.0%)	2 (4.0%)
Unknown	1 (2.0%)	0	0	1 (2.0%)
Race				
n	50	51	100	50
Asian	0	0	0	1 (2.0%)
Black or African American	0	2 (3.9%)	1 (1.0%)	0
Other	0	0	1 (1.0%)	1 (2.0%)
White	50 (100.0%)	49 (96.1%)	97 (97.0%)	47 (94.0%)
Unknown	0	0	1 (1.0%)	1 (2.0%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_AP.out
11JUL2016 21:21

Summary of Demographic Characteristics, All Patients Population
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Weight (kg)				
n	50	51	100	49
Mean (SD)	70.12 (15.83)	73.13 (15.34)	69.82 (13.82)	70.84 (16.09)
Median	66.65	70.60	67.50	69.20
Min - Max	47.7 - 120.0	48.5 - 108.0	48.0 - 105.0	46.4 - 124.1
Height (cm)				
n	50	51	100	49
Mean (SD)	164.70 (9.51)	167.86 (8.45)	163.90 (10.08)	165.33 (9.09)
Median	162.80	167.00	163.00	167.70
Min - Max	139.7 - 188.0	153.0 - 191.0	125.3 - 187.0	139.0 - 184.0
BMI (kg/m ²)				
n	50	51	100	49
Mean (SD)	25.70 (4.46)	25.80 (4.13)	25.97 (4.42)	25.99 (6.15)
Median	24.92	25.35	25.62	24.80
Min - Max	18.0 - 40.1	18.3 - 36.0	18.1 - 38.6	17.8 - 53.4
Smoking History				
n	50	51	100	49
Never	35 (70.0%)	29 (56.9%)	57 (57.0%)	28 (57.1%)
Current	7 (14.0%)	9 (17.6%)	13 (13.0%)	5 (10.2%)
Previous	8 (16.0%)	13 (25.5%)	30 (30.0%)	16 (32.7%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_AP.out
 11JUL2016 21:21

Page 2 of 2

[5.3.5.1-3 Table 10を再掲]

表 2.7.3.7.2-3 人口統計学的特性及びベースライン時特性2 (WA28119試験)

Summary of Diagnosis Features, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age > 50 years				
n	50	51	100	50
Yes	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
History of ESR > 50 mm/hour				
n	50	51	100	50
Yes	49 (98.0%)	51 (100.0%)	94 (94.0%)	47 (94.0%)
No	1 (2.0%)	0	6 (6.0%)	3 (6.0%)
History of CRP > 2.45 mg/d				
n	50	51	100	50
Yes	41 (82.0%)	38 (74.5%)	87 (87.0%)	43 (86.0%)
No	9 (18.0%)	13 (25.5%)	13 (13.0%)	7 (14.0%)
New onset localized headache				
n	50	51	100	50
Yes	29 (58.0%)	34 (66.7%)	68 (68.0%)	38 (76.0%)
No	21 (42.0%)	17 (33.3%)	32 (32.0%)	12 (24.0%)
Scalp tenderness				
n	50	51	100	50
Yes	16 (32.0%)	16 (31.4%)	38 (38.0%)	20 (40.0%)
No	34 (68.0%)	35 (68.6%)	62 (62.0%)	30 (60.0%)
Temporal artery tenderness				
n	50	51	100	50
Yes	14 (28.0%)	14 (27.5%)	26 (26.0%)	18 (36.0%)
No	36 (72.0%)	37 (72.5%)	74 (74.0%)	32 (64.0%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_diag.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_diag_AP.out
11JUL2016 21:24

Summary of Diagnosis Features, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Temporal artery decreased pulsation				
n	50	51	100	50
Yes	8 (16.0%)	6 (11.8%)	7 (7.0%)	8 (16.0%)
No	42 (84.0%)	45 (88.2%)	93 (93.0%)	42 (84.0%)
Ischemia-related vision loss				
n	50	51	100	50
Yes	7 (14.0%)	4 (7.8%)	7 (7.0%)	7 (14.0%)
No	43 (86.0%)	47 (92.2%)	93 (93.0%)	43 (86.0%)
Otherwise unexplained mouth or jaw pain upon mastication				
n	50	51	100	50
Yes	20 (40.0%)	15 (29.4%)	31 (31.0%)	19 (38.0%)
No	30 (60.0%)	36 (70.6%)	69 (69.0%)	31 (62.0%)
Symptoms of PMR				
n	50	51	100	50
Yes	30 (60.0%)	35 (68.6%)	59 (59.0%)	32 (64.0%)
No	20 (40.0%)	16 (31.4%)	41 (41.0%)	18 (36.0%)
Was TAB performed?				
n	50	51	100	50
Yes	38 (76.0%)	33 (64.7%)	64 (64.0%)	37 (74.0%)
No	12 (24.0%)	18 (35.3%)	36 (36.0%)	13 (26.0%)
Positive TAB				
n	38	33	64	37
Yes	36 (94.7%)	29 (87.9%)	57 (89.1%)	34 (91.9%)
No	2 (5.3%)	4 (12.1%)	7 (10.9%)	3 (8.1%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_diag.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_diag_AP.out
11JUL2016 21:24

Page 2 of 3

Summary of Diagnosis Features, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Positive imaging study?				
n	50	51	100	50
Yes	19 (38.0%)	23 (45.1%)	50 (50.0%)	23 (46.0%)
No	31 (62.0%)	28 (54.9%)	50 (50.0%)	27 (54.0%)
Active GCA within 6 Weeks of Baseline				
n	50	51	100	50
Yes	50 (100.0%)	50 (98.0%)	100 (100.0%)	50 (100.0%)
No	0	1 (2.0%)	0	0
Has patient ever been in remission				
n	50	51	100	50
Yes	20 (40.0%)	19 (37.3%)	46 (46.0%)	22 (44.0%)
No	30 (60.0%)	32 (62.7%)	54 (54.0%)	28 (56.0%)
Was an imaging study performed?				
n	27	27	58	27
CTA	1 (3.7%)	1 (3.7%)	7 (12.1%)	4 (14.8%)
MRA	1 (3.7%)	0	6 (10.3%)	1 (3.7%)
MRI	3 (11.1%)	1 (3.7%)	1 (1.7%)	1 (3.7%)
PET-CT	18 (66.7%)	21 (77.8%)	39 (67.2%)	19 (70.4%)
Other	4 (14.8%)	4 (14.8%)	5 (8.6%)	2 (7.4%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_diag.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_diag_AP.out
11JUL2016 21:24

Page 3 of 3

[5.3.5.1-3 Table 11を再掲]

表 2.7.3.7.2-4 人口統計学的特性及びベースライン時特性3 (WA28119試験)

Summary of Baseline Characteristics, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Duration of GCA (days)				
n	50	51	100	50
Mean (SD)	364.66 (569.85)	255.22 (435.45)	306.80 (563.50)	258.38 (500.68)
Median	80.00	53.00	52.00	41.50
Min - Max	12.0 - 2698.0	8.0 - 1789.0	9.0 - 2856.0	13.0 - 2708.0
Disease Onset				
n	50	51	100	50
New Patient	23 (46.0%)	23 (45.1%)	47 (47.0%)	26 (52.0%)
Relapse Patient	27 (54.0%)	28 (54.9%)	53 (53.0%)	24 (48.0%)
Prednisone dose at baseline (mg/day)				
n	50	51	100	49
Mean (SD)	34.60 (12.97)	34.48 (14.20)	34.60 (13.37)	35.92 (13.76)
Median	30.00	30.00	30.00	35.00
Min - Max	20.0 - 60.0	5.0 - 60.0	10.0 - 60.0	5.0 - 60.0
Prednisone dose (<=30mg/day, >30mg/day)				
n	50	51	100	50
<=30 mg/day	27 (54.0%)	26 (51.0%)	52 (52.0%)	25 (50.0%)
>30 mg/day	23 (46.0%)	25 (49.0%)	48 (48.0%)	25 (50.0%)
First steroid for GCA (mg)				
n	50	50	100	49
Mean (SD)	104.74 (197.94)	61.76 (44.95)	79.02 (143.91)	78.40 (150.75)
Median	60.00	60.00	60.00	50.00
Min - Max	20.0 - 1000.0	10.0 - 250.0	2.0 - 1000.0	5.0 - 1000.0

Summary of Baseline Characteristics, All Patients Population
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Baseline C-reactive protein (CRP) (mg/L)				
n	50	51	100	49
Mean (SD)	7.69 (10.32)	8.17 (21.00)	6.78 (8.70)	11.36 (25.38)
Median	3.64	3.56	3.67	4.52
Min - Max	0.2 - 47.1	0.2 - 149.0	0.2 - 45.5	0.2 - 154.0
Baseline erythrocyte sedimentation rate (ESR) (mm/h)				
n	50	51	99	49
Mean (SD)	28.77 (25.43)	24.22 (18.19)	24.62 (18.66)	20.78 (18.13)
Median	23.00	20.00	19.00	15.00
Min - Max	1.0 - 115.0	2.0 - 75.0	2.0 - 95.0	0.0 - 79.0
Patient's Global Assessment VAS (mm)				
n	49	51	100	49
Mean (SD)	35.73 (28.15)	47.78 (27.80)	43.61 (25.66)	46.65 (25.60)
Median	30.00	50.00	48.00	48.00
Min - Max	0.0 - 91.0	0.0 - 100.0	0.0 - 100.0	1.0 - 91.0
Overall EQ-5D Score				
n	50	49	99	49
Mean (SD)	0.742 (0.219)	0.662 (0.264)	0.736 (0.207)	0.737 (0.218)
Median	0.725	0.725	0.760	0.727
Min - Max	0.02 - 1.00	-0.18 - 1.00	-0.14 - 1.00	0.26 - 1.00
Overall FACIT Score				
n	50	49	99	49
Mean (SD)	35.04 (12.77)	31.42 (13.60)	36.05 (11.06)	36.27 (11.55)
Median	37.00	33.00	38.00	39.00
Min - Max	4.0 - 52.0	4.0 - 52.0	8.0 - 52.0	7.0 - 52.0

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm_base.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_base_AP.out
 11JUL2016 21:29 Page 2 of 4

Summary of Baseline Characteristics, All Patients Population
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
SF-36 Mental Component Score				
n	48	49	97	49
Mean (SD)	42.729 (12.132)	40.454 (13.726)	42.769 (12.427)	47.673 (12.593)
Median	42.715	37.863	44.142	48.018
Min - Max	16.08 - 62.20	8.72 - 62.50	8.17 - 68.23	18.04 - 67.51
SF-36 Physical Component Score				
n	48	49	97	49
Mean (SD)	42.647 (10.868)	41.117 (9.972)	43.097 (9.426)	40.618 (7.996)
Median	43.911	41.313	44.265	40.203
Min - Max	16.15 - 59.54	21.71 - 58.77	19.24 - 59.45	21.50 - 56.51
Signs and Symptoms				
n	50	51	100	50
Both	20 (40.0%)	24 (47.1%)	37 (37.0%)	23 (46.0%)
Cranial Only	20 (40.0%)	16 (31.4%)	41 (41.0%)	18 (36.0%)
PMR Only	10 (20.0%)	11 (21.6%)	22 (22.0%)	9 (18.0%)
Baseline Fever (38C or 100.4F)				
n	50	51	100	50
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
Baseline Bilateral Blindness				
n	50	51	100	50
Yes	0	0	0	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (98.0%)
Baseline Ischemic Optic Neuropathy				
n	50	51	100	50
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm_base.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_base_AP.out
 11JUL2016 21:29 Page 3 of 4

Summary of Baseline Characteristics, All Patients Population
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Baseline Amaurosis Fugax				
n	50	51	100	50
Yes	0	0	1 (1.0%)	1 (2.0%)
No	50 (100.0%)	51 (100.0%)	99 (99.0%)	49 (98.0%)
Baseline Blurred Vision				
n	50	51	100	50
Yes	2 (4.0%)	5 (9.8%)	4 (4.0%)	3 (6.0%)
No	48 (96.0%)	46 (90.2%)	96 (96.0%)	47 (94.0%)
Baseline Diplopia				
n	50	51	100	50
No	50 (100.0%)	51 (100.0%)	100 (100.0%)	50 (100.0%)
Baseline Unilateral Blindness				
n	50	51	100	50
Yes	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
No	49 (98.0%)	50 (98.0%)	99 (99.0%)	49 (98.0%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm_base.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_base_AP.out
 11JUL2016 21:29 Page 4 of 4

[5.3.5.1-3 Table 12を再掲]

表 2.7.3.7.2-5 巨細胞性動脈炎の再発率（1人年あたりの再発回数）（WA28119試験）

Summary of Annualized Relapse Rate at Week 52, by Treatment Group, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Annualised Relapse Rate at Week 52				
n	50	51	100	49
Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)
Median	1.00	1.00	0.00	0.00
Min - Max	0.0 - 12.6	0.0 - 10.3	0.0 - 4.0	0.0 - 4.0

Annualised relapse rate is calculated as the number of flares between the first clinical assessment of GCA and the final clinical assessment prior to entry into Part 2, divided by the time period between the two days, multiplied by 365.25.
First GCA assessment date is the one that occurs on or after the first treatment date.
Number of flares is the actual number and includes all the flares that occurred multiple times (scheduled and unscheduled) at an analysis visit.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ef_arr.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ef_arr_IT.out
11JUL2016 23:26

[5.3.5.1-3 Table 29を再掲]

表 2.7.3.7.2-6 ベースライン時の巨細胞性動脈炎の発症（新規発症，再発）で分けた部分集団での52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Disease Onset Status, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
New Onset Patients				
n	23	23	47	26
Sustained remission	5 (21.7%)	5 (21.7%)	28 (59.6%)	15 (57.7%)
Not sustained remission	18 (78.3%)	18 (78.3%)	19 (40.4%)	11 (42.3%)
Relapsing Patients				
n	27	28	53	23
Sustained remission	2 (7.4%)	4 (14.3%)	28 (52.8%)	11 (47.8%)
Not sustained remission	25 (92.6%)	24 (85.7%)	25 (47.2%)	12 (52.2%)

Patients in remission will be classed as responders.
Patients are in sustained remission when they are responders from Week 12 to Week 52.
Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
Elevated ESR which attribute to GCA is reflected in Flare by investigator.
Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_DOS.out
11JUL2016 23:32 Page 1 of 1

[5.3.5.1-3 Page 482を再掲]

表 2.7.3.7.2-7 試験開始時の副腎皮質ステロイド（30 mg/日以下，30 mg/日超）で分けた部分集団での52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Starting Prednisone Dose, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
<= 30 mg				
n	27	26	52	24
Sustained remission	3 (11.1%)	6 (23.1%)	26 (50.0%)	11 (45.8%)
Not sustained remission	24 (88.9%)	20 (76.9%)	26 (50.0%)	13 (54.2%)
> 30 mg				
n	23	25	48	25
Sustained remission	4 (17.4%)	3 (12.0%)	30 (62.5%)	15 (60.0%)
Not sustained remission	19 (82.6%)	22 (88.0%)	18 (37.5%)	10 (40.0%)

Patients in remission will be classed as responders.
 Patients are in sustained remission when they are responders from Week 12 to Week 52.
 Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
 Elevated ESR which attribute to GCA is reflected in Flare by investigator.
 Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
 Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
 Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
 Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_SPD.out
 11JUL2016 23:36 Page 1 of 1

[5.3.5.1-3 Page 487を再掲]

表 2.7.3.7.2-8 巨細胞性動脈炎の寛解歴の有無で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by History of Remission, ITT Population - Relapsing Patients
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=27)	PBO QW + 52 Week Prednisone Taper (N=28)	TCZ QW + 26 Week Prednisone Taper (N=53)	TCZ Q2W + 26 Week Prednisone Taper (N=23)
Had been in remission				
n	18	17	37	16
Sustained remission	0	3 (17.6%)	19 (51.4%)	6 (37.5%)
Not sustained remission	18 (100.0%)	14 (82.4%)	18 (48.6%)	10 (62.5%)
Never been in remission				
n	9	11	16	7
Sustained remission	2 (22.2%)	1 (9.1%)	9 (56.3%)	5 (71.4%)
Not sustained remission	7 (77.8%)	10 (90.9%)	7 (43.8%)	2 (28.6%)

Patients in remission will be classed as responders.
 Patients are in sustained remission when they are responders from Week 12 to Week 52.
 Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
 Elevated ESR which attribute to GCA is reflected in Flare by investigator.
 Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
 Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
 Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
 Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_ITRLPS_HRR.out
 11JUL2016 23:38 Page 1 of 1

[5.3.5.1-3 Page 490を再掲]

表 2.7.3.7.2-9 画像判定で巨細胞性動脈炎と診断された部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52.
 Patients with positive imaging, ITT Population
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=19)	PBO QW + 52 Week Prednisone Taper (N=23)	TCZ QW + 26 Week Prednisone Taper (N=50)	TCZ Q2W + 26 Week Prednisone Taper (N=23)
Achieve Sustained Remission				
n	19	23	50	23
Sustained remission	4 (21.1%)	4 (17.4%)	30 (60.0%)	13 (56.5%)
Not sustained remission	15 (78.9%)	19 (82.6%)	20 (40.0%)	10 (43.5%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp_img_ah105.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_img_ah105_IT.out
 12JUL2016 12:41

表 2.7.3.7.2-10 側頭動脈生検で巨細胞性動脈炎と診断された部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52, ITT
 Population – Patients Diagnosed via Positive TAB
 Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=36)	PBO QW + 52 Week Prednisone Taper (N=29)	TCZ QW + 26 Week Prednisone Taper (N=57)	TCZ Q2W + 26 Week Prednisone Taper (N=33)
Achieve Sustained Remission				
n	36	29	57	33
Sustained remission	4 (11.1%)	5 (17.2%)	29 (50.9%)	18 (54.5%)
Not sustained remission	32 (88.9%)	24 (82.8%)	28 (49.1%)	15 (45.5%)

TAB stands for Temporal Artery Biopsy.

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional GS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_ITPTAB.out
 11JUL2016 23:38

Page 1 of 1

[5.3.5.1-6 表 2.1-1を再掲]

表 2.7.3.7.2-11 画像判定で巨細胞性動脈炎と診断され、側頭動脈の生検結果が陽性でない部分集団での
52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52, ITT
Population – Patients Diagnosed via Imaging only
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=14)	PBO QW + 52 Week Prednisone Taper (N=21)	TCZ QW + 26 Week Prednisone Taper (N=43)	TCZ Q2W + 26 Week Prednisone Taper (N=16)
Achieve Sustained Remission				
n	14	21	43	16
Sustained remission	3 (21.4%)	4 (19.0%)	27 (62.8%)	8 (50.0%)
Not sustained remission	11 (78.6%)	17 (81.0%)	16 (37.2%)	8 (50.0%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_ITLVV0.out
11JUL2016 23:39

Page 1 of 1

[5.3.5.1-3 Page 303を再掲]

表 2.7.3.7.2-12 画像判定で巨細胞性動脈炎と診断され、側頭動脈の生検結果が陽性ではなく、
頭部の症状のない部分集団での52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52, ITT
Population – Patients Diagnosed via Imaging Only Without Cranial Symptoms
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=8)	PBO QW + 52 Week Prednisone Taper (N=7)	TCZ QW + 26 Week Prednisone Taper (N=18)	TCZ Q2W + 26 Week Prednisone Taper (N=9)
Achieve Sustained Remission				
n	8	7	18	9
Sustained remission	2 (25.0%)	2 (28.6%)	9 (50.0%)	3 (33.3%)
Not sustained remission	6 (75.0%)	5 (71.4%)	9 (50.0%)	6 (66.7%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_ITLVV0NC.out
11JUL2016 23:38

Page 1 of 1

[5.3.5.1-3 Page 304を再掲]

表 2.7.3.7.2-13 ACR の基準に合致した巨細胞性動脈炎の判定の有無で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by GCA Diagnosis based on ACR Criteria, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Did not meet ACR Entry Criteria				
n	12	11	21	10
Sustained remission	3 (25.0%)	2 (18.2%)	10 (47.6%)	4 (40.0%)
Not sustained remission	9 (75.0%)	9 (81.8%)	11 (52.4%)	6 (60.0%)
Meet ACR Entry Criteria				
n	38	40	79	39
Sustained remission	4 (10.5%)	7 (17.5%)	46 (58.2%)	22 (56.4%)
Not sustained remission	34 (89.5%)	33 (82.5%)	33 (41.8%)	17 (43.6%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_ACR.out
11JUL2016 23:38

Page 1 of 1

[5.3.5.1-3 Page 493を再掲]

表 2.7.3.7.2-14 年齢（65歳未満，65歳以上）で分けた部分集団での52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Age Group, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Age < 65 (yr)				
n	16	17	32	17
Sustained remission	3 (18.8%)	3 (17.6%)	20 (62.5%)	8 (47.1%)
Not sustained remission	13 (81.3%)	14 (82.4%)	12 (37.5%)	9 (52.9%)
Age >= 65 (yr)				
n	34	34	68	32
Sustained remission	4 (11.8%)	6 (17.6%)	36 (52.9%)	18 (56.3%)
Not sustained remission	30 (88.2%)	28 (82.4%)	32 (47.1%)	14 (43.8%)

Patients in remission will be classed as responders.
 Patients are in sustained remission when they are responders from Week 12 to Week 52.
 Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
 Elevated ESR which attribute to GCA is reflected in Flare by investigator.
 Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
 Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
 Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
 Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_AGE.out
 11JUL2016 23:39 Page 1 of 1

[5.3.5.1-6 表 2.1-2を再掲]

表 2.7.3.7.2-15 体重 (60 kg 未満, 60 kg 以上~100 kg 以下, 100 kg 超) で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Weight Group, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Weight: < 60 (kg)				
n	14	11	27	13
Sustained remission	1 (7.1%)	3 (27.3%)	16 (59.3%)	5 (38.5%)
Not sustained remission	13 (92.9%)	8 (72.7%)	11 (40.7%)	8 (61.5%)
Weight: 60 - 100 (kg)				
n	33	36	70	32
Sustained remission	6 (18.2%)	5 (13.9%)	39 (55.7%)	20 (62.5%)
Not sustained remission	27 (81.8%)	31 (86.1%)	31 (44.3%)	12 (37.5%)
Weight: > 100 (kg)				
n	3	4	3	3
Sustained remission	0	1 (25.0%)	1 (33.3%)	0
Not sustained remission	3 (100.0%)	3 (75.0%)	2 (66.7%)	3 (100.0%)
Weight: Missing				
n	0	0	0	1
Sustained remission	0	0	0	1 (100.0%)
Not sustained remission	0	0	0	0

Patients in remission will be classed as responders.
Patients are in sustained remission when they are responders from Week 12 to Week 52.
Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
Elevated ESR which attribute to GCA is reflected in Flare by investigator.
Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_WGT.out
11JUL2016 23:39 Page 1 of 1

[5.3.5.1-6 表 2.1-3を再掲]

表 2.7.3.7.2-16 性別で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Gender, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Female				
n	38	37	78	34
Sustained remission	2 (5.3%)	6 (16.2%)	44 (56.4%)	15 (44.1%)
Not sustained remission	36 (94.7%)	31 (83.8%)	34 (43.6%)	19 (55.9%)
Male				
n	12	14	22	15
Sustained remission	5 (41.7%)	3 (21.4%)	12 (54.5%)	11 (73.3%)
Not sustained remission	7 (58.3%)	11 (78.6%)	10 (45.5%)	4 (26.7%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_SEX.out
11JUL2016 23:39

Page 1 of 1

[5.3.5.1-6 表 2.1-4を再掲]

表 2.7.3.7.2-17 人種で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Race, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
White				
n	50	49	97	46
Sustained remission	7 (14.0%)	8 (16.3%)	56 (57.7%)	25 (54.3%)
Not sustained remission	43 (86.0%)	41 (83.7%)	41 (42.3%)	21 (45.7%)
Black Or African American				
n	0	2	1	0
Sustained remission	0	1 (50.0%)	0	0
Not sustained remission	0	1 (50.0%)	1 (100.0%)	0
Asian				
n	0	0	0	1
Sustained remission	0	0	0	0
Not sustained remission	0	0	0	1 (100.0%)
Other				
n	0	0	1	1
Sustained remission	0	0	0	0
Not sustained remission	0	0	1 (100.0%)	1 (100.0%)
Unknown				
n	0	0	1	1
Sustained remission	0	0	0	1 (100.0%)
Not sustained remission	0	0	1 (100.0%)	0

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_RACE.out
11JUL2016 23:39

Page 1 of 1

[5.3.5.1-6 表 2.1-5を再掲]

表 2.7.3.7.2-18 地域で分けた部分集団での52週時の寛解維持割合 (WA28119試験)

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by Region, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Europe				
n	40	39	81	38
Sustained remission	6 (15.0%)	6 (15.4%)	41 (50.6%)	21 (55.3%)
Not sustained remission	34 (85.0%)	33 (84.6%)	40 (49.4%)	17 (44.7%)
North America				
n	10	12	19	11
Sustained remission	1 (10.0%)	3 (25.0%)	15 (78.9%)	5 (45.5%)
Not sustained remission	9 (90.0%)	9 (75.0%)	4 (21.1%)	6 (54.5%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_IT_RGN.out
11JUL2016 23:39

Page 1 of 1

[5.3.5.1-6 表 2.1-6を再掲]

表 2.7.3.7.2-19 血清中トシリズマブ濃度（四分位）で分けた部分集団での52週時の寛解維持割合（WA28119試験）

Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52 by TCZ Serum Concentration Quartiles, PK Population
Protocol: WA28119

	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Category: Q1 (16.9 mcg/mL)		
n	3	24
Sustained remission	2 (66.7%)	18 (75.0%)
Not sustained remission	1 (33.3%)	6 (25.0%)
Category: Q2 (42.8 mcg/mL)		
n	17	9
Sustained remission	13 (76.5%)	7 (77.8%)
Not sustained remission	4 (23.5%)	2 (22.2%)
Category: Q3 (78.5 mcg/mL)		
n	26	0
Sustained remission	16 (61.5%)	0
Not sustained remission	10 (38.5%)	0
Category: Q4 (194 mcg/mL)		
n	26	0
Sustained remission	20 (76.9%)	0
Not sustained remission	6 (23.1%)	0
Missing		
n	28	16
Sustained remission	5 (17.9%)	1 (6.3%)
Not sustained remission	23 (82.1%)	15 (93.8%)

Patients in remission will be classed as responders.

Patients are in sustained remission when they are responders from Week 12 to Week 52.

Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.

Elevated ESR which attribute to GCA is reflected in Flare by investigator.

Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.

Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.

Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.

Percentages are based on n.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_pp.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_pp_PK_TCZQ.out
11JUL2016 23:39

Page 1 of 1

[5.3.5.1-3 Page 560を再掲]

表 2.7.3.7.2-20 ベースライン時の巨細胞性動脈炎の発症（新規発症，再発）で分けた部分集団での再発までの期間
(WA28119試験)

Summary and Analysis of Time to First GCA Disease Flare Following Clinical Remission, by disease onset, ITT Population
Protocol: WA28119

Disease Onset: New Onset

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Patients included in analysis	23 (100.0%)	23 (100.0%)	47 (100.0%)	26 (100.0%)
Patients with event (%)	16 (69.6%)	11 (47.8%)	11 (23.4%)	5 (19.2%)
Patients without event (%)	7 (30.4%)	12 (52.2%)	36 (76.6%)	21 (80.8%)
Time to event (days)				
Median	169.0	NE	NE	NE
99% CI for Median	(120.0, NE)	(147.0, NE)	NE	NE
25% and 75%-ile	111.0, NE	116.0, NE	NE	NE
Range	5 to 365	21 to 362	1 to 367	50 to 364
Stratified Analysis (vs PBO + 26 WK Taper)				
p-value			0.0005	0.0019
Hazard Ratio			0.25	0.20
99% CI			(0.09, 0.70)	(0.05, 0.76)
Stratified Analysis (vs PBO + 52 WK Taper)				
p-value			0.0541	0.0546
Hazard Ratio			0.44	0.35
99% CI			(0.14, 1.32)	(0.09, 1.42)

Patients who were never in remission are censored at Day 1.

Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

The treatment groups are compared to Placebo using a Cox proportional hazards model adjusting for the stratification factor of starting prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_fl_km.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_fl_km_IT_DISON.out
11JUL2016 23:32

Page 1 of 2

Summary and Analysis of Time to First GCA Disease Flare Following Clinical Remission, by disease onset, ITT Population
Protocol: WA28119

Disease Onset: Relapsing

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Patients included in analysis	27 (100.0%)	28 (100.0%)	53 (100.0%)	23 (100.0%)
Patients with event (%)	18 (66.7%)	14 (50.0%)	12 (22.6%)	8 (34.8%)
Patients without event (%)	9 (33.3%)	14 (50.0%)	41 (77.4%)	15 (65.2%)
Time to event (days)				
Median	165.0	274.0	NE	NE
99% CI for Median	(61.0, NE)	(141.0, NE)	NE	(162.0, NE)
25% and 75%-ile	61.0, NE	141.0, NE	351.0, NE	143.0, NE
Range	1 to 363	1 to 362	1 to 364	1 to 358
Stratified Analysis (vs PBO + 26 WK Taper)				
p-value			0.0001	0.0459
Hazard Ratio			0.23	0.42
99% CI			(0.09, 0.61)	(0.14, 1.28)
Stratified Analysis (vs PBO + 52 WK Taper)				
p-value			0.0100	0.3666
Hazard Ratio			0.36	0.67
99% CI			(0.13, 1.00)	(0.21, 2.10)

Patients who were never in remission are censored at Day 1.

Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

The treatment groups are compared to Placebo using a Cox proportional hazards model adjusting for the stratification factor of starting prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_fl_km.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_fl_km_IT_DISON.out
11JUL2016 23:32 Page 2 of 2

[5.3.5.1-3 Page 483を再掲]

表 2.7.3.7.2-21 画像判定で巨細胞性動脈炎と診断された部分集団での再発までの期間 (WA28119試験)

Summary and Analysis of Time to First GCA Disease Flare Following Clinical Remission, ITT Population - Patients with Positive Imaging Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=19)	PBO QW + 52 Week Prednisone Taper (N=23)	TCZ QW + 26 Week Prednisone Taper (N=50)	TCZ Q2W + 26 Week Prednisone Taper (N=23)
Patients included in analysis	19 (100.0%)	23 (100.0%)	50 (100.0%)	23 (100.0%)
Patients with event (%)	13 (68.4%)	13 (56.5%)	10 (20.0%)	6 (26.1%)
Patients without event (%)	6 (31.6%)	10 (43.5%)	40 (80.0%)	17 (73.9%)
Time to event (days)				
Median	167.0	295.0	NE	NE
99% CI for Median	(120.0, NE)	(168.0, NE)	NE	(163.0, NE)
25% and 75%-ile	120.0, NE	148.0, NE	NE	163.0, NE
Range	1 to 365	21 to 362	1 to 365	1 to 364
Stratified Analysis (vs PBO + 26 WK Taper)				
p-value			0.0002	0.0098
Hazard Ratio			0.20	0.28
99% CI			(0.07, 0.60)	(0.08, 1.00)
Stratified Analysis (vs PBO + 52 WK Taper)				
p-value			0.0049	0.0825
Hazard Ratio			0.30	0.42
99% CI			(0.10, 0.91)	(0.11, 1.52)

Patients who were never in remission are censored at Day 1.

Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

The treatment groups are compared to Placebo using a Cox proportional hazards model adjusting for the stratification factor of starting prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_fl_km_ah105.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_fl_km_ah105_ITPOS.out
 12JUL2016 12:02

表 2.7.3.7.2-22 52週時の寛解維持割合における MRA-SC QW 群と MRA-SC Q2W 群の差 (WA28119試験)

Summary and Analysis of the Proportion of Patients Achieving Sustained Remission Whilst Adhering to the Protocol-defined Prednisone Taper Regimen at Week 52, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Responders	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Non-Responders	43 (86.0%)	42 (82.4%)	44 (44.0%)	23 (46.9%)
TCZ Q2W + 26 Week Prednisone Taper (N=49) Unadjusted Difference in Response Rates 95% CI			-2.94 (-19.94, 14.06)	

Patients in remission will be classed as responders.
Patients are in sustained remission when they are responders from Week 12 to Week 52.
Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
Elevated ESR which attribute to GCA is reflected in Flare by investigator.
Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
Superiority comparison 'TCZ QW + 26 Week Taper' vs 'TCZ Q2W + 26 Week Taper' uses pooled SE.
The stratification factor, starting prednisone dose (<=30mg/day, >30mg/day) was included in the model.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factor applied at Baseline.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ef_sum_ah136.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ef_sum_ah136_IT.out
13SEP2016 16:13

表 2.7.3.7.2-23 再発までの期間における MRA-SC Q2W 群と MRA-SC QW 群の差 (WA28119試験)

Summary and Analysis of Time to First GCA Disease Flare Following Clinical Remission, by Treatment Group, ITT Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Patients included in analysis	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
Patients with event (%)	34 (68.0%)	25 (49.0%)	23 (23.0%)	13 (26.5%)
Patients without event (%)	16 (32.0%)	26 (51.0%)	77 (77.0%)	36 (73.5%)
Time to event (days)				
Median	165.0	295.0	NE	NE
95% CI for Median	(135.0, 227.0)	(224.0, NE)	NE	NE
25% and 75%-ile	92.0, NE	141.0, NE	NE	183.0, NE
Range	1 to 365	1 to 362	1 to 367	1 to 364
Stratified Analysis (vs TCZ QW + 26 WK Taper)				
Hazard Ratio				1.24
95% CI				(0.63, 2.44)

Patients who were never in remission are censored at Day 1.

Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

The treatment groups are compared using a Cox proportional hazards model adjusting for the stratification factor of starting prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_fl_km_ah136.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_fl_km_ah136_IT.out
13SEP2016 17:31

2.7.3.7.3 MRA632JP 試験と WA28119試験

表 2.7.3.7.3-1 MRA632JP 試験と WA28119試験の主な試験デザインの比較

試験番号	MRA632JP	WA28119	
選択基準	年齢	12歳以上	50歳以上
	疾患の検査と症状	<p>血管炎症候群の診療ガイドライン（JCS 2008）にて高安動脈炎と診断された患者</p> <p>(1) 確定診断は画像診断（DSA, CT, MRA）によって行う。</p> <p>(2) 若年者で血管造影によって大動脈とその第一次分枝に閉塞性あるいは拡張性病変を多発性に認めた場合は、炎症反応が陰性でも高安動脈炎（大動脈炎症候群）を第1に疑う。</p> <p>(3) これに炎症反応が陽性ならば、高安動脈炎（大動脈炎症候群）と診断する。</p> <p>(4) 上記の自覚症状、検査所見を有し、下記の鑑別疾患を否定できるもの。</p> <p>①動脈硬化症 ②炎症性腹部大動脈瘤 ③血管性パーチェット病 ④梅毒性中膜炎 ⑤側頭動脈炎（巨細胞性動脈炎）⑥先天性血管異常 ⑦細菌性動脈瘤</p>	<p>(1) 又は (2) のいずれかで巨細胞性動脈炎と診断され、かつ (3) 又は (4) のいずれかの症状が認められる患者。</p> <p>(1) 巨細胞性動脈炎を特徴づける側頭動脈の生検所見</p> <p>(2) 血管造影又は断層像（MRA, CTA, PET-CT など）による大型血管炎の診断</p> <p>(3) 明確な巨細胞性動脈炎の頭部の症状（新規発症の限局的な頭痛、頭皮の圧痛、側頭動脈痛又は脈拍減弱、局所貧血に関連した失明、その他咀嚼時の口や顎の原因不明の痛み）</p> <p>(4) PMR の症状（炎症性の朝のこわばりを伴う肩及び／又は腰帯痛）</p>
	ESR	—	過去に ESR が50 mm/時以上であった。
	疾患の重症度	0.2 mg/kg/日以上 の副腎皮質ステロイドによる治療にも関わらず、登録前12週間以内に高安動脈炎の再発を認める患者	<p>以下に示す新規発症又は再発の活動性疾患があり、ベースラインの6週以内に疾患活動性が認められる（頭部の症状又は PMR の症状や徴候があり、ESR が30 mm/時以上又は CRP が1 mg/dL 以上）患者</p> <p>新規発症の患者：ベースライン前の6週以内に新たに巨細胞性動脈炎と診断</p> <p>再発の患者：ベースラインの6週より以前に巨細胞性動脈炎と診断され、40 mg/日以上 の副腎皮質ステロイドによる2週間以上の連続した治療歴がある</p>
併用薬（副腎皮質ステロイド）の投与方法	<p>【スクリーニング期間】</p> <p>登録前12週間以内に0.2 mg/kg/日以上で高安動脈炎の再発を認め、その再発時の倍量以上で寛解を1週間以上維持</p> <p>【二重盲検期間】</p> <p>治験薬初回投与後4週間は減量しない。それ以降は以下の計算式に従い、毎週10%ずつ減量。0.1 mg/kg/日以上は減量しない。</p>	<p>【二重盲検期間】</p> <p>副腎皮質ステロイド投与には、非盲検期間と盲検期間を設定した。副腎皮質ステロイドの非盲検期間では、疾患活動性とその病状から20～60 mg/日から投与を開始し、20 mg/日まで減量し、非盲検期間に移動した。引き続いて、副腎皮質ステロイドの盲検期間では、治験実施計画書に規定した方法により0 mg まで漸減投与した。ただし、治験薬の二重盲検期間中の再発時、又は疾患活動性の持続によって副腎皮質ステロイドを予定どおり漸減</p>	

試験番号	MRA632JP	WA28119
	<p>N 週目の投与量 = 治験薬初回投与時の用量 × 0.9^(N-3)</p> <p>【非盲検期間】 治験責任医師又は治験分担医師の裁量によって調整して投与。</p>	<p>投与できなかった時は、その時期が副腎皮質ステロイドの非盲検期間中の場合は漸減投与を中止し、医師の裁量により副腎皮質ステロイドを調整し、副腎皮質ステロイドの盲検期間中の場合も漸減投与を中止し、副腎皮質ステロイドの非盲検期間下に移行して20 mg/日以上へ増量後、医師の裁量により調整した。</p> <p>【非盲検期間】 治験責任医師の裁量によって調整して投与。</p>
<p>主要評価項目</p>	<p>高安動脈炎の再発までの期間（二重盲検期間）</p>	<p>52週時点での寛解維持割合を指標とした、26週間の副腎皮質ステロイド漸減投与下でのプラセボに対する、26週間の副腎皮質ステロイド漸減投与下での MRA-SC の有効性</p>
<p>副次的評価項目</p>	<p>【二重盲検期間】</p> <ul style="list-style-type: none"> ・ Kerr の定義による高安動脈炎の再発までの期間 ・ 臨床症状による高安動脈炎の再発までの期間 ・ 高安動脈炎の再発の各大項目の発現 ・ 再発時又は二重盲検期間の最終観察時の副腎皮質ステロイド投与量 ・ 画像評価のベースラインからの変化 <p>【非盲検期間】</p> <ul style="list-style-type: none"> ・ 高安動脈炎の再発率 ・ 副腎皮質ステロイド投与量の推移など 	<p>< 主要な副次的評価項目 ></p> <ul style="list-style-type: none"> ・ 52週時点での寛解維持割合を指標とした、52週間の副腎皮質ステロイド漸減投与下でのプラセボに対する、26週間の副腎皮質ステロイド漸減投与下での MRA-SC の有効性 <p>< その他の副次的評価項目 ></p> <ul style="list-style-type: none"> ・ 再発までの期間 ・ 副腎皮質ステロイド累積投与量など
<p>再発の定義</p>	<p>5つの大項目のうち2項目以上で再発の徴候ありと判定された場合（一部例外あり）</p> <ol style="list-style-type: none"> ①客観的評価による全身症状 ②主観的評価による全身症状 ③炎症マーカーの上昇 ④血管病変 ⑤臓器病変を伴う虚血症状 	<p>治験責任医師によって判断され、以下の疾患症状や徴候の再発がある状態及び／又は ESR が30 mm/時以上。</p> <ul style="list-style-type: none"> ・ 熱（38°C 又は100.4°F 以上） ・ PMR の症状（肩及び／又は腰帯の朝のこわばり及び／又は痛み） ・ 限局的な頭痛、側頭動脈痛、頭皮の圧痛 ・ 動脈炎性前方虚血性視神経症（A-AION）による急性又は亜急性の失明、一過性の視界不良（一般的に単眼又は一度に少なくとも一方の眼に影響し、潜在的に両眼に影響する）のような視覚に関する症状や徴候 ・ 顎や口の痛み ・ 新規又は悪化した四肢の間欠性跛行 ・ 巨細胞性動脈炎又は PMR の再発と一致して治験責任医師によって判断されるその他の特徴
<p>寛解の定義</p>	<p>上記の再発の定義の5つの大項目のうちすべての症状・徴候が認められない状態（スクリーニング期間のみ）</p>	<p>再発がなく、CRP が正常化（1 mg/dL 未満）の状態。</p>

アクテムラ皮下注162 mg シリンジ・AI (トシリズマブ (遺伝子組換え))

[大型血管炎]

第2部 (モジュール2) : CTD の概要 (サマリー)

2.7.4 臨床的安全性

中外製薬株式会社

略語一覧

略語	英名	和名
AESI	adverse events of special interest	特に注目すべき有害事象
AI	auto injector	オートインジェクター
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
AST	aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
CDS	core data sheet	企業中核データシート
CTCAE	Common Terminology Criteria for Adverse Events	有害事象共通用語規準
DIBD	development international birthday date	開発国際誕生日
DLP	Data Lock Point	データロックポイント
DMARD (s)	disease modifying anti-rheumatic drug (s)	疾患修飾抗リウマチ薬
DSR	drug safety report	医薬品安全性評価報告書
Fab	fragment, antigen binding	抗原結合性断片
HDL	high density lipoprotein	高比重リポ蛋白
IBD	international birth date	国際誕生日
IgE	immunoglobulin E	免疫グロブリン E
IL-6	interleukin 6	インターロイキン6
IV	Intravenous	静脈内
LDL	low density lipoprotein	低比重リポ蛋白
MAH	marketing authorization holder	医薬品市販承認取得者
MedDRA	Medical dictionary for regulatory activities	ICH 国際医薬用語集
MRA	—	トシリズマブ（遺伝子組換え）の略号
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events	米国国立がん研究所－有害事象共通用語規準
PBRER	periodic benefit-risk evaluation report	定期的ベネフィット・リスク評価報告
PFS	pre filled syringe	プレフィルドシリンジ
pJIA	polyarticular juvenile idiopathic arthritis	多関節に活動性を有する若年性特発性関節炎
PSUR	periodic safety update report	定期的安全性最新報告
PT	preferred terms	基本語
QW	every week	週に1回
Q2W	every 2 weeks	2週に1回
RA	rheumatoid arthritis	関節リウマチ
RMP	risk management plan	医薬品リスク管理計画書
SC	subcutaneous	皮下注射
SC 法	screening method	スクリーニング法
sJIA	systemic juvenile idiopathic arthritis	全身型若年性特発性関節炎
SJS	Stevens-Johnson syndrome	スティーブンス・ジョンソン症候群
SMQ	Standard MedDRA Query	MedDRA 標準検索式
SOC	system organ class	器官別大分類
TCZ	Tocilizumab	トシリズマブ

略語	英名	和名
ULN	upper limit of normal	基準値上限
100 PYs	100 patient years	100人・年

目次

	頁
2.7.4 臨床的安全性.....	6
2.7.4.1 医薬品への曝露.....	6
2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述.....	6
2.7.4.1.2 全般的な曝露状況.....	10
2.7.4.1.2.1 安全性評価例数.....	10
2.7.4.1.2.2 投与期間.....	11
2.7.4.1.2.3 中止.....	15
2.7.4.1.3 治験対象集団の人口統計学的特性及びその他の特性.....	17
2.7.4.2 有害事象.....	18
2.7.4.2.1 有害事象の解析.....	18
2.7.4.2.1.2 比較的良好にみられる有害事象.....	21
2.7.4.2.1.2.1 MRA632JP 試験.....	21
2.7.4.2.1.2.2 WA28119 試験.....	24
2.7.4.2.1.3 重症度別有害事象.....	40
2.7.4.2.1.3.1 MRA632JP 試験.....	40
2.7.4.2.1.3.2 WA28119 試験.....	40
2.7.4.2.1.4 発現時期別有害事象.....	41
2.7.4.2.1.4.1 MRA632JP 試験.....	41
2.7.4.2.1.4.2 WA28119 試験.....	43
2.7.4.2.1.5 死亡.....	43
2.7.4.2.1.6 その他の重篤な有害事象.....	43
2.7.4.2.1.7 その他の重要な有害事象.....	54
2.7.4.2.1.7.1 中止に至った有害事象.....	54
2.7.4.2.1.7.2 投与間隔の延長又は休薬に至った有害事象.....	63
2.7.4.2.1.7.3 投与部位反応.....	78
2.7.4.2.1.7.4 特に注目すべき有害事象 (AESI).....	81
2.7.4.2.1.8 器官別又は症候群別有害事象の解析.....	86
2.7.4.2.2 個別有害事象の文章による説明.....	90
2.7.4.3 臨床検査値の評価.....	90
2.7.4.3.1 白血球数, 好中球数及びリンパ球数.....	90
2.7.4.3.2 血小板数.....	91
2.7.4.3.3 肝機能関連項目.....	91
2.7.4.3.4 脂質関連項目.....	92
2.7.4.3.5 抗トシリズマブ抗体.....	93
2.7.4.4 バイタルサイン, 身体的所見及び安全性に関連する他の観察項目.....	93

2.7.4.4.1	バイタルサイン.....	93
2.7.4.4.2	心電図.....	94
2.7.4.5	特別な患者集団及び状況下における安全性.....	94
2.7.4.5.1	内因性要因.....	94
2.7.4.5.2	外因性要因.....	94
2.7.4.5.3	薬物相互作用.....	95
2.7.4.5.4	妊娠及び授乳時の使用.....	95
2.7.4.5.5	過量投与.....	95
2.7.4.5.6	薬物乱用.....	95
2.7.4.5.7	離脱症状及び反跳現象.....	95
2.7.4.5.8	自動車運転及び機械操作に対する影響又は精神機能の障害.....	95
2.7.4.5.9	RA に対して実施された臨床試験.....	95
2.7.4.5.9.1	RA 患者を対象とした国内第 I/II 相試験 (MRA227JP 試験).....	95
2.7.4.5.9.2	RA 患者を対象とした国内第 III 相試験 (MRA229JP 試験).....	96
2.7.4.5.9.3	RA 患者を対象とした第 III 相二重盲検並行群間比較試験 (非劣性試験) 及びそれに続く非盲検延長試験 (WA22762 試験).....	96
2.7.4.5.9.4	RA 患者を対象とした第 III 相プラセボ対照二重盲検並行群間比較試験 及びそれに続く非盲検延長試験 NA25220.....	97
2.7.4.6	市販後データ.....	97
2.7.4.6.1	新医療用医薬品安全性定期報告書 (皮下注第 6 回, 調査単位期間: 2015 年 4 月 11 日~2016 年 4 月 10 日).....	98
2.7.4.6.1.1	通常の医薬品安全性監視活動.....	98
2.7.4.6.1.2	追加の医薬品安全性監視活動.....	99
2.7.4.6.1.3	リスク最小化計画実施結果について.....	100
2.7.4.6.2	PBRER からの安全性情報.....	100
2.7.4.6.2.1	PBRER の概要.....	100
2.7.4.6.2.2	PBRER からの検討結果.....	103
2.7.4.7	参考文献.....	103
2.7.4.8	付録.....	104

2.7.4 臨床的安全性

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

(1) 臨床試験の概要

大型血管炎患者においてトシリズマブ皮下注製剤（以降、本剤又は MRA-SC）162 mg を1回/1週の間隔で皮下投与した際の安全性は、高安動脈炎患者を対象とした国内第 III 相臨床試験（以降、MRA632JP 試験）及び巨細胞性動脈炎患者を対象とした海外第 III 相臨床試験（以降、WA28119試験）を評価資料として評価した。MRA632JP 試験では、まず、二重盲検期間に副腎皮質ステロイド漸減投与下で、プラセボ群とトシリズマブ162 mg/週皮下注群（以降、MRA-SC 群）を比較した。二重盲検期間の後、全例が非盲検期間に移行し、トシリズマブ162 mg/週皮下注の投与を受けた。長期投与時の安全性は、二重盲検期間に MRA-SC 群に割り付けられた被験者と、非盲検期間に MRA-SC を投与された被験者を「二重盲検期間及び非盲検期間（以降、全期間）の本剤全投与例」として、それらの被験者の全期間の本剤投与期間のデータを集計し、安全性を評価した。次に、WA28119試験では、26週間又は52週間の副腎皮質ステロイド漸減投与下のプラセボ群（以降、プラセボ+26週群又はプラセボ+52週群）と26週間の副腎皮質ステロイド漸減投与下のトシリズマブ162 mg/週群又は162 mg/2週群（以降、MRA-SC QW 群又は MRA-SC Q2W 群）を比較した。

更に、本剤を1週間隔で皮下投与した際の安全性の参考資料として、関節リウマチ（以降、RA）患者を対象とした国内第 I/II 相臨床試験（以降、MRA227JP 試験）、国内第 III 相試験（以降、MRA229JP 試験）並びに海外第 III 相臨床試験（以降、WA22762試験及び NA25220試験）を用いた。

安全性評価に用いた臨床試験一覧を表 2.7.4.1.1-1に示す。

表 2.7.4.1.1-1 安全性評価に用いた臨床試験一覧

国内／海外	相	試験番号 評価/参考 資料番号	デザイン	対象	投与期間	投与群	安全性評価例
国内	III	MRA632JP 評価資料 5.3.5.1-1 5.3.5.1-7	多施設共同 【二重盲検期間】 ランダム化二重盲 検 【非盲検期間】 非盲検	高安動 脈炎患 者	【二重盲検期間】 高安動脈炎の再発が認めら れた被験者は再発が認めら れた日から4週間以内に実施 された二重盲検期間の最終 観察日までとし、残りの被 験者は再発した被験者数が 計19例に達した時点から4週 間以内に実施された二重盲 検期間最終観察日までとし た。 【非盲検期間】 二重盲検期間終了後から製 造販売承認が得られるまで (現在実施中)	【二重盲検期間】 プラセボ皮下注群 162 mg/週皮下注群 【非盲検期間】 162 mg/週皮下注	【二重盲検期間】 18例 18例 【全期間の本剤全 投与例】 36例
海外	III	WA28119 評価資料 5.3.5.1-3	多施設共同 【二重盲検期間】 ランダム化二重盲 検 【非盲検期間】 非盲検	巨細胞 性動脈 炎患者	【二重盲検期間】 52週間 【非盲検期間】 104週間 (現在実施中)	【二重盲検期間】* プラセボ+26週群 プラセボ+52週群 162 mg/週皮下注群 162 mg/2週皮下注群	【二重盲検期間】 50例 51例 100例 49例
国内	I/II	MRA227JP 参考資料 5.3.5.4-1	多施設共同 非盲検 個体間漸増	RA 患 者	【第I期】 81 mg/2週群, 162 mg/2週群 : 単回投与後3週間観察 【第II期】 81 mg/2週群, 162 mg/2週群 : 6週間 (3回投与後2週間 観察) 162 mg/週群 : 3週間 (3回投与後1週間 観察) 【第III期】 全群: 6カ月間	81 mg/2週皮下注群 162 mg/2週皮下注群 162 mg/週皮下注群	8例 12例 12例
国内	III	MRA229JP 参考資料 【二重盲検 期間】 5.3.5.4-2 【全期間】 5.3.5.4-3	多施設共同 【二重盲検期間】 ランダム化二重盲 検 【非盲検期間】 非盲検	RA 患 者	【二重盲検期間】 24週間 【非盲検期間】 84週間	【二重盲検期間】 8 mg/kg/4週点滴静注 群 162 mg/2週皮下注群 【非盲検期間】 162 mg/2週皮下注 非盲検期間では、二 重盲検期間完了例の 全例で、原則として 162 mg/2週皮下注 を実施した。被験 者の臨床症状や臨床 検査値の推移に応じ て、投与間隔の短縮 及び延長を可とし た。	【二重盲検期間】 173例 173例 【非盲検期間】 319例 (内、 162 mg/週24例)

国内／海外	相	試験番号 評価/参考 資料番号	デザイン	対象	投与期間	投与群	安全性評価例
海外	III	WA22762 参考資料 【二重盲検 期間】 5.3.5.4-4 【全期間】 5.3.5.4-5	多施設共同 【二重盲検期間】 ランダム化二重盲 検 【非盲検期間】 ランダム化非盲検	RA 患 者	【二重盲検期間】 24週間 【非盲検期間】 72週間	【二重盲検期間】 Group A 162 mg/週皮 下注 Group B 8 mg/kg/4週 点滴静注 【非盲検期間】 Group A から再割付 Group A1 162 mg/週皮 下注 Group A2 8 mg/kg/4週 点滴静注 Group B から再割付 Group B1 8 mg/kg/4週 点滴静注 Group B2 162 mg/週 皮下注	【二重盲検期間】 631例 631例 【非盲検期間】 524例 48例 377例 186例
海外	III	NA25220 参考資料 【二重盲検 期間】 5.3.5.4-6 【全期間】 5.3.5.4-7	多施設共同 【二重盲検期間】 ランダム化二重盲 検 【非盲検期間】 非盲検	RA 患 者	【二重盲検期間】 24週間 【非盲検期間】 72週間	【二重盲検期間】 Group A 162 mg/2週 皮下注 Group B プラセボ皮 下注 【非盲検期間】 Group A, Group B とも162 mg/2週皮下 注 二重盲検期間の12 週以降には、被験 者の臨床症状に応 じて、救済治療と して投与間隔を1週 に短縮することを 可とした。救済治 療を受けた被験者 は、189例であっ た。	【二重盲検期間】 437例 218例 【非盲検期間】 453例

* プラセボ+26週群：プラセボ/週投与と26週間の副腎皮質ステロイド漸減投与
 プラセボ+52週群：プラセボ/週投与と52週間の副腎皮質ステロイド漸減投与
 162 mg/週皮下注群：162 mg/週投与と26週間の副腎皮質ステロイド漸減投与
 162 mg/2週皮下注群：162 mg/2週投与と26週間の副腎皮質ステロイド漸減投与

MRA632JP 試験及び WA28119試験の非盲検期間は現在も継続中である。MRA632JP 試験では中止例を除く全例が非盲検期間で本剤を52週間投与終了した2016年11月10日でカットオフしたデータを集計した。WA28119試験では、最終症例が初回投与後52週の観察を完了した2016年4月11日でカットオフしたデータを集計した。

本申請では、トシリズマブ（以降、本薬）の特に注目すべき有害事象（AESI）として、感染症、治験薬を介して起こった可能性のある感染性病原体の伝播、ビリルビンの上昇又は臨床的黄疸を伴うアラニンアミノトランスフェラーゼ（以降、ALT）又はアスパラギン酸アミノトランスフェラーゼ（以降、AST）のいずれかの上昇、消化管穿孔及び関連疾患、アナフィラキシ

一、出血、肝臓疾患、脳卒中、心筋梗塞／急性冠症候群、悪性腫瘍、脱髄関連疾患について検討した。更に、本剤は皮下注射用の製剤であることから、投与部位反応に注目した。

(2) 安全性の評価方法

有害事象は、MRA632JP 試験及び WA28119試験の二重盲検期間では初回投与から最終観察まで、MRA632JP 試験の非盲検期間ではカットオフ日までに発現した事象を収集した。

有害事象は、治験薬が投与された被験者に生じたあらゆる好ましくない、又は意図しない徴候（臨床検査値の異常を含む）、症状又は病気をいい、当該治験薬との因果関係の有無は問わない。なお、MRA632JP 試験では原疾患の悪化（高安動脈炎の再発、再発以外の徴候の悪化）、WA28119試験では巨細胞性動脈炎に関連する事象については有害事象として取り扱わなかった。ただし、MRA632JP 試験では治験薬との因果関係が否定できない場合又は死亡に至った場合、WA28119試験では重篤な有害事象の場合は、有害事象として取り扱った。

有害事象について、症例報告書に記載された事象名を、MRA632JP 試験及び WA28119試験ではそれぞれ MedDRA Ver.17.1及び Ver.19.0を基に、基本語（PT）に読み替え集計した。

有害事象の重篤性は「重篤でない」、 「重篤である」の2段階で評価した。「重篤である」と判断する基準は、死亡、死亡につながるおそれのあるもの、病院又は診療所への入院又は入院期間の延長が必要とされるもの、障害、障害につながるおそれのあるもの、上記に準じて重篤であるもの、後世代における先天性の疾病又は異常とした。

有害事象の重症度は、MRA632JP 試験においては「高度（働くことができない、又は通常の日常活動を行うことができなくなるような障害）」、「中等度（日常活動量を減少させる、又は日常活動に影響を及ぼす程度の不快感がある）」及び「軽度（不快感の自覚はあるが、通常の日常活動に支障はない）」の3段階で判定した。WA28119試験においては National Cancer Institute Common Terminology Criteria for Adverse Events（以降、NCI-CTCAE）v4.0の有害事象重症度分類で判定した。NCI-CTCAE に記載されていない有害事象の重症度は、表 2.7.4.1.1-2で判定した。

表 2.7.4.1.1-2 有害事象の重症度分類スケール（WA28119試験）

グレード	重症度
1	軽症；症状がない、又は軽度の症状がある；臨床所見又は検査所見のみ；治療を要さない
2	中等症；最小限／局所的／非侵襲的治療を要する；年齢相応の身の回り以外の日常生活動作の制限 ^a
3	重症又は医学的に重大であるが、直ちに生命を脅かすものではない；入院又は入院期間の延長を要する；活動不能／動作不能；身の回りの日常生活動作の制限 ^{b,c}
4	生命を脅かす又は緊急処置を要する ^d
5	有害事象による死亡 ^d

a 身の回り以外の日常生活動作とは、食事の準備、日用品や衣服の買い物、電話の使用、金銭の管理等をさす。

b 身の回りの日常生活動作とは、寝たきりではない患者の入浴、着衣・脱衣、食事の摂取、トイレの使用、薬の内服等をいう。

c 事象が「重大な医学的事象」と評価された場合、重篤な有害事象として報告しなければならない。

d グレード4及び5の事象は、重篤な有害事象の定義に従って、重篤な有害事象として報告しなければならない。

治験薬との因果関係については、「あり」又は「なし」で判定し、「あり」の有害事象を「副作用」とした。WA28119試験では副腎皮質ステロイドとの因果関係も「あり」又は「なし」で判定した。

転帰については、MRA632JP 試験では「回復」、「軽快」、「回復したが後遺症あり」、「未回復」及び「死亡」の5段階で判定した。WA28119試験では、これらに「不明」を加えた6段階で判定した。

有害事象の発現例数の集計においては、同一被験者に同一事象が複数回発現した場合は、同一事象を1件とし、発現時期は最も早い時期を、因果関係は「あり」を、重症度は最も重い判定を代表値とした。観察期間あたりの有害事象発現件数 (Events /100 Patient Years, 以降, Events /100 PYs) は、有害事象ののべ発現件数を各被験者の観察期間の総合計で割ったものに100をかけて算出した。

臨床検査値異常変動は、社内で規定した臨床検査値異常変動範囲から外れ、かつベースラインからの変化率 (増加又は減少) が検査項目ごとの基準を超えた場合は異常変動とした。MRA632JP 試験では、その臨床検査値異常により治験薬の投与方法の変更 (中止/休薬) 又はその他の処置があった場合、臨床検査値異常と臨床症状との関連、重篤な有害事象との関連を考慮して治験責任 (分担) 医師が有害事象とするかを判定した。WA28119試験では臨床症状を伴った場合、治験薬の投与方法の変更に至った場合、医療処置に至った場合、及び治験責任医師が臨床的に重要と判断した場合に有害事象とされた。

2.7.4.1.2 全般的な曝露状況

2.7.4.1.2.1 安全性評価例数

(1) MRA632JP 試験

MRA632JP 試験の安全性評価例数を表 2.7.4.1.2.1-1に示す。安全性評価例は割付後治験薬が1回でも投与された被験者とし、二重盲検期間の安全性の解析はプラセボ群18例、MRA-SC 群18例を対象として、全期間の本剤全投与例は36例を対象として実施した。

表 2.7.4.1.2.1-1 安全性評価例数 (MRA632JP 試験)

二重盲検期間			全期間 (二重盲検期間 + 非盲検期間) 本剤全投与例		
投与群	安全性評価例	完了例*	投与薬剤	安全性評価例	継続例†
プラセボ群	18例	18例	本剤 (162 mg/週)	36例	29例
MRA-SC 群 (162 mg/週)	18例	18例			

* 完了例=途中中止しなかった例数, †継続例=2016年11月10日のカットオフ時点で継続していた被験者数
[5.3.5.1-1 表 10.1-1, 表 11.1-1及び表 2.7.4.1.2.2-3を改変]

(2) WA28119試験

WA28119試験の安全性評価例数を表 2.7.4.1.2.1-2に示す。安全性評価例は割付後治験薬が1回でも投与された被験者とし、安全性の解析はプラセボ+26週群50例、プラセボ+52週群51例、MRA-SC QW 群100例、MRA-SC Q2W 群49例を対象として実施した。

表 2.7.4.1.2.1-2 安全性評価例数 (WA28119試験)

二重盲検期間		
投与群	安全性評価例	完了例*
プラセボ+26週群	50例	41例
プラセボ+52週群	51例	46例
MRA-SC QW 群	100例	82例
MRA-SC Q2W 群	49例	40例

* 完了例=52週まで完了した被験者 [5.3.5.1-3 Table 6, Table 8を改変]

2.7.4.1.2.2 投与期間

(1) MRA632JP 試験

MRA632JP 試験の二重盲検期間、全期間の本剤全投与例における治験薬の投与状況の集計を表 2.7.4.1.2.2-1及び表 2.7.4.1.2.2-2に示す。二重盲検期間の投与期間の中央値（最小値～最大値）はプラセボ群で12.86週（8.0～55.9週），MRA-SC 群で19.00週（5.0～52.0週）であった（表 2.7.4.1.2.2-1）。

MRA632JP 試験の全期間の本剤全投与例において本剤の投与期間の中央値（最小値～最大値）は70.43週（8.1～108.0週）であり（表 2.7.4.1.2.2-2），投与期間が24週未満だった被験者は4例，24週を超え52週未満だった被験者は1例，52週以上であった被験者は31例であった（表 2.7.4.1.2.2-3）。

表 2.7.4.1.2.2-1 投与状況 (MRA632JP 試験-二重盲検期間)

ext01_sp Extent of Exposure to Trial Drug
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Observation Period (weeks)		
n	18	18
mean	17.13	22.94
std	12.27	14.75
min	8.1	5.1
median	13.00	19.07
max	55.9	52.3
Treatment Period (weeks)		
n	18	18
mean	17.02	22.75
std	12.30	14.76
min	8.0	5.0
median	12.86	19.00
max	55.9	52.0
Total Cumulative Dose (mg)		
n	18	18
mean	0.0	3600.0
std	0.0	2307.5
min	0	810
median	0.0	2997.0
max	0	8100
Number of Administration Category		
n	18	18
5 - 8	1 (5.6%)	3 (16.7%)
9 - 12	6 (33.3%)	1 (5.6%)
13 - 16	7 (38.9%)	4 (22.2%)
17 - 20	1 (5.6%)	2 (11.1%)
21 - 24	0	2 (11.1%)
25 - 28	1 (5.6%)	1 (5.6%)
29 - 32	0	2 (11.1%)
37 - 40	1 (5.6%)	0
45 - 48	0	2 (11.1%)
49 - 52	0	1 (5.6%)
53 - 56	1 (5.6%)	0
Treatment Compliance (%)		
n	18	18
mean	98.64	97.23
std	3.95	6.34
min	84.4	75.0
median	100.00	100.00
max	100.0	100.0
Treatment Compliance Category (%)		
n	18	18
75% -< 100%	3 (16.7%)	5 (27.8%)
100%	15 (83.3%)	13 (72.2%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/ext01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/ext01_sp.out
 28DEC2015 18:16

表 2.7.4.1.2.2-2 投与状況 (MRA632JP 試験-全期間の本剤全投与例)

ext01_mt_sp Study Drug Exposure
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)	
Observation Period (week)	
n	36
mean	66.72
std	24.22
min	8.3
median	70.14
max	107.1
Treatment Period (week)	
n	36
mean	66.92
std	24.42
min	8.1
median	70.43
max	108.0
MRA-SC Total Cumulative Dose (mg)	
n	36
mean	10579.5
std	3905.7
min	1296
median	11421.0
max	17496
Treatment Compliance (%)	
n	36
mean	97.71
std	4.01
min	85.1
median	100.00
max	100.0
Treatment Compliance Category (%)	
n	36
75% -< 100%	15 (41.7%)
100%	21 (58.3%)

Treatment duration is the date of the last dose of MRA-SC minus the date of the first dose plus seven day.

Treatment Compliance is the number of doses actually received divided by the expected number of doses.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/ext01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/ext01_mt_sp.out
 12JAN2017 17:12

表 2.7.4.1.2.2-3 時期別完了及び中止例数 (MRA632JP 試験-全期間の本剤全投与例)

sumdsp_mt_sp Disposition of Patients
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

	MRA-SC 162mg/W Total (N=36)
No. With at Least One Dose	36 (100.0%)
No. Withdrawn During 24 weeks Treatment	4 (11.1%)
No. Completing 24-week Treatment	32 (88.9%)
No. Withdrawn During 52 weeks Treatment	5 (13.9%)
No. Completing 52-week Treatment	31 (86.1%)
Total Withdrawn From Treatment	7 (19.4%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/sumdsp.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/sumdsp_mt_sp.out
 12JAN2017 17:17

Page 1 of 1

[5.3.5.1-7 表 11.1-1を再掲]

(2) WA28119試験

WA28119試験の二重盲検期間における治験薬の投与状況の集計を表 2.7.4.1.2.2-4に示す。二重盲検期間の投与期間の中央値（最小値～最大値）はプラセボ+26週群で358.0日（44～368日），プラセボ+52週群で358.0日（43～369日），MRA-SC QW 群で358.0日（9～365日），MRA-SC Q2W 群で358.0日（6～371日）であった（表 2.7.4.1.2.2-4）。なお，WA28119試験の表中，プラセボをPBO，MRA-SCをTCZで表示した。

表 2.7.4.1.2.2-4 投与状況 (WA28119試験-二重盲検期間)

Study Treatment Exposure – SC Double-blind study drug, Safety Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Treatment Duration (D)				
n	50	51	100	49
Mean (SD)	324.0 (79.4)	331.6 (83.4)	317.2 (96.7)	324.3 (82.0)
Median	358.0	358.0	358.0	358.0
Min - Max	44 - 368	43 - 369	9 - 365	6 - 371
Treatment Duration Category (D)				
n	50	51	100	49
0 - 91	3 (6.0%)	4 (7.8%)	8 (8.0%)	1 (2.0%)
92 - 183	1 (2.0%)	0	5 (5.0%)	5 (10.2%)
184 - 274	4 (8.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
275 - 365	41 (82.0%)	43 (84.3%)	84 (84.0%)	38 (77.6%)
>365	1 (2.0%)	3 (5.9%)	0	3 (6.1%)
Dose Intensity (%)				
n	50	51	100	49
Mean (SD)	98.5 (3.4)	98.0 (3.3)	97.9 (4.0)	98.7 (2.7)
Median	100.0	100.0	100.0	100.0
Min - Max	85 - 100	86 - 100	77 - 100	88 - 100
Number of doses				
n	50	51	100	49
Mean (SD)	46.3 (11.1)	47.1 (11.7)	45.1 (13.7)	46.5 (11.6)
Median	52.0	51.0	51.5	52.0
Min - Max	7 - 53	7 - 53	2 - 53	2 - 53
Total cumulative dose (mg)				
n	50	51	100	49
Mean (SD)	0.0 (0.0)	0.0 (0.0)	7304.6 (2215.4)	3785.5 (941.0)
Median	0.0	0.0	8343.0	4212.0
Min - Max	0 - 0	0 - 0	324 - 8586	162 - 4374
Missed Doses				
n	50	51	100	49
No missed dose	37 (74.0%)	29 (56.9%)	58 (58.0%)	36 (73.5%)
One missed dose	6 (12.0%)	12 (23.5%)	24 (24.0%)	5 (10.2%)
Two missed doses	1 (2.0%)	0	6 (6.0%)	4 (8.2%)
Three missed doses	1 (2.0%)	4 (7.8%)	3 (3.0%)	2 (4.1%)
Four missed doses	3 (6.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
At least five missed doses	2 (4.0%)	2 (3.9%)	5 (5.0%)	1 (2.0%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses multiplied by 100.

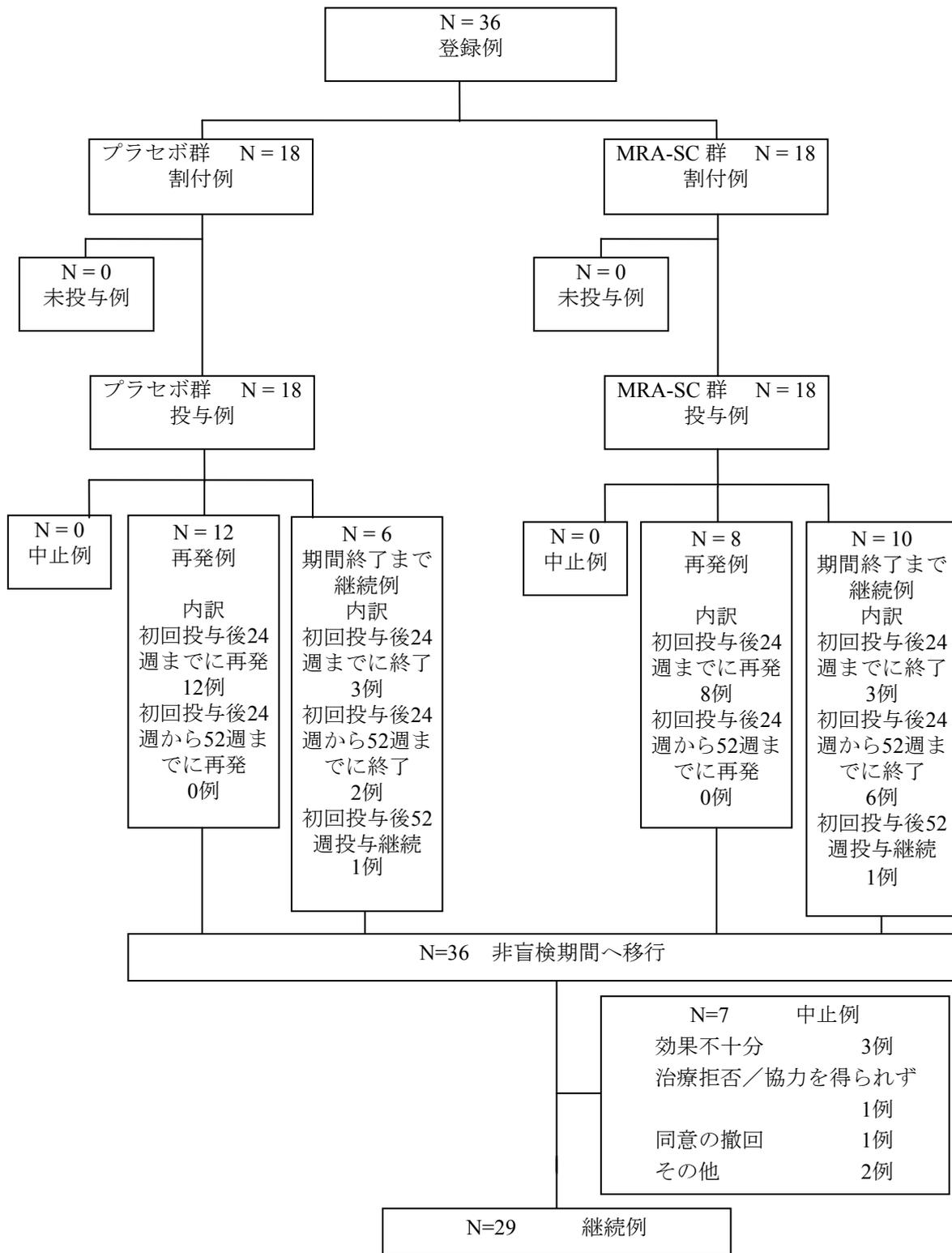
Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ex_sd.sas / Output:
/opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ex_sd_SE.out
11JUL2016 21:40 (PDRD)

2.7.4.1.2.3 中止

(1) MRA632JP 試験

二重盲検期間及び非盲検期間における被験者の内訳を [図 2.7.4.1.2.3-1](#) に示す。治験薬投与前又は二重盲検期間中に治験を中止した被験者はいなかった。非盲検期間に中止となった被験者は7例 (19.4%) であった。中止例の内訳は、効果不十分3例、治療拒否/協力を得られず1例、同意の撤回1例及びその他 (併用禁止療法が必要となったため) 2例であった。

図 2.7.4.1.2.3-1 被験者の内訳 (MRA632JP 試験)



[5.3.5.1-7 図 5-1を再掲]

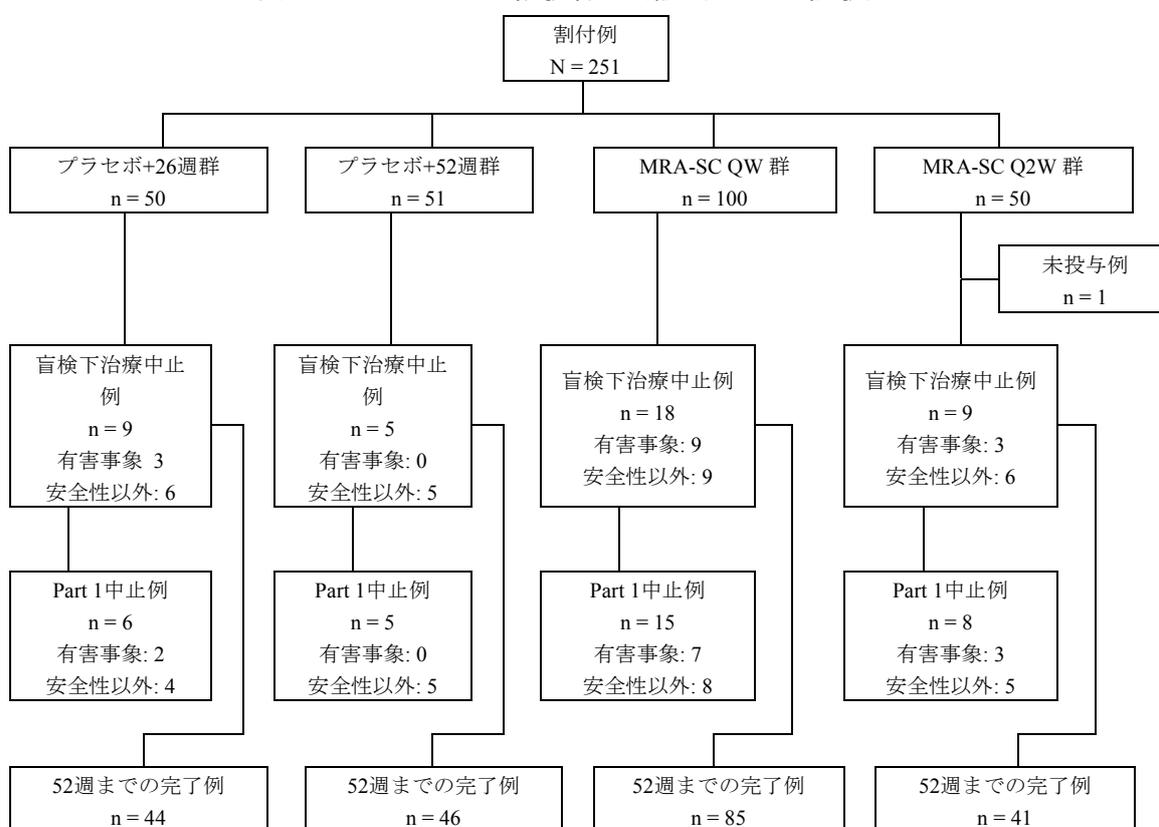
(2) WA28119試験

二重盲検期間における被験者の内訳を図 2.7.4.1.2.3-2に示す。治験薬投与前に中止した被験者は MRA-SC Q2W 群に1例であった。治験薬投与を中止した被験者は二重盲検期間の52週間 (Part 1) の参加を継続し、盲検下の副腎皮質ステロイド漸減レジメンを継続できるとして

た。被験者が再発した場合又は規定された副腎皮質ステロイド漸減レジメンを継続できない場合は、試験参加は継続し医師の処方する用量で副腎皮質ステロイドの治療を受けることができるとしていた。二重盲検期間中に、治験薬投与を中止した被験者はプラセボ+26週群9例、プラセボ+52週群5例、MRA-SC QW 群18例、MRA-SC Q2W 群9例の計41例であった。治験薬投与の中止例の内訳は、有害事象がプラセボ+26週群3例、プラセボ+52週群では認められず、MRA-SC QW 群9例、MRA-SC Q2W 群3例、安全性以外の理由がプラセボ+26週群6例、プラセボ+52週群5例、MRA-SC QW 群9例、MRA-SC Q2W 群6例であった。

治験薬投与を中止した被験者の内、二重盲検期間を中止した被験者はプラセボ+26週群6例、プラセボ+52週群5例、MRA-SC QW 群15例、MRA-SC Q2W 群8例の計34例であった。10例は二重盲検期間を中止したときに試験を中止し、残りの24例はその後中止した。二重盲検期間を中止した理由の内訳は、有害事象がプラセボ+26週群2例、プラセボ+52週群では認められず、MRA-SC QW 群7例、MRA-SC Q2W 群3例、同意撤回10例、その他1例等であった。

図 2.7.4.1.2.3-2 被験者の内訳 (WA28119試験)



[5.3.5.1-3 Figure 2を改変]

2.7.4.1.3 治験対象集団の人口統計学的特性及びその他の特性

MRA632JP 試験及び WA28119試験での安全性評価例の被験者背景を表 2.7.4.8-1及び表 2.7.4.8-2に示す。それぞれの試験において、被験者の性別、年齢、体重、ランダム化時の1日あたりの高安動脈炎に対する1日あたりの副腎皮質ステロイド投与量（プレドニゾン換算量）は投与群間で大きな違いは認められなかった。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

(1) MRA632JP 試験

MRA632JP 試験の二重盲検期間及び全期間の本剤全投与例での有害事象の概要をそれぞれ表 2.7.4.2.1-1及び表 2.7.4.2.1-2に示す。また、観察期間あたりの事象別有害事象発現件数 (Events /100 PYs) を二重盲検期間及び全期間の本剤全投与例についてそれぞれ表 2.7.4.8-4及び表 2.7.4.8-5に示す。

MRA632JP 試験の二重盲検期間において、有害事象の発現頻度は、プラセボ群が11/18例 (61.1%) に31件、MRA-SC 群が14/18例 (77.8%) に38件であり、副作用の発現頻度は、プラセボ群が3/18例 (16.7%) に4件、MRA-SC 群が5/18例 (27.8%) に15件であった。重症度が高度の有害事象の発現は、MRA-SC 群で認められず、プラセボ群の発現頻度は1/18例 (5.6%) であり、重症度が高度の有害事象と治験薬との因果関係は否定された。死亡に至った有害事象は認められず、その他の重篤な有害事象の発現頻度は、プラセボ群が2/18例 (11.1%)、MRA-SC 群が1/18例 (5.6%) であり、いずれの事象も治験薬との因果関係は否定された。治験薬の投与中止に至った有害事象は認められなかった。投与間隔の延長又は休薬に至った有害事象の発現頻度はプラセボ群が2/18例 (11.1%)、MRA-SC 群が3/18例 (16.7%) であり、この内副作用はプラセボ群が1/18例 (5.6%)、MRA-SC 群が3/18例 (16.7%) であった。

有害事象の観察期間あたりの発現件数はプラセボ群が541.6 Events /100 PYs、MRA-SC 群が581.4 Events /100 PYs であり、群間で明らかな違いは認められなかった。

以上、有害事象の発現頻度はいずれのカテゴリでも群間で大きな違いは認められなかった。

MRA632JP 試験の全期間の本剤全投与例において、有害事象の発現頻度は34/36例 (94.4%) であり、副作用の発現頻度は18/36例 (50.0%) であった。重症度が高度の有害事象は2例 (5.6%、急性腎盂腎炎及び複合性局所疼痛症候群) に認められた。いずれの事象も治験薬との因果関係が否定されず、未回復であった。死亡に至った有害事象は認められず、その他の重篤な有害事象の発現頻度は6/36例 (16.7%) であり、うち3例の事象は治験薬との因果関係が否定されなかった。治験薬の投与中止に至った有害事象は認められなかった。投与間隔の延長又は休薬に至った有害事象は、16/36例 (44.4%) であり、この内副作用は12/36例 (33.3%) であった。

有害事象の観察期間あたりの発現件数は536.6 Events /100 PYs であり、二重盲検期間のプラセボ群及び MRA-SC 群と大きな違いはなかった。

表 2.7.4.2.1-1 有害事象の発現状況の要約 (MRA632JP 試験-二重盲検期間)

aet01_sp Adverse Events, Deaths and Withdrawals
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Total number of patients with at least one adverse event	11 (61.1%)	14 (77.8%)
Total number of events	31	38
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	2 (11.1%)	1 (5.6%)
Serious AE leading to withdrawal from treatment	0	0
Serious AE leading to dose modification/interruption	1 (5.6%)	0
Related Serious AE	0	0
AE leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	2 (11.1%)	3 (16.7%)
Related AE	3 (16.7%)	5 (27.8%)
Related AE leading to withdrawal from treatment	0	0
Severe AE	1 (5.6%)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Percentages are based on N.
 Multiple occurrences of the same adverse event in one individual counted only once.
 # Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet01.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet01_sp.out
 21DEC2015 21:22
 Page 1 of 1

[5.3.5.1-1 表 12.2.1-1を再掲]

表 2.7.4.2.1-2 有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)

aet01_mt_sp Safety Summary
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

	MRA-SC 162mg/W Total (N=36)
Total number of patients with at least one adverse event	34 (94.4%)
Total number of events	201
Total number of deaths	0
Total number of patients withdrawn from study due to an AE	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	6 (16.7%)
Serious AE leading to withdrawal from treatment	0
Serious AE leading to dose modification/interruption	3 (8.3%)
Related Serious AE	3 (8.3%)
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	16 (44.4%)
Related AE	18 (50.0%)
Related AE leading to withdrawal from treatment	0
Severe AE	2 (5.6%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.
 Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet01.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet01_mt_sp.out
 12JAN201717:16
 Page 1 of 1

[5.3.5.1-7 表 9.2.1-1を再掲]

(2) WA28119試験

二重盲検期間での有害事象の概要を表 2.7.4.2.1-3に示す。

二重盲検期間の有害事象の発現頻度は、プラセボ+26週群が48/50例 (96.0%)、プラセボ+52週群が47/51例 (92.2%)、MRA-SC QW 群が98/100例 (98.0%)、MRA-SC Q2W 群が47/49例 (95.9%) であり、治験薬の副作用発現頻度は、プラセボ+26週群が21/50例 (42.0%)、プラセボ+52週群が18/51例 (35.3%)、MRA-SC QW 群が52/100例 (52.0%)、MRA-SC Q2W 群が26/49例 (53.1%) であった。治験薬又は副腎皮質ステロイドの副作用の発現頻度は、プラセボ+26週群が32/50例 (64.0%)、プラセボ+52週群が27/51例 (52.9%)、MRA-SC QW 群が68/100例 (68.0%)、MRA-SC Q2W 群が36/49例 (73.5%) であった (表 2.7.6.12.1-4)。重症度がグレード4の有害事象の発現頻度は、プラセボ+26週群が1/50例 (2.0%)、プラセボ+52週群が1/51例 (2.0%)、MRA-SC QW 群が2/100例 (2.0%)、MRA-SC Q2W 群が1/49例 (2.0%) であった。死亡に至った有害事象は認められず、重篤な有害事象の発現頻度は、プラセボ+26週群が11/50例 (22.0%)、プラセボ+52週群が13/51例 (25.5%)、MRA-SC QW 群が15/100例 (15.0%)、MRA-SC Q2W 群が7/49例 (14.3%) であり、この内、治験薬の副作用はプラセボ+26週群が4/50例 (8.0%)、プラセボ+52週群が6/51例 (11.8%)、MRA-SC QW 群が4/100例 (4.0%)、MRA-SC Q2W 群が2/49例 (4.1%) であった。治験薬の投与中止に至った有害事象はプラセボ+26週群が3/50例 (6.0%)、プラセボ+52週群には該当例がなく、MRA-SC QW 群が11/100例 (11.0%)、MRA-SC Q2W 群が5/49例 (10.2%) であった。治験薬又は副腎皮質ステロイドの投与中止に至った有害事象はプラセボ+26週群が6/50例 (12.0%)、プラセボ+52週群には該当例がなく、MRA-SC QW 群が11/100例 (11.0%)、MRA-SC Q2W 群が6/49例 (12.2%) であった。治験薬の投与間隔の延長又は休薬に至った有害事象の発現頻度はプラセボ+26週群が10/50例 (20.0%)、プラセボ+52週群が11/51例 (21.6%)、MRA-SC QW 群が28/100例 (28.0%)、MRA-SC Q2W 群が8/49例 (16.3%) であり、治験薬若しくは副腎皮質ステロイドの投与間隔の延長、休薬、又は非盲検副腎皮質ステロイドの休薬若しくは減量に至った有害事象の発現頻度はプラセボ+26週群が12/50例 (24.0%)、プラセボ+52週群が17/51例 (33.3%)、MRA-SC QW 群が33/100例 (33.0%)、MRA-SC Q2W 群が10/49例 (20.4%) であった。この内治験薬の副作用はプラセボ+26週群が6/50例 (12.0%)、プラセボ+52週群が6/51例 (11.8%)、MRA-SC QW 群が12/100例 (12.0%)、MRA-SC Q2W 群が4/49例 (8.2%) であった。

有害事象の観察期間あたりの発現件数 (Events /100 PYs) はプラセボ+26週群が990.8 Events /100 PYs、プラセボ+52週群が1011.2 Events /100 PYs、MRA-SC QW 群が872.0 Events /100 PYs、MRA-SC Q2W 群が948.0 Events /100 PYs であり、群間で明らかな違いは認められなかった。

以上、有害事象の発現頻度はいずれのカテゴリでも群間で大きな違いは認められなかった。

表 2.7.4.2.1-3 有害事象の発現状況の要約 (WA28119試験)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one AE	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
Total number of events	470	486	810	432
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	2 (4.0%)	0	6 (6.0%)	3 (6.1%)
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	11 (22.0%)	13 (25.5%)	15 (15.0%)	7 (14.3%)
Serious AE related to TCZ	4 (8.0%)	6 (11.8%)	4 (4.0%)	2 (4.1%)
Serious AE related to Prednisone	5 (10.0%)	4 (7.8%)	3 (3.0%)	1 (2.0%)
AE leading to withdrawal from treatment	6 (12.0%)	0	11 (11.0%)	6 (12.2%)
AE leading to withdrawal from blinded TCZ/placebo	3 (6.0%)	0	11 (11.0%)	5 (10.2%)
AE leading to dose modification/interruption	12 (24.0%)	17 (33.3%)	33 (33.0%)	10 (20.4%)
AE leading to dose modification/interruption of blinded TCZ/placebo	10 (20.0%)	11 (21.6%)	28 (28.0%)	8 (16.3%)
AE related to TCZ	21 (42.0%)	18 (35.3%)	52 (52.0%)	26 (53.1%)
AE related to Prednisone	31 (62.0%)	25 (49.0%)	50 (50.0%)	30 (61.2%)

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

* The events matching an anaphylactic reaction based on Sampson's criteria (eye pruritus, dyspnoea) were clinically not considered to be anaphylactic in nature. The investigator did not consider either of these events to be related to study drug and there were no modifications to either the TCZ or prednisone dose.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview.sas / Output:
/opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_SE.out 28SEP2016 11:32 (PDRD)

[5.3.5.1-3 Table 34を改変]

2.7.4.2.1.2 比較的良好にみられる有害事象

2.7.4.2.1.2.1 MRA632JP 試験

(1) 二重盲検期間

二重盲検期間において、いずれかの群の2例以上に発現した有害事象とその副作用の発現例数を表 2.7.4.2.1.2.1-1に示す。いずれかの群の2例以上に認められた有害事象は鼻咽頭炎（プラセボ群, MRA-SC 群：16.7%, 33.3%, 以下同様）、上気道感染（0%, 16.7%）、胃腸炎、咽頭炎（いずれも0%, 11.1%）、口腔咽頭痛及び体重増加（いずれも11.1%, 0%）であった。これらの内、副作用は鼻咽頭炎（5.6%, 16.7%）、上気道感染（0%, 16.7%）、胃腸炎（0%, 11.1%）及び咽頭炎（0%, 5.6%）であった。

MRA-SC 群でプラセボ群に比べて10%以上発現頻度が高かった有害事象は、鼻咽頭炎、上気道感染、胃腸炎及び咽頭炎であった。

表 2.7.4.2.1.2.1-1 いずれかの群の2例以上に発現した有害事象とその副作用発現例数 (%)
(MRA632JP 試験-二重盲検期間)

aeaer_sp Adverse Events and Adverse Drug Reactions with an Incidence Rate of at Least 10% in Any Group
Protocol: MRA632JP
Analysis: SAFETY

Adverse Event	Adverse Events		Related Adverse Events	
	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
鼻咽頭炎	3 (16.7%)	6 (33.3%)	1 (5.6%)	3 (16.7%)
上気道感染	0	3 (16.7%)	0	3 (16.7%)
胃腸炎	0	2 (11.1%)	0	2 (11.1%)
咽頭炎	0	2 (11.1%)	0	1 (5.6%)
口腔咽頭痛	2 (11.1%)	0	0	0
体重増加	2 (11.1%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aeaer.sas
Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aeaer_sp.out
28DEC2015 18:25

Page 1 of 1

[5.3.5.1-1 表 12.2.3-1を再掲]

(2) 全期間の本剤全投与例

全期間の本剤全投与例において、2例以上に認められた有害事象とその副作用発現例数を表 2.7.4.2.1.2.1-2に示す。2例以上に認められた有害事象は、鼻咽頭炎 (50.0%)、上気道感染及び咽頭炎 (いずれも19.4%)、胃腸炎 (13.9%)、感染性腸炎、下痢、筋肉痛、背部痛及び鉄欠乏性貧血 (いずれも11.1%)、口腔ヘルペス、膀胱炎、悪心、腹痛、齲歯、ざ瘡、皮下出血、失神寸前の状態、頭痛、挫傷、不眠症及びアラニンアミノトランスフェラーゼ増加 (いずれも8.3%)、インフルエンザ、外陰部腔カンジダ症、副鼻腔炎、口唇炎、口内炎、腹部不快感、湿疹、発疹、皮膚乾燥、蕁麻疹、四肢痛、感覚鈍麻、肋骨骨折、肺梗塞、アスパラギン酸アミノトランスフェラーゼ増加及び肝機能異常 (いずれも5.6%)であった。

これらの内、副作用は鼻咽頭炎及び上気道感染 (いずれも13.9%)、胃腸炎 (11.1%)、咽頭炎及び外陰部腔カンジダ症 (いずれも5.6%)、感染性腸炎、口腔ヘルペス、インフルエンザ、下痢、腹痛、口唇炎、口内炎、頭痛、アラニンアミノトランスフェラーゼ増加及び肝機能異常 (いずれも2.8%)であった。

表 2.7.4.2.1.2.1-2 2例以上に認められた有害事象とその副作用発現例数 (%)
(MRA632JP 試験-全期間の本剤全投与例)

aeaer_mt_sp Adverse Events and Adverse Drug Reactions
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)	
	Adverse Events	Related Adverse Events
感染症および寄生虫症		
鼻咽頭炎	18 (50.0%)	5 (13.9%)
咽頭炎	7 (19.4%)	2 (5.6%)
上気道感染	7 (19.4%)	5 (13.9%)
胃腸炎	5 (13.9%)	4 (11.1%)
感染性腸炎	4 (11.1%)	1 (2.8%)
口腔ヘルペス	3 (8.3%)	1 (2.8%)
膀胱炎	3 (8.3%)	0
インフルエンザ	2 (5.6%)	1 (2.8%)
外陰部腔カンジダ症	2 (5.6%)	2 (5.6%)
副鼻腔炎	2 (5.6%)	0
胃腸障害		
下痢	4 (11.1%)	1 (2.8%)
悪心	3 (8.3%)	0
腹痛	3 (8.3%)	1 (2.8%)
歯菌	3 (8.3%)	0
口唇炎	2 (5.6%)	1 (2.8%)
口内炎	2 (5.6%)	1 (2.8%)
腹部不快感	2 (5.6%)	0
皮膚および皮下組織障害		
さ瘡	3 (8.3%)	0
皮下出血	3 (8.3%)	0
湿疹	2 (5.6%)	0
発疹	2 (5.6%)	0
皮膚乾燥	2 (5.6%)	0
蕁麻疹	2 (5.6%)	0
筋骨格系および結合組織障害		
筋肉痛	4 (11.1%)	0
背部痛	4 (11.1%)	0
四肢痛	2 (5.6%)	0
神経系障害		
失神寸前の状態	3 (8.3%)	0
頭痛	3 (8.3%)	1 (2.8%)
感覚鈍麻	2 (5.6%)	0
傷害、中毒および処置合併症		
挫傷	3 (8.3%)	0
肋骨骨折	2 (5.6%)	0
呼吸器、胸郭および縦隔障害		
肺梗塞	2 (5.6%)	0

Percentages are based on N in the column headings.
Investigator text for Adverse Events encoded using MedDRA version 17.1.
Multiple occurrences of the same adverse event in one individual counted only once.

aeaeer_mt_sp Adverse Events and Adverse Drug Reactions
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)	
	Adverse Events	Related Adverse Events
血液およびリンパ系障害 鉄欠乏性貧血	4 (11.1%)	0
精神障害 不眠症	3 (8.3%)	0
臨床検査 アラニンアミノトランスフェラーゼ増加	3 (8.3%)	1 (2.8%)
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	0
肝胆道系障害 肝機能異常	2 (5.6%)	1 (2.8%)

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Multiple occurrences of the same adverse event in one individual counted only once.

Page 2 of 2

[5.3.5.1-7 表 11.3-4を改変]

2.7.4.2.1.2.2 WA28119試験

二重盲検期間において、いずれかの群の3%以上に発現した有害事象及びその治験薬又は副腎皮質ステロイドの副作用の発現例数をそれぞれ表 2.7.4.2.1.2.2-1及び表 2.7.4.2.1.2.2-2に示す。また、治験薬に対する副作用の発現例数を表 2.7.4.8-3に示す。いずれかの群の10%以上に認められた有害事象は、頭痛（プラセボ+26週群，プラセボ+52週群，MRA-SC QW 群，MRA-SC Q2W 群：32.0%，23.5%，27.0%，20.4%，以下同様），鼻咽頭炎（18.0%，25.5%，29.0%，24.5%），末梢性浮腫（16.0%，11.8%，16.0%，24.5%），関節痛（22.0%，15.7%，13.0%，16.3%），背部痛（14.0%，19.6%，14.0%，14.3%），浮動性めまい（12.0%，15.7%，6.0%，20.4%），下痢（16.0%，9.8%，12.0%，6.1%），上気道感染（10.0%，13.7%，10.0%，12.2%），高血圧（8.0%，7.8%，12.0%，12.2%），筋骨格痛（10.0%，3.9%，12.0%，12.2%），疲労（16.0%，5.9%，8.0%，10.2%），口腔咽頭痛（10.0%，15.7%，7.0%，8.2%），四肢痛（10.0%，9.8%，8.0%，10.2%），気管支炎（10.0%，9.8%，8.0%，8.2%），脱毛症（6.0%，9.8%，5.0%，14.3%），筋痙縮（12.0%，7.8%，4.0%，12.2%），尿路感染（4.0%，7.8%，10.0%，8.2%），咳嗽（14.0%，5.9%，6.0%，6.1%），悪心（10.0%，7.8%，8.0%，4.1%），発疹（8.0%，3.9%，7.0%，10.2%），錯感覚（10.0%，7.8%，4.0%，4.1%），口腔ヘルペス（6.0%，3.9%，4.0%，10.2%），無力症（10.0%，0%，5.0%，6.1%）及び不安（12.0%，2.0%，3.0%，2.0%）であった。これらの内、治験薬又は副腎皮質ステロイドの副作用は、頭痛（4.0%，2.0%，3.0%，0%），鼻咽頭炎（2.0%，7.8%，7.0%，4.1%），末梢性浮腫（4.0%，3.9%，3.0%，4.1%），関節痛（2.0%，0%，1.0%，4.1%），背部痛（0%，0%，2.0%，0%），浮動性めまい（2.0%，5.9%，2.0%，4.1%），下痢（2.0%，3.9%，0%，2.0%），上気道感染（6.0%，5.9%，4.0%，4.1%），高血圧（2.0%，3.9%，4.0%，4.1%），筋骨格痛（2.0%，0%，0%，2.0%），疲労（0%，0%，1.0%，0%），口腔咽頭痛（4.0%，3.9%，3.0%，0%），四肢痛（2.0%，0%，0%，0%），気管支炎（4.0%，5.9%，4.0%，0%），脱毛症（2.0%，3.9%，2.0%，6.1%），筋痙縮（0%，0%，0%，2.0%），尿路感染（0%，3.9%，2.0%，2.0%），咳嗽（2.0%，2.0%，2.0%，0%），発疹（0%，2.0%，1.0%，4.1%），錯感覚（2.0%，3.9%，0%，0%），口腔ヘルペス（4.0%，3.9%，2.0%，4.1%），無力症（6.0%，0%，2.0%，2.0%），不安（8.0%，2.0%，0%，2.0%）であった。

MRA-SC QW 群で、プラセボ+26週群に比べて10%以上発現頻度が高かった有害事象は鼻咽頭炎であり、プラセボ+52週群に比べて10%以上発現頻度が高かった有害事象はなかった。MRA-SC Q2W 群で、プラセボ+26週群に比べて10%以上発現頻度が高かった有害事象はなく、プラセボ+52週群に比べて10%以上発現頻度が高かった有害事象は末梢性浮腫であった。

表 2.7.4.2.1.2.2-1 いずれかの群の3%以上に発現した有害事象の発現例数 (%) (WA28119試験-二重盲検期間)

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	48 (96.0%)	46 (90.2%)	94 (94.0%)	46 (93.9%)
Overall total number of events	354	363	570	314

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
感染症および寄生虫症				
Total number of patients with at least one adverse event	32 (64.0%)	29 (56.9%)	66 (66.0%)	31 (63.3%)
Total number of events	52	82	144	58
鼻咽頭炎	9 (18.0%)	13 (25.5%)	29 (29.0%)	12 (24.5%)
上気道感染	5 (10.0%)	7 (13.7%)	10 (10.0%)	6 (12.2%)
気管支炎	5 (10.0%)	5 (9.8%)	8 (8.0%)	4 (8.2%)
尿路感染	2 (4.0%)	4 (7.8%)	10 (10.0%)	4 (8.2%)
胃腸炎	4 (8.0%)	4 (7.8%)	3 (3.0%)	4 (8.2%)
鼻炎	2 (4.0%)	3 (5.9%)	6 (6.0%)	4 (8.2%)
口腔ヘルペス	3 (6.0%)	2 (3.9%)	4 (4.0%)	5 (10.2%)
膀胱炎	2 (4.0%)	3 (5.9%)	7 (7.0%)	0
結膜炎	4 (8.0%)	1 (2.0%)	4 (4.0%)	1 (2.0%)
副鼻腔炎	1 (2.0%)	2 (3.9%)	3 (3.0%)	4 (8.2%)
带状疱疹	0	2 (3.9%)	5 (5.0%)	2 (4.1%)
咽頭炎	1 (2.0%)	3 (5.9%)	4 (4.0%)	0
喉頭炎	0	2 (3.9%)	3 (3.0%)	1 (2.0%)
歯肉炎	1 (2.0%)	2 (3.9%)	2 (2.0%)	0
ウイルス性胃腸炎	0	1 (2.0%)	3 (3.0%)	0
下気道感染	0	1 (2.0%)	3 (3.0%)	0
歯膿瘍	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
消化管感染	1 (2.0%)	0	3 (3.0%)	0
膿疱性皮膚疹	0	2 (3.9%)	2 (2.0%)	0
麦粒腫	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
皮膚真菌感染	0	0	4 (4.0%)	0
気道感染	0	2 (3.9%)	0	1 (2.0%)
歯周炎	1 (2.0%)	2 (3.9%)	0	0
爪真菌症	0	2 (3.9%)	1 (1.0%)	0
ウイルス感染	0	0	0	2 (4.1%)
口腔真菌感染	0	0	0	2 (4.1%)

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 040CT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	32 (64.0%)	28 (54.9%)	59 (59.0%)	26 (53.1%)
Total number of events	64	57	98	66
関節痛	11 (22.0%)	8 (15.7%)	13 (13.0%)	8 (16.3%)
背部痛	7 (14.0%)	10 (19.6%)	14 (14.0%)	7 (14.3%)
筋骨格痛	5 (10.0%)	2 (3.9%)	12 (12.0%)	6 (12.2%)
四肢痛	5 (10.0%)	5 (9.8%)	8 (8.0%)	5 (10.2%)
筋肉痛	4 (8.0%)	4 (7.8%)	9 (9.0%)	4 (8.2%)
筋痙縮	6 (12.0%)	4 (7.8%)	4 (4.0%)	6 (12.2%)
変形性関節症	3 (6.0%)	4 (7.8%)	7 (7.0%)	2 (4.1%)
頸部痛	2 (4.0%)	4 (7.8%)	6 (6.0%)	1 (2.0%)
滑液包炎	2 (4.0%)	1 (2.0%)	1 (1.0%)	4 (8.2%)
顎痛	2 (4.0%)	0	3 (3.0%)	1 (2.0%)
筋骨格硬直	1 (2.0%)	0	4 (4.0%)	1 (2.0%)
骨粗鬆症	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
脊椎痛	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
腱炎	1 (2.0%)	0	4 (4.0%)	0
関節炎	0	0	3 (3.0%)	1 (2.0%)
筋力低下	2 (4.0%)	0	2 (2.0%)	0
四肢不快感	2 (4.0%)	0	1 (1.0%)	0
線維筋痛	2 (4.0%)	1 (2.0%)	0	0
腱付着部症	0	2 (3.9%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

Page 3 of 10

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
神経系障害				
Total number of patients with at least one adverse event	22 (44.0%)	19 (37.3%)	36 (36.0%)	17 (34.7%)
Total number of events	47	43	60	36
頭痛	16 (32.0%)	12 (23.5%)	27 (27.0%)	10 (20.4%)
浮動性めまい	6 (12.0%)	8 (15.7%)	6 (6.0%)	10 (20.4%)
錯感覚	5 (10.0%)	4 (7.8%)	4 (4.0%)	2 (4.1%)
感覚鈍麻	2 (4.0%)	0	3 (3.0%)	1 (2.0%)
坐骨神経痛	2 (4.0%)	0	2 (2.0%)	2 (4.1%)
振戦	3 (6.0%)	3 (5.9%)	0	0
失神	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	20 (40.0%)	12 (23.5%)	31 (31.0%)	22 (44.9%)
Total number of events	27	19	47	37
末梢性浮腫	8 (16.0%)	6 (11.8%)	16 (16.0%)	12 (24.5%)
疲労	8 (16.0%)	3 (5.9%)	8 (8.0%)	5 (10.2%)
無力症	5 (10.0%)	0	5 (5.0%)	3 (6.1%)
発熱	2 (4.0%)	2 (3.9%)	1 (1.0%)	2 (4.1%)
非心臓性胸痛	1 (2.0%)	3 (5.9%)	1 (1.0%)	2 (4.1%)
末梢腫脹	0	2 (3.9%)	4 (4.0%)	1 (2.0%)
倦怠感	1 (2.0%)	0	3 (3.0%)	0
胸痛	0	0	1 (1.0%)	2 (4.1%)
注射部位そう痒感	0	0	0	2 (4.1%)
注射部位反応	0	0	0	2 (4.1%)

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
胃腸障害				
Total number of patients with at least one adverse event	17 (34.0%)	14 (27.5%)	28 (28.0%)	14 (28.6%)
Total number of events	53	39	53	21
下痢	8 (16.0%)	5 (9.8%)	12 (12.0%)	3 (6.1%)
悪心	5 (10.0%)	4 (7.8%)	8 (8.0%)	2 (4.1%)
上腹部痛	3 (6.0%)	4 (7.8%)	3 (3.0%)	3 (6.1%)
嘔吐	2 (4.0%)	3 (5.9%)	2 (2.0%)	2 (4.1%)
便秘	3 (6.0%)	4 (7.8%)	0	1 (2.0%)
胃食道逆流性疾患	2 (4.0%)	1 (2.0%)	2 (2.0%)	2 (4.1%)
腹痛	2 (4.0%)	2 (3.9%)	3 (3.0%)	0
胃炎	0	1 (2.0%)	2 (2.0%)	2 (4.1%)
鼓腸	2 (4.0%)	2 (3.9%)	1 (1.0%)	0
口腔内潰瘍形成	0	2 (3.9%)	3 (3.0%)	0
口内乾燥	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
歯痛	0	2 (3.9%)	3 (3.0%)	0
消化不良	4 (8.0%)	1 (2.0%)	0	0
痔核	2 (4.0%)	1 (2.0%)	0	1 (2.0%)
腹部膨満	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
アフタ性潰瘍	0	0	1 (1.0%)	2 (4.1%)
胃腸障害	2 (4.0%)	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	13 (26.0%)	12 (23.5%)	23 (23.0%)	18 (36.7%)
Total number of events	19	27	26	28
脱毛症	3 (6.0%)	5 (9.8%)	5 (5.0%)	7 (14.3%)
発疹	4 (8.0%)	2 (3.9%)	7 (7.0%)	5 (10.2%)
そう痒症	1 (2.0%)	1 (2.0%)	2 (2.0%)	4 (8.2%)
紅斑	1 (2.0%)	2 (3.9%)	3 (3.0%)	1 (2.0%)
湿疹	2 (4.0%)	2 (3.9%)	2 (2.0%)	0
寝汗	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
多汗症	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
斑状出血	1 (2.0%)	3 (5.9%)	0	2 (4.1%)
皮膚乾燥	0	0	2 (2.0%)	3 (6.1%)
紅斑性皮疹	0	0	1 (1.0%)	2 (4.1%)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	14 (28.0%)	13 (25.5%)	15 (15.0%)	9 (18.4%)
Total number of events	22	19	22	14
口腔咽頭痛	5 (10.0%)	8 (15.7%)	7 (7.0%)	4 (8.2%)
咳嗽	7 (14.0%)	3 (5.9%)	6 (6.0%)	3 (6.1%)
呼吸困難	1 (2.0%)	3 (5.9%)	3 (3.0%)	4 (8.2%)
鼻出血	4 (8.0%)	0	3 (3.0%)	1 (2.0%)
労作性呼吸困難	3 (6.0%)	1 (2.0%)	1 (1.0%)	0
鼻漏	0	0	0	2 (4.1%)

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血管障害				
Total number of patients with at least one adverse event	7 (14.0%)	6 (11.8%)	19 (19.0%)	9 (18.4%)
Total number of events	10	9	24	9
高血圧	4 (8.0%)	4 (7.8%)	12 (12.0%)	6 (12.2%)
血腫	3 (6.0%)	1 (2.0%)	5 (5.0%)	3 (6.1%)
深部静脈血栓症	0	0	3 (3.0%)	0
低血圧	2 (4.0%)	0	1 (1.0%)	0
血栓性静脈炎	0	2 (3.9%)	0	0
眼障害				
Total number of patients with at least one adverse event	11 (22.0%)	8 (15.7%)	10 (10.0%)	8 (16.3%)
Total number of events	15	11	11	10
白内障	3 (6.0%)	5 (9.8%)	5 (5.0%)	1 (2.0%)
眼乾燥	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
霧視	2 (4.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
結膜出血	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
眼充血	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
緑内障	2 (4.0%)	0	0	1 (2.0%)
眼そう痒症	0	0	0	2 (4.1%)
精神障害				
Total number of patients with at least one adverse event	12 (24.0%)	6 (11.8%)	10 (10.0%)	7 (14.3%)
Total number of events	14	7	11	9
不眠症	4 (8.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
不安	6 (12.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
うつ病	3 (6.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
睡眠障害	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
臨床検査				
Total number of patients with at least one adverse event	5 (10.0%)	7 (13.7%)	16 (16.0%)	6 (12.2%)
Total number of events	6	9	22	10
アラニンアミノトランスフェラーゼ増加	2 (4.0%)	0	5 (5.0%)	2 (4.1%)
眼圧上昇	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.0%)	0	4 (4.0%)	1 (2.0%)
肝酵素上昇	0	2 (3.9%)	4 (4.0%)	0
体重増加	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
補体成分C3減少	0	0	3 (3.0%)	1 (2.0%)
体温上昇	0	2 (3.9%)	0	1 (2.0%)
低比重リポ蛋白増加	0	2 (3.9%)	0	1 (2.0%)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	4 (8.0%)	9 (17.6%)	15 (15.0%)	4 (8.2%)
Total number of events	5	12	22	5
転倒	2 (4.0%)	2 (3.9%)	7 (7.0%)	2 (4.1%)
挫傷	0	2 (3.9%)	4 (4.0%)	2 (4.1%)
裂傷	1 (2.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
節足動物咬傷	0	2 (3.9%)	2 (2.0%)	0
創傷	0	2 (3.9%)	1 (1.0%)	0
肋骨骨折	2 (4.0%)	0	1 (1.0%)	0
耳および迷路障害				
Total number of patients with at least one adverse event	5 (10.0%)	5 (9.8%)	6 (6.0%)	4 (8.2%)
Total number of events	5	14	6	4
回転性めまい	3 (6.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
耳痛	1 (2.0%)	0	2 (2.0%)	2 (4.1%)
耳鳴	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
頭位性回転性めまい	0	2 (3.9%)	2 (2.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
代謝および栄養障害				
Total number of patients with at least one adverse event	2 (4.0%)	4 (7.8%)	4 (4.0%)	4 (8.2%)
Total number of events	2	6	4	4
高コレステロール血症	0	1 (2.0%)	2 (2.0%)	3 (6.1%)
低カリウム血症	0	3 (5.9%)	0	1 (2.0%)
糖尿病	2 (4.0%)	0	2 (2.0%)	0
心臓障害				
Total number of patients with at least one adverse event	4 (8.0%)	4 (7.8%)	2 (2.0%)	2 (4.1%)
Total number of events	6	4	2	2
動悸	4 (8.0%)	2 (3.9%)	2 (2.0%)	2 (4.1%)
慢性心不全	0	2 (3.9%)	0	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	8 (8.0%)	1 (2.0%)
Total number of events	2	0	11	1
好中球減少症	0	0	4 (4.0%)	1 (2.0%)
白血球減少症	0	0	4 (4.0%)	0
貧血	2 (4.0%)	0	2 (2.0%)	0
腎および尿路障害				
Total number of patients with at least one adverse event	2 (4.0%)	3 (5.9%)	4 (4.0%)	0
Total number of events	2	3	6	0
排尿困難	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
尿意切迫	0	2 (3.9%)	1 (1.0%)	0
内分泌障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	1 (1.0%)	0
Total number of events	0	2	1	0
クッシング様症状	0	2 (3.9%)	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

t_ae_3per_sp Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
外科および内科処置				
Total number of patients with at least one adverse event	2 (4.0%)	0	0	0
Total number of events	3	0	0	0
白内障手術	2 (4.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_sp.out
 04OCT2016 17:51

Page 10 of 10
 [5.3.5.3-1 表 2.4-1を再掲]

表 2.7.4.2.1.2.2-2 いずれかの群の3%以上に発現した有害事象の、治験薬又は副腎皮質ステロイドに対する副作用発現例数 (%) (WA28119試験-二重盲検期間)

t_ae_3per_rel_sp Related Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	23 (46.0%)	23 (45.1%)	48 (48.0%)	23 (46.9%)
Overall total number of events	45	63	95	40
感染症および寄生虫症				
Total number of patients with at least one adverse event	8 (16.0%)	11 (21.6%)	27 (27.0%)	11 (22.4%)
Total number of events	10	25	41	12
鼻咽頭炎	1 (2.0%)	4 (7.8%)	7 (7.0%)	2 (4.1%)
上気道感染	3 (6.0%)	3 (5.9%)	4 (4.0%)	2 (4.1%)
気管支炎	2 (4.0%)	3 (5.9%)	4 (4.0%)	0
口腔ヘルペス	2 (4.0%)	2 (3.9%)	2 (2.0%)	2 (4.1%)
膀胱炎	1 (2.0%)	1 (2.0%)	6 (6.0%)	0
带状疱疹	0	2 (3.9%)	3 (3.0%)	2 (4.1%)
鼻炎	0	3 (5.9%)	3 (3.0%)	1 (2.0%)
尿路感染	0	2 (3.9%)	2 (2.0%)	1 (2.0%)
副鼻腔炎	0	0	2 (2.0%)	2 (4.1%)
皮膚真菌感染	0	0	3 (3.0%)	0
神経系障害				
Total number of patients with at least one adverse event	5 (10.0%)	5 (9.8%)	5 (5.0%)	2 (4.1%)
Total number of events	6	8	5	2
浮動性めまい	1 (2.0%)	3 (5.9%)	2 (2.0%)	2 (4.1%)
頭痛	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
錯感覚	1 (2.0%)	2 (3.9%)	0	0
振戦	2 (4.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per_rel.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_rel_sp.out
 04OCT2016 17:52

t_ae_3per_rel_sp Related Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	3 (6.0%)	2 (3.9%)	6 (6.0%)	5 (10.2%)
Total number of events	3	3	6	5
脱毛症	1 (2.0%)	2 (3.9%)	2 (2.0%)	3 (6.1%)
多汗症	2 (4.0%)	0	3 (3.0%)	0
発疹	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
臨床検査				
Total number of patients with at least one adverse event	1 (2.0%)	3 (5.9%)	9 (9.0%)	3 (6.1%)
Total number of events	1	4	13	5
アラニンアミノトランスフェラーゼ増加	1 (2.0%)	0	3 (3.0%)	2 (4.1%)
肝酵素上昇	0	2 (3.9%)	3 (3.0%)	0
アスパラギン酸アミノトランスフェラーゼ増加	0	0	3 (3.0%)	1 (2.0%)
補体成分C3減少	0	0	3 (3.0%)	1 (2.0%)
低比重リポ蛋白増加	0	2 (3.9%)	0	1 (2.0%)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	5 (10.0%)	2 (3.9%)	5 (5.0%)	2 (4.1%)
Total number of events	5	2	5	3
末梢性浮腫	2 (4.0%)	2 (3.9%)	3 (3.0%)	2 (4.1%)
無力症	3 (6.0%)	0	2 (2.0%)	1 (2.0%)
精神障害				
Total number of patients with at least one adverse event	5 (10.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
Total number of events	6	3	2	1
不安	4 (8.0%)	1 (2.0%)	0	1 (2.0%)
不眠症	2 (4.0%)	2 (3.9%)	2 (2.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per_rel.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_rel_sp.out
 04OCT2016 17:52

t_ae_3per_rel_sp Related Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血管障害				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	4 (4.0%)	2 (4.1%)
Total number of events	1	2	4	2
高血圧	1 (2.0%)	2 (3.9%)	4 (4.0%)	2 (4.1%)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	3 (3.0%)	4 (8.2%)
Total number of events	2	0	3	5
筋肉痛	1 (2.0%)	0	2 (2.0%)	2 (4.1%)
関節痛	1 (2.0%)	0	1 (1.0%)	2 (4.1%)
心臓障害				
Total number of patients with at least one adverse event	2 (4.0%)	3 (5.9%)	2 (2.0%)	1 (2.0%)
Total number of events	2	3	2	1
動悸	2 (4.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
慢性心不全	0	2 (3.9%)	0	0
眼障害				
Total number of patients with at least one adverse event	3 (6.0%)	2 (3.9%)	2 (2.0%)	0
Total number of events	3	3	2	0
白内障	1 (2.0%)	2 (3.9%)	2 (2.0%)	0
緑内障	2 (4.0%)	0	0	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	2 (4.0%)	2 (3.9%)	3 (3.0%)	0
Total number of events	2	3	3	0
口腔咽頭痛	2 (4.0%)	2 (3.9%)	3 (3.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per_rel.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_rel_sp.out
 04OCT2016 17:52

t_ae_3per_rel_sp Related Adverse Events with Incidence Rates of at Least 3% in Any Group (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
胃腸障害				
Total number of patients with at least one adverse event	3 (6.0%)	2 (3.9%)	0	1 (2.0%)
Total number of events	4	2	0	1
下痢	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
消化不良	2 (4.0%)	0	0	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	0	0	5 (5.0%)	1 (2.0%)
Total number of events	0	0	7	1
好中球減少症	0	0	3 (3.0%)	1 (2.0%)
白血球減少症	0	0	3 (3.0%)	0
代謝および栄養障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
Total number of events	0	1	1	2
高コレステロール血症	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
内分泌障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	1 (1.0%)	0
Total number of events	0	2	1	0
クッシング様症状	0	2 (3.9%)	1 (1.0%)	0
腎および尿路障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	0	0
Total number of events	0	2	0	0
尿意切迫	0	2 (3.9%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_3per_rel.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_3per_rel_sp.out
 04OCT2016 17:52

Page 4 of 4

[5.3.5.3-1 表 2.4-2を再掲]

2.7.4.2.1.3 重症度別有害事象

2.7.4.2.1.3.1 MRA632JP 試験

重症度別の事象別有害事象発現例数を二重盲検期間及び全期間の本剤全投与例についてそれぞれ表 2.7.4.8-6及び表 2.7.4.8-7に示した。

二重盲検期間では、重症度が高度の有害事象は、MRA-SC 群では認められず、プラセボ群では1/18例 (5.6%) に2件 (出血性ショック, 出血性胃潰瘍) 認められた。これらの事象はいずれも重篤な有害事象でもあった。これらの事象と治験薬との因果関係はいずれも否定された。重症度が中等度と判定された有害事象は、プラセボ群では4/18例 (22.2%) , MRA-SC 群では1/18例 (5.6%) に認められた。重症度が軽度と判定された有害事象は、プラセボ群では6/18例 (33.3%) , MRA-SC 群では13/18例 (72.2%) に認められた。いずれの群においても、ほとんどの事象の重症度は軽度又は中等度であり、両群間で大きな違いはなかった。

非盲検期間では、重症度が高度の有害事象が2例 (5.6%) に2件 (急性腎盂腎炎及び複合性局所疼痛症候群) 認められた。これらの事象はいずれも重篤な有害事象でもあった。全期間の本剤投与例では、重症度が高度, 中等度及び軽度の有害事象はそれぞれ2/36例 (5.6%) , 10/36例 (27.8%) 及び22/36例 (61.1%) に認められた。重症度が中等度で2例以上に発現した有害事象はなかった。

2.7.4.2.1.3.2 WA28119試験

重症度別の有害事象発現頻度及び重症度別の事象別有害事象発現例数をそれぞれ表 2.7.4.2.1.3.2-1及び表 2.7.4.8-8に示した。

重症度がグレード4と判定された有害事象発現頻度は、プラセボ+26週群が1/50例 (2.0%) に1件 (関節痛) , プラセボ+52週群が1/51例 (2.0%) に5件 (肝酵素上昇, 低カリウム血症, 慢性心不全, 心不全, 腎機能障害) , MRA-SC QW 群が2/100例 (2.0%) に2件 (肺塞栓症, 好中球減少症) , MRA-SC Q2W 群が1/49例 (2.0%) に1件 (血栓性脳卒中) 認められた。重症度がグレード4の有害事象の発現頻度は投与群間で異ならなかった。MRA-SC QW 群の好中球減少症を除き、これらの事象は重篤な有害事象でもあった。また、グレード4の有害事象の内、治験薬の副作用はプラセボ+52週群の肝酵素上昇, 慢性心不全, MRA-SC QW 群の好中球減少症であった。

重症度がグレード3と判定された有害事象は、プラセボ+26週群が11/50例 (22.0%) , プラセボ+52週群が13/51例 (25.5%) , MRA-SC QW 群が24/100例 (24.0%) , MRA-SC Q2W 群が11/49例 (22.4%) に認められた。MRA-SC QW 群又は MRA-SC Q2W 群ではプラセボ+26週群又はプラセボ+52週群に比べて重症度が高い事象が多く認められるということとはなかった。重症度がグレード1と判定された有害事象及びグレード2と判定された有害事象の発現頻度は表 2.7.4.2.1.3.2-1に示すとおりであった。

表 2.7.4.2.1.3.2-1 重症度別の有害事象発現頻度 (WA28119試験-二重盲検期間)

Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
- Any Grade -	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
1	16 (32.0%)	20 (39.2%)	33 (33.0%)	16 (32.7%)
2	20 (40.0%)	13 (25.5%)	39 (39.0%)	19 (38.8%)
3	11 (22.0%)	13 (25.5%)	24 (24.0%)	11 (22.4%)
4	1 (2.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)

[表 2.7.4.8-8を改変]

2.7.4.2.1.4 発現時期別有害事象

2.7.4.2.1.4.1 MRA632JP 試験

全期間の本剤全投与例において、有害事象の初発時期について12週ごとに集計し、10%以上発現した時期別有害事象発現頻度を表 2.7.4.2.1.4.1-1に示す。また、すべての事象ごとの時期別有害事象発現頻度を表 2.7.4.8-9に示す。

有害事象発現頻度は、観察期間が長い一部の被験者を除いて、本剤投与初期で高い傾向があり、投与を継続することによって発現頻度が上昇する傾向は認められなかった。

いずれの有害事象の発現頻度においても時期的な特徴はなく、MRA632JP 試験において、投与期間に依存して発現する有害事象は認められなかった。

表 2.7.4.2.1.4.1-1 有害事象の時期別発現頻度（10%以上発現の事象のみ、MRA632JP 試験-全期間の本剤全投与例）

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY
 Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
No. of Pts treated in each period	36	36	35	32	32	31	24	16	8	3
ALL BODY SYSTEMS										
Total Pts with at Least one AE	34 (94.4)	24 (66.7)	21 (60.0)	17 (53.1)	14 (43.8)	13 (41.9)	13 (54.2)	9 (56.3)	3 (37.5)	2 (66.7)
Total Number of AEs	201	47	38	27	25	26	19	13	4	2
感染症および寄生虫症										
鼻咽頭炎	18 (50.0)	6 (16.7)	6 (17.1)	-	2 (6.3)	1 (3.2)	1 (4.2)	1 (6.3)	1 (12.5)	-
咽頭炎	7 (19.4)	3 (8.3)	1 (2.9)	-	2 (6.3)	-	-	1 (6.3)	-	-
上気道感染	7 (19.4)	4 (11.1)	-	2 (6.3)	1 (3.1)	-	-	-	-	-
胃腸炎	5 (13.9)	1 (2.8)	2 (5.7)	1 (3.1)	1 (3.1)	-	-	-	-	-
感染性腸炎	4 (11.1)	-	1 (2.9)	1 (3.1)	1 (3.1)	-	-	-	1 (12.5)	-
胃腸障害										
下痢	4 (11.1)	1 (2.8)	-	-	-	1 (3.2)	1 (4.2)	1 (6.3)	-	-
筋骨格系および結合組織障害										
筋肉痛	4 (11.1)	1 (2.8)	-	1 (3.1)	1 (3.1)	1 (3.2)	-	-	-	-
背部痛	4 (11.1)	-	1 (2.9)	-	-	1 (3.2)	2 (8.3)	-	-	-
血液およびリンパ系障害										
鉄欠乏性貧血	4 (11.1)	-	1 (2.9)	-	-	1 (3.2)	1 (4.2)	1 (6.3)	-	-

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

[5.3.5.1-7 表 9.2.4-1を再掲]

2.7.4.2.1.4.2 WA28119試験

有害事象の初発時期について12週ごとに集計し、時期別有害事象発現頻度を表 2.7.4.2.1.4.2-1に示す。また、すべての事象ごとの時期別有害事象発現頻度を表 2.7.4.8-10に示す。

有害事象発現頻度は、初回投与後12週に至る前までが最も多く、その後12週ごとの発現頻度は減少傾向であり、初回投与後48週時以降で25.6~36.6%であった。

プラセボ+26週群又はプラセボ+52週群に比べてMRA-SC QW群又はMRA-SC Q2W群で10%以上発現頻度が高かった有害事象（鼻咽頭炎，末梢性浮腫）の発現時期別発現頻度の集計は、概ね全事象の頻度傾向と同様であった。その他のいずれの有害事象の発現頻度においても時期的な特徴はなく、本試験において、投与期間に依存して発現する有害事象は認められなかった。

表 2.7.4.2.1.4.2-1 有害事象の時期別発現頻度（WA28119試験-二重盲検期間）

投与群		0週以降 12週前まで	12週以降 24週前まで	24週以降 36週前まで	36週以降 48週前まで	48週以降
各期間に投与されていた被験者数	プラセボ	n = 50	n = 49	n = 46	n = 43	n = 41
1件以上発現した被験者数 (%)	+26週群	43 (86.0)	40 (81.6)	29 (63.0)	30 (69.8)	15 (36.6)
発現件数		175	97	65	54	17
各期間に投与されていた被験者数	プラセボ	51	47	47	46	46
1件以上発現した被験者数 (%)	+52週群	41 (80.4)	34 (72.3)	28 (59.6)	30 (65.2)	13 (28.3)
発現件数		149	83	76	56	19
各期間に投与されていた被験者数	MRA-SC	100	93	87	84	82
1件以上発現した被験者数 (%)	QW群	78 (78.0)	68 (73.1)	59 (67.8)	51 (60.7)	21 (25.6)
発現件数		279	170	137	93	34
各期間に投与されていた被験者数	MRA-SC	49	48	44	41	40
1件以上発現した被験者数 (%)	Q2W群	39 (79.6)	33 (68.8)	33 (75.0)	25 (61.0)	12 (30.0)
発現件数		159	77	76	57	15
事象名						
鼻咽頭炎	プラセボ+26週群	1 (2.0)	4 (8.2)	1 (2.2)	2 (4.7)	1 (2.4)
	プラセボ+52週群	7 (13.7)	2 (4.3)	-	4 (8.7)	-
	MRA-SC QW群	11 (11.0)	8 (8.6)	7 (8.0)	3 (3.6)	-
	MRA-SC Q2W群	6 (12.2)	2 (4.2)	3 (6.8)	1 (2.4)	-
末梢性浮腫	プラセボ+26週群	5 (10.0)	1 (2.0)	1 (2.2)	1 (2.3)	-
	プラセボ+52週群	4 (7.8)	1 (2.1)	-	1 (2.2)	-
	MRA-SC QW群	4 (4.0)	3 (3.2)	8 (9.2)	-	1 (1.2)
	MRA-SC Q2W群	5 (10.2)	3 (6.3)	2 (4.5)	1 (2.4)	1 (2.5)

[表 2.7.4.8-10を改変]

2.7.4.2.1.5 死亡

MRA632JP試験及びWA28119試験では死亡例は認められなかった。

2.7.4.2.1.6 その他の重篤な有害事象

(1) MRA632JP試験

二重盲検期間及び全期間の本剤全投与例の重篤な有害事象の事象別発現例数を表 2.7.4.2.1.6-1に、二重盲検期間及び全期間の本剤全投与例の重篤な有害事象一覧をそれぞれ表 2.7.4.8-11及び表 2.7.4.8-12に示した。

二重盲検期間の重篤な有害事象の発現頻度は、プラセボ群が2/18例（11.1%，白内障1例，及び、1例に発現した出血性ショック及び出血性胃潰瘍），MRA-SC群が1/18例（5.6%，白内障1

例)であった。いずれの事象も治験薬との因果関係は否定された。重篤な有害事象の発現頻度で、両群間で大きな違いはなかった。

全期間の本剤全投与例における重篤な有害事象の発現頻度は、6/36例(16.7%)であった。この内、非盲検期間に発現した重篤な有害事象は5例(急性腎盂腎炎、肺炎、齲歯、肺梗塞及び複合性局所疼痛症候群)であり、治験薬との因果関係が否定されなかったのは3例(急性腎盂腎炎、肺炎及び複合性局所疼痛症候群)であった。

表 2.7.4.2.1.6-1 重篤な有害事象の集計

(上 : MRA632JP 試験-二重盲検期間, 下 : MRA632JP 試験-全期間の本剤全投与例)

aet02_sae_sp Serious Adverse Events
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Overall total number of patients with at least one adverse event	2 (11.1%)	1 (5.6%)
Overall total number of events	3	1
眼障害		
Total number of patients with at least one adverse event	1 (5.6%)	1 (5.6%)
Total number of events	1	1
白内障	1 (5.6%)	1 (5.6%)
胃腸障害		
Total number of patients with at least one adverse event	1 (5.6%)	0
Total number of events	1	0
出血性胃潰瘍	1 (5.6%)	0
血管障害		
Total number of patients with at least one adverse event	1 (5.6%)	0
Total number of events	1	0
出血性ショック	1 (5.6%)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Percentages are based on N.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet02.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet02_sae_sp.out
 21DEC2015 21:19

aet02_sae_mt_sp Serious Adverse Events
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)
Overall total number of patients with at least one adverse event	6 (16.7%)
Overall total number of events	6
感染症および寄生虫症	
Total number of patients with at least one adverse event	2 (5.6%)
Total number of events	2
急性腎盂腎炎	1 (2.8%)
肺炎	1 (2.8%)
胃腸障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
齦菌	1 (2.8%)
眼障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
白内障	1 (2.8%)
呼吸器、胸郭および縦隔障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
肺梗塞	1 (2.8%)
神経系障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
複合性局所疼痛症候群	1 (2.8%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet02.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet02_sae_mt_sp.out
 12JAN2017 17:03

(2) WA28119試験

二重盲検期間の重篤な有害事象の事象別発現例数を表 2.7.4.2.1.6-2に、治験薬又は副腎皮質ステロイドの重篤な副作用の事象別発現例数を表 2.7.4.2.1.6-3に、それらの重篤な有害事象一覧を表 2.7.4.8-13にそれぞれ示した。

重篤な有害事象の発現頻度は、プラセボ+26週群が11/50例（22.0%）、プラセボ+52週群が13/51例（25.5%）、MRA-SC QW 群が15/100例（15.0%）、MRA-SC Q2W 群が7/49例（14.3%）であり、プラセボ投与群に比べて MRA-SC 投与群で低かった。重篤な有害事象の内、治験薬の副作用はプラセボ+26週群が4/50例（8.0%）、プラセボ+52週群が6/51例（11.8%）、MRA-SC QW 群が4/100例（4.0%）、MRA-SC Q2W 群が2/49例（4.1%）であった。治験薬又は副腎皮質ステロイドに対する副作用はプラセボ+26週群が7/50例（14.0%）、プラセボ+52週群が6/51例（11.8%）、MRA-SC QW 群が6/100例（6.0%）、MRA-SC Q2W 群が2/49例（4.1%）であった。いずれかの群に2例以上認められた重篤な治験薬又は副腎皮質ステロイドの副作用は帯状疱疹（プラセボ+52週群に2例、MRA-SC QW 群に1例）であった。その他の事象は、プラセボ+26週群の肺炎、丹毒、鼻の炎症、口腔咽頭痛、錯感覚、失神、緑内障、口内炎、関節痛各1例、プラセボ+52週群の陰部帯状疱疹、気道感染、労作性呼吸困難、慢性心不全、肝酵素上昇各1例、MRA-SC QW 群の肺炎、胃腸炎、ヘモフィルス性肺炎、腎盂腎炎、頻脈性不整脈各1例、MRA-SC Q2W 群の過敏症、感染性胆管炎各1例であった（表 2.7.4.2.1.6-3）。重篤な治験薬に対する副作用の内、転帰が未回復であった慢性心不全以外はいずれも回復に至った。

表 2.7.4.2.1.6-2 重篤な有害事象の集計 (WA28119試験-二重盲検期間)

t_ae_se_ser_sp Serious Adverse Events (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	11 (22.0%)	13 (25.5%)	15 (15.0%)	7 (14.3%)
Overall total number of events	15	21	27	10
感染症および寄生虫症				
Total number of patients with at least one adverse event	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Total number of events	2	6	9	2
胃腸炎	0	2 (3.9%)	1 (1.0%)	0
带状疱疹	0	2 (3.9%)	1 (1.0%)	0
肺炎	1 (2.0%)	0	1 (1.0%)	0
蜂巣炎	0	0	1 (1.0%)	1 (2.0%)
ヘモフィルス性肺炎	0	0	1 (1.0%)	0
陰部带状疱疹	0	1 (2.0%)	0	0
感染性胆管炎	0	0	0	1 (2.0%)
気道感染	0	1 (2.0%)	0	0
腎盂腎炎	0	0	1 (1.0%)	0
丹毒	1 (2.0%)	0	0	0
尿路感染	0	0	1 (1.0%)	0
尿路性敗血症	0	0	1 (1.0%)	0
慢性副鼻腔炎	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_ser.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_ser_sp.out
 04OCT2016 17:55

t_ae_se_ser_sp Serious Adverse Events (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血管障害				
Total number of patients with at least one adverse event	2 (4.0%)	1 (2.0%)	4 (4.0%)	2 (4.1%)
Total number of events	2	1	5	2
側頭動脈炎	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
高血圧クリーゼ	0	0	2 (2.0%)	0
乾性壊疽	0	0	0	1 (2.0%)
高血圧	1 (2.0%)	0	0	0
深部静脈血栓症	0	0	1 (1.0%)	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
Total number of events	2	2	2	1
胸水	0	0	1 (1.0%)	0
呼吸困難	0	0	0	1 (2.0%)
口腔咽頭痛	1 (2.0%)	0	0	0
肺塞栓症	0	0	1 (1.0%)	0
鼻の炎症	1 (2.0%)	0	0	0
労作性呼吸困難	0	1 (2.0%)	0	0
喘息	0	1 (2.0%)	0	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
Total number of events	1	0	3	1
アルコール中毒	0	0	1 (1.0%)	0
術後創合併症	1 (2.0%)	0	0	0
半月板損傷	0	0	0	1 (2.0%)
裂傷	0	0	1 (1.0%)	0
腱断裂	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_ser. sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_ser_sp.out
 04OCT2016 17:55

t_ae_se_ser_sp Serious Adverse Events (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
神経系障害				
Total number of patients with at least one adverse event	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
Total number of events	2	1	1	1
一過性脳虚血発作	0	1 (2.0%)	0	0
血栓性脳卒中	0	0	0	1 (2.0%)
錯感覚	1 (2.0%)	0	0	0
失神	1 (2.0%)	0	0	0
頭痛	0	0	1 (1.0%)	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	1 (1.0%)	0
Total number of events	1	2	1	0
関節痛	1 (2.0%)	0	0	0
線維筋痛	0	1 (2.0%)	0	0
変形性関節症	0	1 (2.0%)	0	0
腱痛	0	0	1 (1.0%)	0
心臓障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	2 (2.0%)	0
Total number of events	0	3	2	0
上室性頻脈	0	0	1 (1.0%)	0
心不全	0	1 (2.0%)	0	0
大動脈弁狭窄	0	1 (2.0%)	0	0
頻脈性不整脈	0	0	1 (1.0%)	0
慢性心不全	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_ser.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_ser_sp.out
 04OCT2016 17:55

Page 3 of 5

t_ae_se_ser_sp Serious Adverse Events (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
胃腸障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	1 (1.0%)	0
Total number of events	3	0	1	0
びらん性胃炎	1 (2.0%)	0	0	0
下痢	0	0	1 (1.0%)	0
口内炎	1 (2.0%)	0	0	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）				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	0	1 (2.0%)
Total number of events	1	1	0	1
悪性黒色腫	0	1 (2.0%)	0	0
乳癌	1 (2.0%)	0	0	0
卵巣腺腫	0	0	0	1 (2.0%)
眼障害				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	0	0
Total number of events	1	2	0	0
白内障	0	1 (2.0%)	0	0
緑内障	1 (2.0%)	0	0	0
代謝および栄養障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	1 (2.0%)
Total number of events	0	1	0	1
低カリウム血症	0	1 (2.0%)	0	0
低ナトリウム血症	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_ser.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_ser_sp.out
 04OCT2016 17:55

Page 4 of 5

t_ae_se_ser_sp Serious Adverse Events (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
免疫系障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	1 (2.0%)
Total number of events	0	0	1	1
過敏症	0	0	0	1 (2.0%)
薬物過敏症	0	0	1 (1.0%)	0
腎および尿路障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	0
Total number of events	0	1	0	0
腎機能障害	0	1 (2.0%)	0	0
精神障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	2	0
ストレス	0	0	1 (1.0%)	0
不安	0	0	1 (1.0%)	0
臨床検査				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	0
Total number of events	0	1	0	0
肝酵素上昇	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_ser.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_ser_sp.out
 04OCT2016 17:55

表 2.7.4.2.1.6-3 重篤な治験薬又は副腎皮質ステロイドの副作用の集計 (WA28119試験-二重盲検期間)

Serious Adverse Events Related to Study Treatment, Safety Population
Protocol: WA28119

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one adverse event	7 (14.0%)	6 (11.8%)	6 (6.0%)	2 (4.1%)
Overall total number of events	9	7	6	2
感染症および寄生虫症				
Total number of patients with at least one adverse event	2 (4.0%)	4 (7.8%)	5 (5.0%)	1 (2.0%)
Total number of events	2	4	5	1
帯状疱疹	0	2 (3.9%)	1 (1.0%)	0
肺炎	1 (2.0%)	0	1 (1.0%)	0
感染性胆管炎	0	0	0	1 (2.0%)
丹毒	1 (2.0%)	0	0	0
胃腸炎	0	0	1 (1.0%)	0
陰部帯状疱疹	0	1 (2.0%)	0	0
ヘモフィルス性肺炎	0	0	1 (1.0%)	0
腎盂腎炎	0	0	1 (1.0%)	0
気道感染	0	1 (2.0%)	0	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	2 (4.0%)	1 (2.0%)	0	0
Total number of events	2	1	0	0
労作性呼吸困難	0	1 (2.0%)	0	0
鼻の炎症	1 (2.0%)	0	0	0
口腔咽頭痛	1 (2.0%)	0	0	0
心臓障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	1 (1.0%)	0
Total number of events	0	1	1	0
慢性心不全	0	1 (2.0%)	0	0
頻脈性不整脈	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Study Treatment refers to SC TCZ/Placebo and/or Prednisone.

Serious Adverse Events Related to Study Treatment, Safety Population
Protocol: WA28119

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
神経系障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	0	0
Total number of events	2	0	0	0
錯感覚	1 (2.0%)	0	0	0
失神	1 (2.0%)	0	0	0
眼障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
緑内障	1 (2.0%)	0	0	0
胃腸障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
口内炎	1 (2.0%)	0	0	0
免疫系障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
過敏症	0	0	0	1 (2.0%)
臨床検査				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	0
Total number of events	0	1	0	0
肝酵素上昇	0	1 (2.0%)	0	0
筋骨格および結合組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
関節痛	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Study Treatment refers to SC TCZ/Placebo and/or Prednisone.

2.7.4.2.1.7 その他の重要な有害事象

その他重要な有害事象として、中止に至った有害事象、投与間隔の延長又は休薬に至った有害事象、投与部位反応、特に注目すべき有害事象（AESI）について以下に記載する。

2.7.4.2.1.7.1 中止に至った有害事象

(1) MRA632JP 試験

二重盲検期間及び非盲検期間を通じて治験薬の投与中止に至った有害事象は認められなかった。

(2) WA28119試験

治験薬の投与中止に至った有害事象はプラセボ+26週群が3/50例（6.0%）、プラセボ+52週群には該当例がなく、MRA-SC QW 群が11/100例（11.0%）、MRA-SC Q2W 群が5/49例（10.2%）であった（表 2.7.4.2.1.7.1-1）。治験薬又は副腎皮質ステロイドの投与中止に至った有害事象はプラセボ+26週群が6/50例（12.0%）、プラセボ+52週群には該当例がなく、MRA-SC QW 群が11/100例（11.0%）、MRA-SC Q2W 群が6/49例（12.2%）であった。いずれかの群に2例以上認められた有害事象はなかった（表 2.7.4.2.1.7.1-2）。この内治験薬に対する副作用はプラセボ+26週群が1/50例（2.0%）、MRA-SC QW 群が6/100例（6.0%）、MRA-SC Q2W 群が2/49例（4.1%）であった。その内訳は、プラセボ+26週群の1例に発現した鼻の炎症及び口内炎、MRA-SC QW 群の好中球減少症、肺炎、帯状疱疹、胃腸炎、辺縁帯リンパ腫各1例、1例に発現したヘモフィルス性肺炎及び敗血症、MRA-SC Q2W 群の発疹、過敏症各1例であった（5.3.5.1-3 Page 3323）。これらの内、治験薬の副作用は未回復であった辺縁帯リンパ腫及び転帰不明であった発疹を除いていずれも回復に至った。

表 2.7.4.2.1.7.1-1 治験薬の投与中止に至った有害事象の集計 (WA28119試験-二重盲検期間)

t_ae_se_dsct_sp Adverse Events leading to Discontinuation of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	3 (6.0%)	0	11 (11.0%)	5 (10.2%)
Overall total number of events	4	0	22	6
感染症および寄生虫症				
Total number of patients with at least one adverse event	0	0	5 (5.0%)	1 (2.0%)
Total number of events	0	0	7	1
ヘモフィルス性肺炎	0	0	1 (1.0%)	0
胃腸炎	0	0	1 (1.0%)	0
帯状疱疹	0	0	1 (1.0%)	0
敗血症	0	0	1 (1.0%)	0
肺炎	0	0	1 (1.0%)	0
蜂巣炎	0	0	0	1 (2.0%)
慢性副鼻腔炎	0	0	1 (1.0%)	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	3 (3.0%)	0
Total number of events	1	0	3	0
筋力低下	1 (2.0%)	0	0	0
四肢痛	0	0	1 (1.0%)	0
脊椎炎	0	0	1 (1.0%)	0
変形性関節症	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsct.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsct_sp.out
 120CT2016 18:53

t_ae_se_dsct_sp Adverse Events leading to Discontinuation of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血管障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	2 (4.1%)
Total number of events	0	0	2	2
乾性壊疽	0	0	0	1 (2.0%)
深部静脈血栓症	0	0	1 (1.0%)	0
側頭動脈炎	0	0	0	1 (2.0%)
胃腸障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
悪心	0	0	1 (1.0%)	0
口内炎	1 (2.0%)	0	0	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	0	0	2 (2.0%)	0
Total number of events	0	0	3	0
好中球減少症	0	0	1 (1.0%)	0
白血球増加症	0	0	1 (1.0%)	0
貧血	0	0	1 (1.0%)	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
胸水	0	0	1 (1.0%)	0
鼻の炎症	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsct.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsct_sp.out
 120CT2016 18:53

t_ae_se_dsct_sp Adverse Events leading to Discontinuation of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
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）				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
乳癌	1 (2.0%)	0	0	0
辺縁帯リンパ腫	0	0	1 (1.0%)	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
末梢性浮腫	0	0	1 (1.0%)	0
眼障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
虚血性視神経症	0	0	0	1 (2.0%)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
腱断裂	0	0	1 (1.0%)	0
精神障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
不安	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsct.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsct_sp.out
 120CT2016 18:53

Page 3 of 4

t_ae_se_dsct_sp Adverse Events leading to Discontinuation of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
発疹	0	0	0	1 (2.0%)
免疫系障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
過敏症	0	0	0	1 (2.0%)
臨床検査				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
血中クレアチンホスホキナーゼ増加	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
 Table includes AEs that lead to blinded SC discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsct.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsct_sp.out
 12OCT2016 18:53

Page 4 of 4

[5.3.5.3-1 表 2.4-9を再掲]

表 2.7.4.2.1.7.1-2 治験薬又は副腎皮質ステロイドの投与中止に至った有害事象の集計 (WA28119試験-二重盲検期間)

t_ae_se_dsc_sp Adverse Events leading to Discontinuation of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	6 (12.0%)	0	11 (11.0%)	6 (12.2%)
Overall total number of events	7	0	22	7
感染症および寄生虫症				
Total number of patients with at least one adverse event	1 (2.0%)	0	5 (5.0%)	1 (2.0%)
Total number of events	1	0	7	1
肺炎	1 (2.0%)	0	1 (1.0%)	0
ヘモフィルス性肺炎	0	0	1 (1.0%)	0
胃腸炎	0	0	1 (1.0%)	0
带状疱疹	0	0	1 (1.0%)	0
敗血症	0	0	1 (1.0%)	0
蜂巣炎	0	0	0	1 (2.0%)
慢性副鼻腔炎	0	0	1 (1.0%)	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	3 (3.0%)	0
Total number of events	2	0	3	0
筋肉痛	1 (2.0%)	0	0	0
筋力低下	1 (2.0%)	0	0	0
四肢痛	0	0	1 (1.0%)	0
脊椎炎	0	0	1 (1.0%)	0
変形性関節症	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
 Table includes AEs that lead to blinded SC and/or prednisone discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsc_sp.out
 04OCT2016 17:56

t_ae_se_dsc_sp Adverse Events leading to Discontinuation of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
胃腸障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
Total number of events	1	0	1	1
悪心	0	0	1 (1.0%)	0
口内炎	1 (2.0%)	0	0	0
歯の知覚過敏	0	0	0	1 (2.0%)
血管障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	2 (4.1%)
Total number of events	0	0	2	2
乾性壞疽	0	0	0	1 (2.0%)
深部静脈血栓症	0	0	1 (1.0%)	0
側頭動脈炎	0	0	0	1 (2.0%)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	0	0	2 (2.0%)	0
Total number of events	0	0	3	0
好中球減少症	0	0	1 (1.0%)	0
白血球増加症	0	0	1 (1.0%)	0
貧血	0	0	1 (1.0%)	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
胸水	0	0	1 (1.0%)	0
鼻の炎症	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC and/or prednisone discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsc_sp.out
 04OCT2016 17:56

Page 2 of 4

t_ae_se_dsc_sp Adverse Events leading to Discontinuation of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
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）				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
乳癌	1 (2.0%)	0	0	0
辺縁帯リンパ腫	0	0	1 (1.0%)	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
末梢性浮腫	0	0	1 (1.0%)	0
眼障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
虚血性視神経症	0	0	0	1 (2.0%)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
腱断裂	0	0	1 (1.0%)	0
神経系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
坐骨神経痛	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC and/or prednisone discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsc_sp.out
 04OCT2016 17:56

Page 3 of 4

t_ae_se_dsc_sp Adverse Events leading to Discontinuation of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
精神障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
不安	0	0	1 (1.0%)	0
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
発疹	0	0	0	1 (2.0%)
免疫系障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
過敏症	0	0	0	1 (2.0%)
臨床検査				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
血中クレアチンホスホキナーゼ増加	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table includes AEs that lead to blinded SC and/or prednisone discontinuation.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsc_sp.out
 04OCT2016 17:56

Page 4 of 4

[5.3.5.3-1 表 2.4-10を再掲]

2.7.4.2.1.7.2 投与間隔の延長又は休薬に至った有害事象

(1) MRA632JP 試験

二重盲検期間における投与間隔の延長又は休薬に至った有害事象の発現頻度はプラセボ群が2/18例 (11.1%) , MRA-SC 群が3/18例 (16.7%) であった (表 2.7.4.2.1.7.2-1) 。MRA-SC 群ではいずれも「感染症および寄生虫症」に分類される事象であった。副作用は、プラセボ群では帯状疱疹、MRA-SC 群では上気道感染、胃腸炎及び鼻咽頭炎であった。プラセボ群に認められた出血性胃潰瘍は重症度が高度であり、重篤な有害事象であった。その他の事象はいずれも重症度は軽度であった。いずれの事象も回復に至った。

全期間の本剤全投与例における投与間隔の延長又は休薬に至った有害事象の発現頻度は16/36例 (44.4%) であり (表 2.7.4.2.1.7.2-2) , この内、副作用は12/36例 (33.3%) であった。その内訳は、胃腸炎2例、ヘモフィルス性肺炎、急性腎盂腎炎、肺炎、肝機能異常、せつ、インフルエンザ、上気道感染及び鼻咽頭炎各1例、上気道感染及びβ溶血性レンサ球菌感染を発現した1例、胃腸炎及び鼻咽頭炎を発現した1例であった。この内、重症度が高度であった急性腎盂腎炎を除き、重症度は中等度又は軽度であり、急性腎盂腎炎、肺炎、肝機能異常、上気道感染以外の事象は回復に至った。

表 2.7.4.2.1.7.2-1 治験薬の投与間隔の延長又は休薬に至った有害事象の集計 (MRA632JP 試験-二重盲検期間)

aet02_mod_sp Adverse Events Leading to Modification or Interruption of Trial Drug
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Overall total number of patients with at least one adverse event	2 (11.1%)	3 (16.7%)
Overall total number of events	3	4
感染症および寄生虫症		
Total number of patients with at least one adverse event	1 (5.6%)	3 (16.7%)
Total number of events	1	4
上気道感染	0	2 (11.1%)
胃腸炎	0	1 (5.6%)
帯状疱疹	1 (5.6%)	0
鼻咽頭炎	0	1 (5.6%)
胃腸障害		
Total number of patients with at least one adverse event	1 (5.6%)	0
Total number of events	1	0
出血性胃潰瘍	1 (5.6%)	0
呼吸器、胸郭および縦隔障害		
Total number of patients with at least one adverse event	1 (5.6%)	0
Total number of events	1	0
喀血	1 (5.6%)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Percentages are based on N.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet02.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet02_mod_sp.out
 21DEC2015 21:20

表 2.7.4.2.1.7.2-2 治験薬の投与間隔の延長又は休薬に至った有害事象の集計
(MRA632JP 試験-全期間の本剤全投与例)

aet02_mod_mt_sp Adverse Events Leading to Modification or Interruption of Trial Drug
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)
Overall total number of patients with at least one adverse event	16 (44.4%)
Overall total number of events	22
感染症および寄生虫症	
Total number of patients with at least one adverse event	14 (38.9%)
Total number of events	20
胃腸炎	3 (8.3%)
上気道感染	3 (8.3%)
鼻咽頭炎	3 (8.3%)
咽頭炎	2 (5.6%)
感染性腸炎	2 (5.6%)
せつ	1 (2.8%)
インフルエンザ	1 (2.8%)
ヘモフィルス性肺炎	1 (2.8%)
β溶血性レンサ球菌感染	1 (2.8%)
急性腎盂腎炎	1 (2.8%)
爪囲炎	1 (2.8%)
肺炎	1 (2.8%)
肝胆道系障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
肝機能異常	1 (2.8%)
呼吸器、胸郭および縦隔障害	
Total number of patients with at least one adverse event	1 (2.8%)
Total number of events	1
肺梗塞	1 (2.8%)

Percentages are based on N in the column headings.
Investigator text for Adverse Events encoded using MedDRA version 17.1.
Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet02.sas
Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet02_mod_mt_sp.out
12JAN2017 17:03

(2) WA28119試験

二重盲検期間に治験薬の投与間隔の延長、休薬に至った有害事象はプラセボ+26週群が10/50例 (20.0%)、プラセボ+52週群が11/51例 (21.6%)、MRA-SC QW 群が28/100例 (28.0%)、MRA-SC Q2W 群が8/49例 (16.3%)であった(表 2.7.4.2.1.7.2-3)。治験薬若しくは副腎皮質ステロイドの投与間隔の延長、休薬、又は非盲検副腎皮質ステロイドの減量に至った有害事象の発現頻度はプラセボ+26週群が12/50例 (24.0%)、プラセボ+52週群が17/51例 (33.3%)、MRA-SC QW 群が33/100例 (33.0%)、MRA-SC Q2W 群が10/49例 (20.4%)であった。いずれかの群に2例以上認められた有害事象は、鼻咽頭炎(プラセボ+52週群に2例、MRA-SC QW 群に4例、MRA-SC Q2W 群に1例)、上気道感染(プラセボ+26週群に1例、MRA-SC QW 群に3例、MRA-SC Q2W 群に1例)、気管支炎(プラセボ+52週群に2例、MRA-SC QW 群に1例、MRA-SC Q2W 群に1例)、尿路感染(プラセボ+26週群に1例、プラセボ+52週群に1例、MRA-SC QW 群に2例)、ALT 増加(MRA-SC QW 群に4例、MRA-SC Q2W 群に1例)、AST 増加及び好中球減少症(いずれも MRA-SC QW 群に3例)、下気道感染及び白血球減少症(いずれも MRA-SC QW 群に2例)であった(表 2.7.4.2.1.7.2-4)。治験薬の副作用はプラセボ+26週群が6/50例 (12.0%)、プラセボ+52週群が6/51例 (11.8%)、MRA-SC QW 群が12/100例 (12.0%)、

MRA-SC Q2W 群が4/49例（8.2%）であった。この内、重症度がグレード2であった大腸炎1例（MRA-SC QW 群）は未回復であったが、その事象以外はいずれの事象も回復に至った。

表 2.7.4.2.1.7.2-3 治験薬の投与間隔の延長又は休薬に至った有害事象の集計 (WA28119試験-二重盲検期間)

t_ae_se_dsmt_sp Adverse Events Leading to Modification or Interruption of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	10 (20.0%)	11 (21.6%)	28 (28.0%)	8 (16.3%)
Overall total number of events	21	23	43	12
感染症および寄生虫症				
Total number of patients with at least one adverse event	7 (14.0%)	9 (17.6%)	17 (17.0%)	5 (10.2%)
Total number of events	14	16	21	7
鼻咽頭炎	0	1 (2.0%)	4 (4.0%)	1 (2.0%)
上気道感染	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
気管支炎	0	2 (3.9%)	1 (1.0%)	1 (2.0%)
尿路感染	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
丹毒	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
下気道感染	0	0	2 (2.0%)	0
喉頭炎	0	1 (2.0%)	1 (1.0%)	0
帯状疱疹	0	1 (2.0%)	1 (1.0%)	0
副鼻腔炎	0	1 (2.0%)	0	1 (2.0%)
膀胱炎	1 (2.0%)	1 (2.0%)	0	0
せつ	1 (2.0%)	0	0	0
ウイルス感染	0	0	0	1 (2.0%)
サイトメガロウイルス感染	0	1 (2.0%)	0	0
ヘルペスウイルス感染	1 (2.0%)	0	0	0
胃腸炎	0	1 (2.0%)	0	0
陰部帯状疱疹	0	1 (2.0%)	0	0
感染性腸炎	0	1 (2.0%)	0	0
気道感染	0	1 (2.0%)	0	0
憩室炎	0	1 (2.0%)	0	0
限局性感染	0	0	1 (1.0%)	0
細菌性眼感染	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

t_ae_se_dsmt_sp Adverse Events Leading to Modification or Interruption of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
歯周炎	0	1 (2.0%)	0	0
歯髄炎	0	0	0	1 (2.0%)
腎盂腎炎	1 (2.0%)	0	0	0
創傷感染	0	0	1 (1.0%)	0
乳房蜂巣炎	0	0	1 (1.0%)	0
肺炎	1 (2.0%)	0	0	0
肺感染	1 (2.0%)	0	0	0
蜂巣炎	0	0	1 (1.0%)	0
胃腸障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	5 (5.0%)	0
Total number of events	0	2	6	0
垂イレウス	0	0	1 (1.0%)	0
悪心	0	1 (2.0%)	0	0
胃炎	0	0	1 (1.0%)	0
下痢	0	0	1 (1.0%)	0
歯肉潰瘍	0	0	1 (1.0%)	0
上腹部痛	0	1 (2.0%)	0	0
大腸炎	0	0	1 (1.0%)	0
腸憩室	0	0	1 (1.0%)	0
臨床検査				
Total number of patients with at least one adverse event	0	1 (2.0%)	4 (4.0%)	1 (2.0%)
Total number of events	0	1	7	2
アラニンアミノトランスフェラーゼ増加	0	0	4 (4.0%)	1 (2.0%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	3 (3.0%)	0
肝酵素上昇	0	1 (2.0%)	0	0
血小板数減少	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsmt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsmt_sp.out
 12OCT2016 18:54

Page 2 of 5

t_ae_se_dsmt_sp Adverse Events Leading to Modification or Interruption of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	4 (4.0%)	0
Total number of events	1	0	5	0
好中球減少症	0	0	3 (3.0%)	0
白血球減少症	0	0	2 (2.0%)	0
リンパ節症	1 (2.0%)	0	0	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
Total number of events	1	3	0	1
発熱	1 (2.0%)	1 (2.0%)	0	0
悪寒	0	1 (2.0%)	0	0
嚢胞	0	1 (2.0%)	0	0
末梢性浮腫	0	0	0	1 (2.0%)
血管障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	1 (2.0%)
Total number of events	1	0	0	1
リンパうっ滞	0	0	0	1 (2.0%)
側頭動脈炎	1 (2.0%)	0	0	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
歯牙破折	0	0	1 (1.0%)	0
術後創合併症	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsmt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsmt_sp.out
 120CT2016 18:54

Page 3 of 5

t_ae_se_dsmt_sp Adverse Events Leading to Modification or Interruption of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
外科および内科処置				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
股関節形成	1 (2.0%)	0	0	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
背部痛	0	0	1 (1.0%)	0
心臓障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
動悸	1 (2.0%)	0	0	0
神経系障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
頭痛	0	0	1 (1.0%)	0
製品の問題				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
医療機器破損	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsmt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsmt_sp.out
 12OCT2016 18:54

t_ae_se_dsmt_sp Adverse Events Leading to Modification or Interruption of TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
代謝および栄養障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
低ナトリウム血症	0	0	0	1 (2.0%)
免疫系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
薬物過敏症	1 (2.0%)	0	0	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)				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	0
Total number of events	0	1	0	0
消化器の良性新生物	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsmt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsmt_sp.out
 12OCT2016 18:54

表 2.7.4.2.1.7.2-4 治験薬又は副腎皮質ステロイドの投与間隔の延長又は休薬に至った有害事象の集計 (WA28119試験-二重盲検期間)

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	12 (24.0%)	17 (33.3%)	33 (33.0%)	10 (20.4%)
Overall total number of events	24	31	52	16
感染症および寄生虫症				
Total number of patients with at least one adverse event	7 (14.0%)	10 (19.6%)	18 (18.0%)	7 (14.3%)
Total number of events	14	18	22	9
鼻咽頭炎	0	2 (3.9%)	4 (4.0%)	1 (2.0%)
上気道感染	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
気管支炎	0	2 (3.9%)	1 (1.0%)	1 (2.0%)
尿路感染	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
丹毒	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
胃腸炎	0	1 (2.0%)	0	1 (2.0%)
下気道感染	0	0	2 (2.0%)	0
喉頭炎	0	1 (2.0%)	1 (1.0%)	0
带状疱疹	0	1 (2.0%)	1 (1.0%)	0
肺炎	1 (2.0%)	0	1 (1.0%)	0
副鼻腔炎	0	1 (2.0%)	0	1 (2.0%)
蜂巣炎	0	0	1 (1.0%)	1 (2.0%)
膀胱炎	1 (2.0%)	1 (2.0%)	0	0
せつ	1 (2.0%)	0	0	0
ウイルス感染	0	0	0	1 (2.0%)
サイトメガロウイルス感染	0	1 (2.0%)	0	0
ヘルペスウイルス感染	1 (2.0%)	0	0	0
陰部带状疱疹	0	1 (2.0%)	0	0
感染性腸炎	0	1 (2.0%)	0	0
気道感染	0	1 (2.0%)	0	0
憩室炎	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
限局性感染	0	0	1 (1.0%)	0
細菌性眼感染	1 (2.0%)	0	0	0
歯周炎	0	1 (2.0%)	0	0
歯髄炎	0	0	0	1 (2.0%)
腎盂腎炎	1 (2.0%)	0	0	0
創傷感染	0	0	1 (1.0%)	0
乳房蜂巣炎	0	0	1 (1.0%)	0
肺感染	1 (2.0%)	0	0	0
胃腸障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	5 (5.0%)	0
Total number of events	0	2	6	0
垂イレウス	0	0	1 (1.0%)	0
悪心	0	1 (2.0%)	0	0
胃炎	0	0	1 (1.0%)	0
下痢	0	0	1 (1.0%)	0
歯肉潰瘍	0	0	1 (1.0%)	0
上腹部痛	0	1 (2.0%)	0	0
大腸炎	0	0	1 (1.0%)	0
腸憩室	0	0	1 (1.0%)	0
臨床検査				
Total number of patients with at least one adverse event	0	1 (2.0%)	4 (4.0%)	1 (2.0%)
Total number of events	0	1	7	2
アラニンアミノトランスフェラーゼ増加	0	0	4 (4.0%)	1 (2.0%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	3 (3.0%)	0
肝酵素上昇	0	1 (2.0%)	0	0
血小板数減少	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp.out
 04OCT2016 17:57

Page 2 of 7

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	4 (4.0%)	0
Total number of events	1	0	5	0
好中球減少症	0	0	3 (3.0%)	0
白血球減少症	0	0	2 (2.0%)	0
リンパ節症	1 (2.0%)	0	0	0
血管障害				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
Total number of events	1	1	1	2
側頭動脈炎	1 (2.0%)	1 (2.0%)	0	0
リンパうっ滞	0	0	0	1 (2.0%)
乾性壊疽	0	0	0	1 (2.0%)
高血圧クリーゼ	0	0	1 (1.0%)	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
Total number of events	1	3	0	1
発熱	1 (2.0%)	1 (2.0%)	0	0
悪寒	0	1 (2.0%)	0	0
膿胞	0	1 (2.0%)	0	0
末梢性浮腫	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp.out
 04OCT2016 17:57

Page 3 of 7

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
Total number of events	1	1	2	0
関節炎	0	0	1 (1.0%)	0
頸部痛	1 (2.0%)	0	0	0
線維筋痛	0	1 (2.0%)	0	0
背部痛	0	0	1 (1.0%)	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	1 (2.0%)	0	3 (3.0%)	0
Total number of events	1	0	4	0
歯牙破折	0	0	1 (1.0%)	0
術後創合併症	1 (2.0%)	0	0	0
転倒	0	0	1 (1.0%)	0
腱断裂	0	0	1 (1.0%)	0
靭帯捻挫	0	0	1 (1.0%)	0
心臓障害				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Total number of events	1	1	1	0
心不全	0	1 (2.0%)	0	0
動悸	1 (2.0%)	0	0	0
頻脈性不整脈	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp.out
 04OCT2016 17:57

Page 4 of 7

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
眼障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	1 (1.0%)	0
Total number of events	0	1	1	0
白内障	0	1 (2.0%)	0	0
霧視	0	0	1 (1.0%)	0
神経系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	1 (1.0%)	0
Total number of events	1	0	1	0
頭痛	1 (2.0%)	0	1 (1.0%)	0
精神障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	0	0
Total number of events	0	2	0	0
易刺激性	0	1 (2.0%)	0	0
不眠症	0	1 (2.0%)	0	0
外科および内科処置				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
股関節形成	1 (2.0%)	0	0	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
鼻茸	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp.out
 04OCT2016 17:57

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
耳および迷路障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
前庭障害	1 (2.0%)	0	0	0
製品の問題				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
医療機器破損	0	0	1 (1.0%)	0
代謝および栄養障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
低ナトリウム血症	0	0	0	1 (2.0%)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
皮膚出血	0	0	0	1 (2.0%)
免疫系障害				
Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
薬物過敏症	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm. sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp. out
 04OCT2016 17:57

t_ae_se_dsm_sp Adverse Events Leading to Modification or Interruption of Trial Drug (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
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）				
Total number of patients with at least one adverse event	0	1 (2.0%)	0	0
Total number of events	0 0	1	0 0	0 0
消化器の良性新生物	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_se_dsm.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_se_dsm_sp.out
 04OCT2016 17:57

Page 7 of 7

[5.3.5.3-1 表 2.4-12を再掲]

2.7.4.2.1.7.3 投与部位反応

(1) MRA632JP 試験

MRA632JP 試験で、治験責任医師又は治験分担医師が投与部位反応と判定した有害事象は、二重盲検期間では認められず、非盲検期間では1/36例（2.8%、注射部位出血）に認められた。この事象と治験薬との因果関係は否定された（5.3.5.1-1 表 15.3.1-7, 5.3.5.1-7 表 11.3-13）。

(2) WA28119試験

WA28119試験の二重盲検期間で、治験責任医師又は治験分担医師が投与部位反応と判定した有害事象は、プラセボ+26週群が5/50例（10.0%）、プラセボ+52週群が1/51例（2.0%）、MRA-SC QW 群が6/100例（6.0%）、MRA-SC Q2W 群が7/49例（14.3%）であった。いずれかの群に2例以上認められた有害事象は、注射部位そう痒感、注射部位反応（いずれも MRA-SC Q2W 群に2例）であった（表 2.7.4.2.1.7.3-1）。

表 2.7.4.2.1.7.3-1 重症度別投与部位反応の集計 (WA28119試験-二重盲検期間)

System Organ Class Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
- Any adverse events -	- Any Grade -	5	1	6	7
	1	4	1	5	7
	2	1	0	1	0
一般・全身障害および投与部位の状態 - Overall -	- Any Grade -	2	1	2	6
	1	1	1	2	6
	2	1	0	0	0
注射部位血腫	- Any Grade -	0	1	1	0
	1	0	1	1	0
注射部位疼痛	- Any Grade -	1	0	0	1
	1	0	0	0	1
	2	1	0	0	0
注射部位そう痒感	- Any Grade -	0	0	0	2
	1	0	0	0	2
注射部位反応	- Any Grade -	0	0	0	2
	1	0	0	0	2
注射部位内出血	- Any Grade -	0	0	0	1
	1	0	0	0	1
注射部位紅斑	- Any Grade -	0	0	0	1
	1	0	0	0	1
注射部位出血	- Any Grade -	0	0	1	0
	1	0	0	1	0
注射部位蕁麻疹	- Any Grade -	0	0	0	1
	1	0	0	0	1
末梢性浮腫	- Any Grade -	1	0	0	0
	1	1	0	0	0
皮膚および皮下組織障害 - Overall -	- Any Grade -	1	0	2	0
	1	1	0	1	0
	2	0	0	1	0

Investigator text for AEs encoded using MedDRA version 19.0. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for the highest grade AE within that SOC. Injection site reactions include AEs that have a 'Yes' response for the 'Did the event occur at injection site?' tick box or if there is a preferred term with High Level Term Injection Site Reactions.

System Organ Class Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
紅斑	- Any Grade -	0	0	1	0
	2	0	0	1	0
発疹	- Any Grade -	0	0	1	0
	1	0	0	1	0
皮膚灼熱感	- Any Grade -	1	0	0	0
	1	1	0	0	0
傷害、中毒および処置合併症	- Any Grade -	0	0	1	1
- Overall -	1	0	0	1	1
挫傷	- Any Grade -	0	0	0	1
	1	0	0	0	1
注射に伴う反応	- Any Grade -	0	0	1	0
	1	0	0	1	0
胃腸障害	- Any Grade -	1	0	0	0
- Overall -	1	1	0	0	0
腹腔内血腫	- Any Grade -	1	0	0	0
	1	1	0	0	0
感染症および寄生虫症	- Any Grade -	0	0	1	0
- Overall -	1	0	0	1	0
膿疱性皮疹	- Any Grade -	0	0	1	0
	1	0	0	1	0
血管障害	- Any Grade -	1	0	0	0
- Overall -	1	1	0	0	0
血腫	- Any Grade -	1	0	0	0
	1	1	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for the highest grade AE within that SOC. Injection site reactions include AEs that have a 'Yes' response for the 'Did the event occur at injection site?' tick box or if there is a preferred term with High Level Term Injection Site Reactions.

2.7.4.2.1.7.4 特に注目すべき有害事象 (AESI)

特に注目すべき有害事象（以降、AESI）として、MRA632JP 試験では、感染症、治験薬を介して起こった可能性のある感染性病原体の伝播、ビリルビンの上昇又は臨床的黄疸を伴う ALT 又は AST のいずれかの上昇、消化管穿孔及び関連疾患、アナフィラキシー、出血、肝臓疾患、脳卒中、心筋梗塞／急性冠症候群、悪性腫瘍、脱髄関連疾患を表 2.7.4.2.1.7.4-1 に示す定義により集計した。WA28119試験でも MRA632JP 試験と同様に、感染症、日和見感染、消化管穿孔及び関連疾患、Medical Review により確認された消化管穿孔及び関連疾患、アナフィラキシー、出血、肝臓疾患、脳卒中、心筋梗塞／急性冠症候群、悪性腫瘍、脱髄関連疾患を集計した。

表 2.7.4.2.1.7.4-1 AESI の定義

項目	結果における表記	定義 (MRA632JP 試験)	定義 (WA28119試験)
感染症	Infection (including opportunistic infections)	SOC で「感染症および寄生虫症」に分類される有害事象	
日和見感染	Opportunistic infections	—	Roche Standard AEGT Basket
治験薬を介して起こった可能性のある感染性病原体の伝播	Suspected transmission of infectious agents by Medical Product (STIAMP)	医師により該当すると判断された有害事象 (M5.3.5.1-1 「9.5.4.2(4) 特に注目すべき有害事象」参照)	
ビリルビンの上昇又は臨床的黄疸を伴う ALT 又は AST いずれかの上昇	Potential Hy's Law Cases	正常値上限の2倍を超える総ビリルビン値の上昇を伴う正常値上限の3倍を超える ALT 又は AST の上昇 臨床的な黄疸を伴う正常値上限の3倍を超える ALT 又は AST の上昇	
消化管穿孔及び関連疾患	Gastrointestinal Perforation (Events)	Gastrointestinal Perforation SMQ Wide and Serious に該当する有害事象	Gastrointestinal perforation SMQ Wide
	Gastrointestinal Perforation	—	Gastrointestinal perforation SMQ Wide which confirmed by medical review
アナフィラキシー	Anaphylactic Reactions (Events)	Anaphylactic Reaction SMQ Narrow に該当し、投与後24時間以内に発現した有害事象	
	Anaphylactic Reaction Events	—	Roche Standard AEGT Basket according to Sampson's criteria ¹⁾ which occurring immediately after or within 24 hours of injection of TCZ
出血	Bleeding Events	Hemorrhage terms (excluding lab terms) SMQ Wide に該当する有害事象	
肝臓疾患	Hepatic Events	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ Wide 又は Hepatitis non-infectious SMQ Wide に該当する有害事象	

項目	結果における表記	定義 (MRA632JP 試験)	定義 (WA28119試験)
脳卒中	Stroke	Hemorrhagic cerebrovascular conditions SMQ Narrow 又は Ischemic cerebrovascular conditions SMQ Narrow に該当する有害事象	
心筋梗塞／急性冠症候群	Myocardial infarction/ acute coronary syndrome	Myocardial Infarction SMQ Narrow に該当する有害事象	
悪性腫瘍	Malignancies	Malignant or unspecified Tumors SMQ Narrow に該当する有害事象	
	Malignancies without NMSC	—	Malignancies without NMSC
脱髄関連疾患	Demyelination Events	Demyelination SMQ Narrow に該当する有害事象	

TCZ : トシリズマブ, NMSC : 非黒色腫皮膚がん, AEGT : adverse event grouped term, SMQ : MedDRA 標準検索式

[5.3.5.1-1 表 12.3.1.3-2, 5.3.5.1-3 3.9.7.1項を改変]

AESI の集計を MRA632JP 試験は表 2.7.4.2.1.7.4-2及び表 2.7.4.2.1.7.4-3に, WA28119試験は表 2.7.4.2.1.7.4-4に示す。

表 2.7.4.2.1.7.4-2 AESI の集計 (MRA632JP 試験-二重盲検期間)

aesi_sp Adverse Events of Special Interest
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Total number of patients with at least one adverse event	6 (33.3%)	10 (55.6%)
Total number of events	11	27
Suspected transmission of infectious agents by Medical Product (STIAMP)	0	0
Potential Hy's Law Cases	0	0
Infection (including opportunistic infections)	6 (33.3%)	9 (50.0%)
Gastrointestinal Perforation Events	0	0
Anaphylactic Reactions	0	0
Bleeding Events	3 (16.7%)	2 (11.1%)
Hepatic Events	0	0
Stroke	0	0
Myocardial infarction/ acute coronary syndrome	0	0
Malignancies	0	0
Demyelination Events	0	0
Other	0	0

Percentages are based on N.
 Total number of events : Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aesi.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aesi_sp.out
 28DEC2015 18:18

[5.3.5.1-1 表 12.3.1.3-3を再掲]

表 2.7.4.2.1.7.4-3 AESI の集計 (MRA632JP 試験-全期間の本剤全投与例)

aesi_mt_sp Adverse Events of Special Interest
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

	MRA-SC 162mg/W Total (N=36)
Total number of patients with at least one AESI	31 (86.1%)
Total number of events	123
Potential Hy's Law Cases	0
Suspected transmission of infectious agents by Medical Product (STIAMP)	0
Infection (including opportunistic infections)	31 (86.1%)
Gastrointestinal Perforation Events	0
Anaphylactic Reactions	0
Bleeding Events	9 (25.0%)
Hepatic Events	0
Stroke	0
Myocardial infarction/ acute coronary syndrome	0
Malignancies	0
Demyelination Events	0
Other	0

Percentages are based on N in the column headings.

Total number of events : Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aesi.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aesi_mt_sp.out
 12JAN2017 17:14

Page 1 of 1

[5.3.5.1-7 表 11.3-15を再掲]

表 2.7.4.2.1.7.4-4 AESI の集計 (WA28119試験-二重盲検期間)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Adverse Events of Special Interest:				
Infections and Infestations	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
Serious Infections	2 (4.0%)	6 (11.8%)	7 (7.0%)	2 (4.1%)
Opportunistic Infections	0	2 (3.9%)	0	1 (2.0%)
Malignancy AEs	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Malignancy AEs (excluding NMSC)	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
Serious Hepatic AEs	0	0	0	0
Serious Stroke	0	1 (2.0%)	0	1 (2.0%)
Serious Myocardial Infarction	0	0	0	0
Anaphylactic Reaction AEs (SMQN)	0	0	0	0
Anaphylactic Reaction AEs (Sampson's criteria)	0	0	0	1 (2.0%)*
Serious Gastrointestinal Perforation Adverse Events	0	0	0	0
Gastrointestinal Perforation AE Confirmed by Medical Review	0	0	0	0
Serious Bleeding AEs	0	0	0	0
Serious Demyelinating AEs	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

* The events matching an anaphylactic reaction based on Sampson's criteria (eye pruritus, dyspnoea) were clinically not considered to be anaphylactic in nature. The investigator did not consider either of these events to be related to study drug and there were no modifications to either the TCZ or prednisone dose.

[5.3.5.1-3 Table 34を改変]

(1) 感染症の有害事象

MRA632JP 試験の二重盲検期間において感染症はプラセボ群の6例 (33.3%) , MRA-SC 群の9例 (50.0%) に認められた。例数が少ないものの、MRA-SC 群ではプラセボ群に比べて、10%以上発現頻度が高かった。感染症の内、重篤な有害事象及び重症度が高度であった有害事象は認められず、中等度であった有害事象はプラセボ群の1例に認められた気管支炎であった。気

管支炎は、治験薬との因果関係は否定されており、治療が行われたものの二重盲検期間終了時未回復となった。気管支炎以外の事象の重症度はいずれも軽度であった。感染症の内、プラセボ群の1/6例（帯状疱疹）及び MRA-SC 群の3/9例（上気道感染2例、胃腸炎及び鼻咽頭炎を発現した1例）では治験薬の投与間隔の延長又は休薬が行われ、回復に至った。

MRA632JP 試験の全期間の本剤全投与例において感染症は31例（86.1%）に認められた。重篤な有害事象は2例（急性腎盂腎炎及び肺炎各1例）、重症度が高度であった有害事象は1例（急性腎盂腎炎）認められた。中等度であった有害事象は1例に発現したせつ及び感染性腸炎、別の1例に発現した上気道感染及び咽頭炎、並びにヘモフィルス性肺炎、肺炎、ウイルス性腸炎各1例であった。これらの事象の内、感染性腸炎とウイルス性腸炎以外では、治験薬の投与間隔の延長又は休薬が行われ、ヘモフィルス性肺炎、急性腎盂腎炎、肺炎、せつ、感染性腸炎及びウイルス性腸炎は治験薬との因果関係は否定されなかった。未回復であった急性腎盂腎炎、肺炎及びウイルス性腸炎を除き、いずれも回復に至った（5.3.5.1-7 表 11.4-27）。

WA28119試験の二重盲検期間において感染症の発現頻度は各群で64.7～76.0%であり、群間で大きな違いは認められなかった。感染症の内、重篤な有害事象はプラセボ+26週群が2/50例（4.0%）、プラセボ+52週群が6/51例（11.8%）、MRA-SC QW 群が7/100例（7.0%）、MRA-SC Q2W 群が2/49例（4.1%）であった。その内訳はプラセボ+26週群が肺炎及び丹毒各1例、プラセボ+52週群が胃腸炎及び帯状疱疹各2例、陰部帯状疱疹及び気道感染各1例、MRA-SC QW 群が胃腸炎、帯状疱疹、蜂巣炎、肺炎、慢性副鼻腔炎、ヘモフィルス性肺炎、腎盂腎炎、尿路感染及び尿路性敗血症各1例、MRA-SC Q2W 群が蜂巣炎及び感染性胆管炎各1例であった。感染症で重篤な有害事象の内、投与中止に至った有害事象はプラセボ+26週群に1例（肺炎）、MRA-SC QW 群に5例（肺炎、慢性副鼻腔炎、胃腸炎、帯状疱疹、ヘモフィルス性肺炎）、MRA-SC Q2W 群に1例（蜂巣炎）であった。

(2) 治験薬を介して起こった可能性のある感染性病原体の伝播

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、治験責任医師又は治験担当医師により治験薬を介して起こった可能性のある感染性病原体の伝播と判断された有害事象はいずれの群にも認められなかった。

(3) ビリルビンの上昇又は臨床的黄疸を伴う ALT 又は AST いずれかの上昇

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

(4) 消化管穿孔及び関連疾患

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、消化管穿孔は認められなかった。

(5) アナフィラキシー

MRA632JP 試験の二重盲検期間及び非盲検期間及び WA28119試験の二重盲検期間を通して、Anaphylactic Reaction SMQ Narrow に該当する有害事象はいずれの群にも認められなかった。

一方、WA28119試験の二重盲検期間では、Sampson's criteria でのアナフィラキシーが MRA-SC Q2W 群に1例（眼そう痒症及び呼吸困難）認められた。本被験者では、9日目にグレード1の眼そう痒症が、10日目に呼吸困難が発現した。いずれの事象も治験薬との因果関係が否定され、いずれの事象も回復に至った。治験薬は休薬されなかった。

(6) 出血

出血に該当する有害事象は、MRA632JP 試験の二重盲検期間では、プラセボ群の3例

(16.7%)、MRA-SC 群の2例 (11.1%) に認められた。その内訳は、プラセボ群の1例に認められた出血性ショック及び出血性胃潰瘍、舌出血、喀血各1例、MRA-SC 群の皮下出血、点状出血各1例であった。いずれの事象も治験薬との因果関係は否定された。出血に該当する有害事象の内、重症度が高度であった有害事象はプラセボ群の1例に認められた出血性ショック及び出血性胃潰瘍であり、いずれも重篤な有害事象と判断された。出血性ショック及び出血性胃潰瘍以外の事象の重症度はいずれも軽度であった。出血に該当する有害事象の内、プラセボ群の2例 (出血性胃潰瘍、喀血) では治験薬の投与間隔の延長又は休薬、及び治療が行われ回復に至った。MRA-SC 群の点状出血1例は二重盲検期間終了時未回復であったが、皮下出血1例は回復に至った。

出血に該当する有害事象は MRA632JP 試験の全期間の本剤全投与例では9例 (25.0%) に認められた。その内、非盲検期間に発現した出血に該当する有害事象の内訳は、皮下出血及び挫傷各3例、注射部位出血、血尿、鼻出血及び喀血各1例であり、いずれも治験薬との因果関係は否定された。また、いずれも軽度の有害事象であった (5.3.5.1-7 表 11.4-32)。

WA28119試験の二重盲検期間での出血に該当する有害事象の発現頻度は各群で15.7~24.0%であり、群間で大きな違いは認められなかった。その内、重篤な出血に該当する有害事象は認められなかった (表 2.7.4.2.1.7.4-4)。内訳は、プラセボ+26週群の鼻出血4例、血腫3例、結膜出血2例、斑状出血、肛門出血、腹腔内血腫及び血尿各1例、プラセボ+52週群の斑状出血3例、挫傷2例、骨挫傷、血腫、結膜出血及び注射部位血腫各1例、MRA-SC QW 群の血腫5例、挫傷4例、鼻出血3例、骨挫傷、眼窩周囲血腫、皮下血腫、点状出血、結膜出血、眼出血、注射部位血腫、注射部位出血、腔出血及び出血性関節症各1例、MRA-SC Q2W 群の血腫3例、挫傷2例、斑状出血2例、骨挫傷、外傷性血腫、鼻出血、皮膚出血、結膜出血、注射部位内出血、胃腸出血及び不正子宮出血各1例であった。治験薬との因果関係が否定されなかったのは、プラセボ+26週群の腹腔内血腫1例、MRA-SC QW 群の注射部位血腫1例、MRA-SC Q2W 群の胃腸出血1例であった。これら3例の内、注射部位血腫の転帰は未回復、残り2例は回復に至った。重症度がグレード3であった MRA-SC QW 群の骨挫傷及び出血性関節症各1例以外の重症度はグレード1又は2であった。

(7) 肝臓疾患

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、肝臓疾患は認められなかった。

(8) 脳卒中

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、脳卒中がプラセボ+52週群 (一過性脳虚血発作) 及び MRA-SC Q2W 群 (血栓性脳卒中) に各1例認められた。いずれの事象も重篤と判断され、また、治験薬との因果関係は否定された。いずれの事象も回復に至った。

(9) 心筋梗塞/急性冠症候群

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、心筋梗塞/急性冠症候群は認められなかった。

(10) 悪性腫瘍

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、悪性腫瘍がプラセボ+26週群（乳癌，腎新生物），プラセボ+52週群（悪性黒色腫）及び MRA-SC QW 群（辺縁帯リンパ腫）に各1例認められた。この内、重篤な有害事象は乳癌及び悪性黒色腫であり、いずれも回復又は軽快に至った。腎新生物及び辺縁帯リンパ腫の転帰はいずれも未回復であった。また、悪性腫瘍の内、治験薬との因果関係が否定されなかったのは辺縁帯リンパ腫であった。

(11) 脱髄関連疾患

MRA632JP 試験の二重盲検期間及び非盲検期間を通して、該当する有害事象はいずれの群にも認められなかった。

WA28119試験の二重盲検期間では、脱髄関連疾患は認められなかった。

2.7.4.2.1.8 器官別又は症候群別有害事象の解析

MRA632JP 試験の二重盲検期間において有害事象の発現頻度が最も高かった SOC は、「感染症および寄生虫症」 [プラセボ群6/18例 (33.3%)，MRA-SC 群9/18例 (50.0%)] であり、次に高かったのは「胃腸障害」 [プラセボ群5/18例 (27.8%)，MRA-SC 群3/18例 (16.7%)] であった (表 2.7.4.2.1.8-1)。「感染症および寄生虫症」では MRA-SC 群でプラセボ群に比べて10%以上高かった。また、副作用の発現頻度が最も高かった SOC は、「感染症および寄生虫症」 [プラセボ群3/18例 (16.7%)，MRA-SC 群5/18例 (27.8%)]，「皮膚および皮下組織障害」 [プラセボ群で認められず，MRA-SC 群2/18例 (11.1%)] であった。これらの SOC では MRA-SC 群でプラセボ群に比べて10%以上高かった。

MRA632JP 試験の全期間の本剤全投与例において有害事象の発現頻度が最も高かった SOC は、「感染症および寄生虫症」 [31/36例 (86.1%)] であり、次に高かったのは「胃腸障害」及び「皮膚および皮下組織障害」 [いずれも16/36例 (44.4%)] であった (表 2.7.4.2.1.8-2)。

WA28119試験の二重盲検期間において有害事象の発現頻度が最も高かった SOC は、「感染症および寄生虫症」 [プラセボ+26週群が38/50例 (76.0%)，プラセボ+52週群が33/51例 (64.7%)，MRA-SC QW 群が75/100例 (75.0%)，MRA-SC Q2W 群が36/49例 (73.5%)] であり、次に高かったのは「筋骨格系および結合組織障害」 [プラセボ+26週群が34/50例 (68.0%)，プラセボ+52週群が32/51例 (62.7%)，MRA-SC QW 群が63/100例 (63.0%)，MRA-SC Q2W 群が28/49例 (57.1%)] であった (表 2.7.4.2.1.8-3)。

表 2.7.4.2.1.8-1 器官別大分類別有害事象の集計 (MRA632JP 試験-二重盲検期間)

MedDRA System Organ Class	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Overall total number of patients with at least one adverse event	11 (61.1%)	14 (77.8%)
Overall total number of events	31	38
感染症および寄生虫症 Total number of patients with at least one adverse event	6 (33.3%)	9 (50.0%)
胃腸障害 Total number of patients with at least one adverse event	5 (27.8%)	3 (16.7%)
皮膚および皮下組織障害 Total number of patients with at least one adverse event	1 (5.6%)	6 (33.3%)
眼障害 Total number of patients with at least one adverse event	2 (11.1%)	1 (5.6%)
呼吸器、胸郭および縦隔障害 Total number of patients with at least one adverse event	3 (16.7%)	0
神経系障害 Total number of patients with at least one adverse event	1 (5.6%)	2 (11.1%)
精神障害 Total number of patients with at least one adverse event	1 (5.6%)	1 (5.6%)
臨床検査 Total number of patients with at least one adverse event	2 (11.1%)	0
一般・全身障害および投与部位の状態 Total number of patients with at least one adverse event	1 (5.6%)	0
肝胆道系障害 Total number of patients with at least one adverse event	1 (5.6%)	0
筋骨格系および結合組織障害 Total number of patients with at least one adverse event	0	1 (5.6%)
血液およびリンパ系障害 Total number of patients with at least one adverse event	1 (5.6%)	0
血管障害 Total number of patients with at least one adverse event	1 (5.6%)	0
傷害、中毒および処置合併症 Total number of patients with at least one adverse event	0	1 (5.6%)
代謝および栄養障害 Total number of patients with at least one adverse event	0	1 (5.6%)
内分泌障害 Total number of patients with at least one adverse event	1 (5.6%)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Percentages are based on N.

Multiple occurrences of the same adverse event in one individual counted only once.

[5.3.5.1-1 表 12.2.3-2を改変]

表 2.7.4.2.1.8-2 器官別大分類別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)

aeae_mt_sp Adverse Events and Adverse Drug Reactions
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)	
	Adverse Events	Related Adverse Events
Overall total number of patients with at least one adverse event	34 (94.4%)	18 (50.0%)
Overall total number of events	201	49
感染症および寄生虫症 Total Pts With at Least one AE Total Number of AEs	31 (86.1%) 70	15 (41.7%) 29
胃腸障害 Total Pts With at Least one AE Total Number of AEs	16 (44.4%) 24	5 (13.9%) 7
皮膚および皮下組織障害 Total Pts With at Least one AE Total Number of AEs	16 (44.4%) 22	2 (5.6%) 3
筋骨格系および結合組織障害 Total Pts With at Least one AE Total Number of AEs	11 (30.6%) 17	0 0
神経系障害 Total Pts With at Least one AE Total Number of AEs	9 (25.0%) 12	2 (5.6%) 2
傷害、中毒および処置合併症 Total Pts With at Least one AE Total Number of AEs	7 (19.4%) 8	0 0
眼障害 Total Pts With at Least one AE Total Number of AEs	6 (16.7%) 7	0 0
呼吸器、胸郭および縦隔障害 Total Pts With at Least one AE Total Number of AEs	6 (16.7%) 7	1 (2.8%) 1
血液およびリンパ系障害 Total Pts With at Least one AE Total Number of AEs	5 (13.9%) 5	0 0
精神障害 Total Pts With at Least one AE Total Number of AEs	5 (13.9%) 6	0 0
臨床検査 Total Pts With at Least one AE Total Number of AEs	5 (13.9%) 9	3 (8.3%) 5
一般・全身障害および投与部位の状態 Total Pts With at Least one AE Total Number of AEs	3 (8.3%) 3	0 0
肝胆道系障害 Total Pts With at Least one AE Total Number of AEs	2 (5.6%) 2	1 (2.8%) 1
腎および尿路障害 Total Pts With at Least one AE Total Number of AEs	2 (5.6%) 2	1 (2.8%) 1
生殖系および乳房障害 Total Pts With at Least one AE Total Number of AEs	2 (5.6%) 3	0 0
代謝および栄養障害 Total Pts With at Least one AE Total Number of AEs	2 (5.6%) 2	0 0

aeaer_mt_sp Adverse Events and Adverse Drug Reactions
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)	
	Adverse Events	Related Adverse Events
内分泌障害		
Total Pts With at Least one AE	1 (2.8%)	0
Total Number of AEs	1	0
免疫系障害		
Total Pts With at Least one AE	1 (2.8%)	0
Total Number of AEs	1	0
造影剤アレルギー	1 (2.8%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.
 [5.3.5.1-7 表 9.2.2-1を再掲]

表 2.7.4.2.1.8-3 器官別大分類別有害事象の集計 (WA28119試験-二重盲検期間)

MedDRA System Organ Class	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one adverse event	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
Total number of events	470	486	810	432
感染症および寄生虫症	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
筋骨格系および結合組織障害	34 (68.0%)	32 (62.7%)	63 (63.0%)	28 (57.1%)
神経系障害	23 (46.0%)	22 (43.1%)	43 (43.0%)	22 (44.9%)
一般・全身障害および投与部位の状態	21 (42.0%)	14 (27.5%)	37 (37.0%)	25 (51.0%)
皮膚および皮下組織障害	17 (34.0%)	17 (33.3%)	33 (33.0%)	25 (51.0%)
胃腸障害	19 (38.0%)	15 (29.4%)	36 (36.0%)	18 (36.7%)
呼吸器、胸郭および縦隔障害	16 (32.0%)	17 (33.3%)	22 (22.0%)	11 (22.4%)
眼障害	15 (30.0%)	14 (27.5%)	18 (18.0%)	13 (26.5%)
傷害、中毒および処置合併症	10 (20.0%)	14 (27.5%)	26 (26.0%)	10 (20.4%)
血管障害	13 (26.0%)	9 (17.6%)	23 (23.0%)	13 (26.5%)
臨床検査	9 (18.0%)	8 (15.7%)	23 (23.0%)	7 (14.3%)
精神障害	13 (26.0%)	8 (15.7%)	12 (12.0%)	8 (16.3%)
代謝および栄養障害	4 (8.0%)	7 (13.7%)	10 (10.0%)	7 (14.3%)
心臓障害	6 (12.0%)	6 (11.8%)	8 (8.0%)	3 (6.1%)
耳および迷路障害	6 (12.0%)	6 (11.8%)	7 (7.0%)	4 (8.2%)
腎および尿路障害	4 (8.0%)	6 (11.8%)	7 (7.0%)	0
血液およびリンパ系障害	4 (8.0%)	1 (2.0%)	8 (8.0%)	1 (2.0%)
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)	3 (6.0%)	3 (5.9%)	2 (2.0%)	3 (6.1%)
免疫系障害	3 (6.0%)	2 (3.9%)	2 (2.0%)	3 (6.1%)
生殖系および乳房障害	0	2 (3.9%)	5 (5.0%)	3 (6.1%)
内分泌障害	1 (2.0%)	2 (3.9%)	6 (6.0%)	0
外科および内科処置	3 (6.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
製品の問題	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
Percentages are based on N in the column headings.

[5.3.5.1-3 Table 38及び5.3.5.3-1 表 2.4-3を改変]

2.7.4.2.2 個別有害事象の文章による説明

重篤な有害事象の詳細については2.7.6.12.2に示した。

2.7.4.3 臨床検査値の評価

MRA632JP 試験の二重盲検期間の臨床検査値については、各臨床検査値の推移 (5.3.5.1-1 表 15.3.4-1) , CTCAE 項目のグレード別集計 (表 2.7.4.8-18) をプラセボ群と MRA-SC 群とで比較した。長期の臨床検査値については全期間の本剤全投与例で二重盲検期間と同様に検討した (5.3.5.1-7 表 11.3-24, 表 2.7.4.8-19) 。WA28119試験の二重盲検期間についても同様に検討した (表 2.7.4.8-20) 。

血液学検査及び血液生化学検査項目は、社内臨床検査値処理ルールに基づいて変換した。

2.7.4.3.1 白血球数、好中球数及びリンパ球数

(1) MRA632JP 試験の二重盲検期間

初回投与後12週の白血球数及び好中球数は、MRA-SC 群では投与開始前に比べて減少したものの、多くは基準値の下限を下回らない変化であった。初回投与後12週のリンパ球数は、いずれの群でも投与開始前と大きな違いはなかった。

白血球数がCTCAEグレードでグレード3 (< 2.0~1.0 × 10⁹/L) 以上に減少した被験者、好中球数がグレード3 (< 1.0~0.5 × 10⁹/L) 以上に減少した被験者は、いずれの群でも認められなかった。リンパ球数がグレード3 (< 0.5~0.2 × 10⁹/L) 以上に減少した被験者はプラセボ群 (症例番号60904, 60401) 及びMRA-SC 群 (症例番号60103, 61001) で各2例であった。

(2) MRA632JP 試験の全期間の本剤全投与例

初回投与後52週の白血球数及び好中球数は投与開始前に比べて減少していたものの、多くは基準値の下限を下回らない変化であった。リンパ球数は、投与開始前と大きな違いはなかった。

白血球数が CTCAE グレードでグレード3に減少した被験者は1例（症例番号61204）であった。好中球数がグレード3に減少した被験者は2例（症例番号61201, 61204）であった。症例番号61201の被験者は、好中球数減少後に感染症は認められなかった。白血球数と好中球数がグレード3に減少した1例（症例番号61204）は、好中球数がグレード3以上に減少した前後2週間以内に感染症に分類される感染性腸炎及び鼻咽頭炎を発現したが、いずれも治験薬との因果関係は否定され、重症度は軽度であり、感染性腸炎は短期間で回復に至り、鼻咽頭炎は未回復であった。リンパ球数がグレード3に減少した被験者は4例（症例番号60103, 60401, 60501, 61001）であった。白血球数、好中球数及びリンパ球数のいずれにおいてもグレード4に減少した被験者は認められなかった。

(3) WA28119試験の二重盲検期間

MRA-SC 投与群の好中球数の平均値及び中央値は、初回投与後基準値（ $1.80\sim 7.70 \times 10^9/L$ ）の範囲内で減少し、52週間の間、基準値下限付近で推移した。MRA-SC 投与群の白血球数の平均値は初回投与後24週にかけて減少し、以降52週間の間、基準値下限付近で推移した。

白血球数が CTCAE グレードでグレード3以上に減少した被験者は MRA-SC QW 群で1例認められた。好中球数がグレード3に減少した被験者はプラセボ+26週群及びプラセボ+52週群に認められず、MRA-SC QW 群で4例、MRA-SC Q2W 群で2例であった。好中球数がグレード4に減少した被験者は認められなかった。好中球数がグレード3以上に減少した被験者の内3例（症例番号10983, 10544, 11041）は、グレード3以上に減少した前後2週間以内に感染症に分類される有害事象（尿路感染2例、気管支炎及び胃腸炎を発現した1例）を発現したが、いずれの事象も重症度はグレード2以下で、重篤な有害事象ではなく、回復に至った。リンパ球数がグレード3以上に減少した被験者はプラセボ+26週群で2例、プラセボ+52週群に認められず、MRA-SC QW 群で2例、MRA-SC Q2W 群で2例であった。

2.7.4.3.2 血小板数

(1) MRA632JP 試験の二重盲検期間

初回投与後12週の血小板数は、いずれの群でも投与開始前と大きな違いはなかった。

血小板数が CTCAE グレードでグレード2（ $< 75.0\sim 50.0 \times 10^9/L$ ）以上に減少した被験者はいずれの群にも認められなかった。

(2) MRA632JP 試験の全期間の本剤全投与例

血小板数は、投与開始前と大きな違いはなかった。

血小板数が CTCAE グレードでグレード2以上に減少した被験者は認められなかった。

(3) WA28119試験の二重盲検期間

MRA-SC 投与群の血小板数の平均値及び中央値は、初回投与後減少し、以降52週間の間、基準値（ $150\sim 350 \times 10^9/L$ ）下限付近で推移した。

血小板数が CTCAE グレードでグレード2以上に減少した被験者はいずれの群にも認められなかった。

2.7.4.3.3 肝機能関連項目

(1) MRA632JP 試験の二重盲検期間

初回投与後12週の AST, ALT, 総ビリルビン及びアルカリホスファターゼ（以降、ALP）は、いずれの群でも投与開始前と大きな違いはなかった。γ-GTP は投与開始前から高い被験者がい

ずれの群にも多く、副腎皮質ステロイド投与によると考えられた。初回投与後12週の値は投与開始前と比較して大きな違いはなかった。

AST が CTCAE グレードでグレード3 [$> 5.0 \sim 20.0 \times$ 基準値上限 (ULN)] 以上に上昇した被験者、及び、総ビリルビンが CTCAE グレードでグレード2 ($> 1.5 \sim 3.0 \times$ ULN) 以上に上昇した被験者はいずれの群でも認められなかった。ALT がグレード3 ($> 5.0 \sim 20.0 \times$ ULN) 以上に投与開始後新たに上昇した被験者はいずれの群にも認められなかった。

(2) MRA632JP 試験の全期間の本剤全投与例

初回投与後52週の AST, ALT, 総ビリルビン及び ALP は、投与開始前と大きな違いはなかった。γ-GTP 値は中央値では治験期間を通して変化はなかったが、投与開始前に高値 (1235 U/L) の被験者が認められ、平均値では投与開始後にわずかに減少した。

AST が CTCAE グレードでグレード3以上に上昇した被験者、総ビリルビンが CTCAE グレードでグレード2以上に上昇した被験者、ALT がグレード3以上に投与開始後新たに上昇した被験者は、いずれも認められなかった。

(3) WA28119試験の二重盲検期間

AST, ALT, 総ビリルビン, ALP の平均値及び中央値は、いずれの群においても大きな変化はなかった。

AST がグレード3以上に投与開始後新たに上昇した被験者は MRA-SC Q2W 群で1例であった。ALT が CTCAE グレードでグレード3以上に上昇した被験者は、プラセボ+26週群で認められず、プラセボ+52週群で1例、MRA-SC QW 群で2例、MRA-SC Q2W 群で1例であった。総ビリルビンが CTCAE グレードでグレード2以上に上昇した被験者は、MRA-SC QW 群で4例、MRA-SC Q2W 群で1例であった。

2.7.4.3.4 脂質関連項目

(1) MRA632JP 試験の二重盲検期間

初回投与後12週の総コレステロール, HDL コレステロール, LDL コレステロール及びトリグリセライドは、いずれの群でも投与開始前と大きな違いはなかった。

総コレステロールが CTCAE グレードでグレード2 ($> 7.75 \sim 10.34$ mmol/L) 以上に上昇した被験者は、プラセボ群では0例、MRA-SC 群では3例であった。トリグリセライドがグレード2 ($> 3.42 \sim 5.7$ mmol/L) 以上に上昇した被験者は、プラセボ群及び MRA-SC 群で各2例であった。

脂質検査値上昇に伴う心血管及び脳血管事象に関連した有害事象は認められなかった。

(2) MRA632JP 試験の全期間の本剤全投与例

初回投与後52週の総コレステロール, HDL コレステロール, LDL コレステロール及びトリグリセライドは、投与開始前と大きな違いはなかった。

総コレステロールが CTCAE グレードでグレード2に投与開始後新たに上昇した被験者は3例であったが、グレード3以上に投与開始後新たに上昇した被験者は認められなかった。トリグリセライドがグレード2に上昇した被験者は6例、グレード3に上昇した被験者は1例であり、グレード4以上に上昇した被験者は認められなかった。

脂質検査値上昇に伴う心血管及び脳血管事象に関連した有害事象は認められなかった。

(3) WA28119試験の二重盲検期間

両 MRA-SC 群の総コレステロール及び LDL コレステロールの平均値及び中央値は、両プラセボ群と同様の推移であった。

総コレステロールが CTCAE グレードでグレード2以上に投与開始後新たに上昇した被験者

はプラセボ+26週群で1例，MRA-SC QW 群で3例であった。

脂質検査値上昇に伴う心血管及び脳血管事象に関連した有害事象は，総コレステロール増加を1測定ポイント（57日目）で認めたプラセボ+52週群の1例で重篤な脳卒中（一過性脳虚血発作，135日目に発現）を認めた。一方，MRA-SC Q2W 群の1例で重篤な脳卒中（血栓性脳卒中）を認めたものの，本被験者の総コレステロール値は治験期間を通して基準範囲を下回っていた。これらの事象はいずれも治験薬との因果関係は否定され，回復に至った。これらの被験者以外では重篤な脳卒中又は重篤な心筋梗塞／急性冠症候群は認めなかった。

2.7.4.3.5 抗トシリズマブ抗体

(1) MRA632JP 試験

本剤の免疫原性を，これまでの海外臨床試験にて用いられていた抗トシリズマブ抗体を検出するスクリーニング（SC）法，トシリズマブの Fab 部分に対する抗体を測定する抗トシリズマブ-Fab 抗体測定法及びトシリズマブに対する IgE 型抗体を測定する抗トシリズマブ IgE 型抗体測定法の3種の測定法を用いて評価した。

全期間の本剤全投与例において投与開始後抗トシリズマブ抗体が検出された被験者はいなかった（5.3.5.1-7 表 11.3-31）。

(2) WA28119試験

スクリーニング検査を実施し，陽性であった場合確認試験を行った。確認試験で陽性であった場合，2段階目として，検出された抗体の characterize のために中和アッセイと IgE アッセイを行った（5.3.5.1-3 3.9.7.5）。

投与開始後抗トシリズマブ抗体が検出された被験者は MRA-SC QW 群で1/95例（1.1%），MRA-SC Q2W 群で3/46例（6.5%）であった（表 2.7.4.3.5-1）。いずれの被験者もアナフィラキシー，重篤又は臨床的に重要な過敏症，投与部位反応を認めず，効果不十分による中止もなかった。

表 2.7.4.3.5-1 治験薬投与開始後の新規抗トシリズマブ抗体検出例の集計
(WA28119試験-二重盲検期間)

	PBO QW + 26 week Prednisone taper (N=50)	PBO QW + 52 week Prednisone taper (N=51)	TCZ QW + 26 week Prednisone taper (N=100)	TCZ Q2W + 26 week Prednisone taper (N=49)
Post-Baseline				
No. of evaluable patients (%)	49 (98.0)	47 (92.2)	95 (95.0)	46 (93.9)
No. of patients with treatment-induced ADA (%)	1 (2.0)	1 (2.1)	1 (1.1)	3 (6.5)
Post-Baseline ADA Characterization				
No. of patients with treatment-induced ADA of neutralizing potential (%)	0	0	1 (1.1)	3 (6.5)
No. of patients with treatment-induced ADA of IgE isotype (%)	0	0	0	0

ADA：抗薬物抗体

[5.3.5.1-3 Table 45を改変]

2.7.4.4 バイタルサイン，身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1 バイタルサイン

(1) MRA632JP 試験

二重盲検期間及び全期間の本剤全投与例のバイタルサイン（血圧・脈拍数・体温）の推移に

は、プラセボ群及び MRA-SC 群とも臨床問題となる特記すべき変化は認められなかった。

(2) WA28119試験

二重盲検期間のバイタルサイン（血圧・脈拍数・体温）の推移には、いずれの群においても臨床問題となる変化は認められなかった。

2.7.4.4.2 心電図

(1) MRA632JP 試験

心電図で、投与開始後に新たに異常と判定された被験者は二重盲検期間では認められず、全期間の本剤全投与例で2例認められた。SOC の心臓障害に分類される有害事象は、二重盲検期間及び非盲検期間を通して認められなかった。

(2) WA28119試験

WA28119試験では投与開始後の心電図検査を規定しなかった。

SOC の心臓障害に分類される有害事象はプラセボ+26週群で6/50例（12.0%）、プラセボ+52週群で6/51例（11.8%）、MRA-SC QW 群で8/100例（8.0%）、MRA-SC Q2W 群で3/49例（6.1%）であり、投与群間で大きな違いはなかった。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

MRA632JP 試験の全期間の本剤全投与例に発現した有害事象、副作用、重篤な有害事象、中止に至った有害事象、投与間隔の延長又は休薬に至った有害事象の発現頻度、及び有害事象の事象ごとの集計を、被験者背景〔年齢（18歳未満、18歳以上65歳未満、65歳以上）、性別、初回投与前の体重（54.9 kg 未満、54.9 kg 以上）〕の部分集団ごとに比較した（表 2.7.4.8-21～表 2.7.4.8-26）。WA28119試験での二重盲検期間に発現した有害事象の概要を体重（60 kg 未満、60 kg 以上100 kg 以下、100 kg 超）別に比較した（表 2.7.4.8-27）。

全体としては層ごとの被験者数に偏りのある背景因子もあり、すべての因子について明確に結論することは困難であったが、一定の傾向は認められなかった。

2.7.4.5.2 外因性要因

MRA632JP 試験の全期間の本剤全投与例に発現した有害事象、副作用、重篤な有害事象、中止に至った有害事象、投与間隔の延長又は休薬に至った有害事象の発現頻度、及び有害事象の事象ごとの集計を、治験薬投与開始時の副腎皮質ステロイドの投与量別（0.6 mg/kg 未満、0.6 mg/kg 以上0.8 mg/kg 未満、0.8 mg/kg 以上）に比較した（表 2.7.4.8-28、表 2.7.4.8-29）。集計では、同一被験者にて同一の有害事象が副腎皮質ステロイド投与量の同じ区分内で複数回発現した場合は1件とし、各副腎皮質ステロイド投与量での評価例数は、各副腎皮質ステロイド投与量の開始時点の例数とした。治験薬投与開始時の副腎皮質ステロイドの投与量別では一貫した傾向はみられなかった。

WA28119試験の二重盲検期間に発現した有害事象の内、副腎皮質ステロイドによると考えられる有害事象（抽出リストはメディカルレビューにより作成）を集計した（表 2.7.4.8-30）。副腎皮質ステロイドによると考えられる有害事象は、プラセボ+26週群で14/50例（28.0%）、プラセボ+52週群で15/51例（29.4%）、MRA-SC QW 群で21/100例（21.0%）、MRA-SC Q2W 群9/49例（18.4%）であり、プラセボ+26週群又はプラセボ+52週群に比べて MRA-SC QW 群及び MRA-SC Q2W 群でわずかに低かった。なお、本集計は、標準的あるいは事前に規定した基準に基づいたものではなく、また二重盲検期間は1年間とこれらの事象を引き起こすと考えられる期間より短い。

これまでに RA 患者を対象とした全例調査等で重篤な感染症の発現に關与している特定された患者集団〔65歳以上、罹病期間10年以上、呼吸器疾患の既往又は合併、5 mg/日を超える副腎皮質ステロイド（プレドニゾロン換算）²⁾〕が確認されているが、今回新たに注意を要する部分集団は認められなかった。

2.7.4.5.3 薬物相互作用

いずれの試験においても新たな情報は得られていない。

2.7.4.5.4 妊娠及び授乳時の使用

MRA632JP 試験では、妊婦、授乳中の女性、閉経前又は閉経後1年以内で妊娠反応が陽性の女性及び避妊する意思のない女性を治験対象から除外し、WA28119試験では、妊娠の可能性のある女性及び授乳中の女性を除外しており、新たな情報は得られていない。

2.7.4.5.5 過量投与

MRA632JP 試験及び WA28119試験では、治験実施計画書で規定された1回あたりの最大投与量である162 mg を超える投与量が投与された被験者はいなかった。

2.7.4.5.6 薬物乱用

いずれの試験においても新たな情報は得られていない。

2.7.4.5.7 離脱症状及び反跳現象

いずれの試験においても新たな情報は得られていない。

2.7.4.5.8 自動車運転及び機械操作に対する影響又は精神機能の障害

自動車運転、機械運転に影響するような有害事象は認められていない。

2.7.4.5.9 RA に対して実施された臨床試験

申請者が本剤の皮下投与での開発のために国内又は海外で実施し、本申請ではその安全性データを参考として使用した4試験の試験方法及び結果の概要を以下に示す。

2.7.4.5.9.1 RA 患者を対象とした国内第 I/II 相試験（MRA227JP 試験）

（資料番号：5.3.5.4-1）

本試験は1剤以上の DMARDs が効果不十分であった RA 患者を対象とした非盲検・個体間用量漸増第 I/II 相臨床試験であり、本剤81 mg/2週群、162 mg/2週群及び162 mg/週群の3群からなる。

本剤81 mg/2週群及び162 mg/2週群は、それぞれ本剤81 mg 及び162 mg を単回皮下投与し、投与3週後までの安全性、薬物動態及び注射時の疼痛を評価した（第 I 期）。その後、同一投与量を2週間隔で3回反復投与し、反復投与時の安全性、薬物動態及び有効性を検討した（第 II 期）。更に、同一の用法・用量で6カ月間反復投与し、安全性、有効性及び薬物動態を検討した（第 III 期）。162 mg/週群は第 II 期から開始して本剤162 mg を1週間隔で3回反復投与し、安全性、薬物動態及び有効性を検討し（第 II 期）、更に同一の用法・用量で6カ月間反復投与した（第 III 期）。

本剤を1週間隔で皮下投与した期間に重篤な有害事象を発生した被験者は認められず、死亡例も認められなかった。

本剤81 mg/1～2週又は162 mg/1～2週を35週間皮下投与した際の忍容性が確認された。

2.7.4.5.9.2 RA患者を対象とした国内第III相試験（MRA229JP試験）

（資料番号：5.3.5.4-2及び5.3.5.4-3）

本試験は1剤以上のDMARDsが効果不十分であったRA患者を対象とし、24週間の二重盲検期間と、84週間の非盲検期間で構成されている。

二重盲検期間では、トシリズマブを8 mg/kg/4週で点滴静脈内投与するMRA-IV群を対照群とし、本剤を162 mg/2週で皮下投与するMRA-SC群の有効性及び安全性を検討した。

非盲検期間では、二重盲検期間の24週間の観察を終了した後、MRA-SC群、MRA-IV群に関わらず本剤を162 mg/2週で84週間皮下投与し、長期皮下投与時の有効性及び安全性を検討した。非盲検期間には、被験者の臨床症状や臨床検査値の推移に応じて、投与間隔を短縮及び延長することを可とした。

(1) 二重盲検期間と非盲検期間を併せた期間での安全性

有害事象は98.3%（340/346例）に2473件、副作用は96.5%（334/346例）に1921件認められた。全例での発現頻度が10%以上であった有害事象及びその発現頻度は、鼻咽頭炎（46.5%）、上気道感染（21.1%）、血中コレステロール増加（20.2%）、咽頭炎（15.0%）、低比重リポ蛋白増加（18.5%）、血中トリグリセリド増加（13.3%）、アラニン・アミノトランスフェラーゼ増加（13.0%）、口内炎（11.3%）、湿疹（11.3%）、 γ -グルタミルトランスフェラーゼ増加（10.7%）、白血球数減少（10.7%）及び注射部位紅斑（10.7%）であった。発現頻度が30%以上であった事象（SOC）及びその発現頻度は、「感染症および寄生虫症」（80.1%）、「臨床検査」（62.7%）、「胃腸障害」（49.1%）及び「皮膚および皮下組織障害」（44.2%）であった。

死亡の一覧を表 2.7.4.8-14に、重篤な有害事象が発現した被験者の有害事象の一覧を表 2.7.4.8-15に示した。

(2) 非盲検期間で投与間隔を1週間に短縮した際の安全性

投与間隔を短縮した24例の内、22例（91.7%）に82件の有害事象が短縮期間中に発現した。短縮期間及びそれ以外の期間の有害事象の発現頻度はそれぞれ414.8 Events / PYs 及び538.0 Events / PYs と同程度であり、投与間隔の短縮による発現頻度の上昇は認められなかった。また、短縮期間に特有な有害事象は認められなかった。

2.7.4.5.9.3 RA患者を対象とした第III相二重盲検並行群間比較試験（非劣性試験）及びそれに続く非盲検延長試験（WA22762試験）

（資料番号：5.3.5.4-4及び5.3.5.4-5）

本試験は、中等度～重度の活動性を有するRA患者を対象に、DMARDs併用下での本剤162 mg/週の皮下投与（MRA-SC群）のトシリズマブ8 mg/kg/4週の点滴静脈内投与（MRA-IV群）に対する非劣性を検討する24週間の二重盲検並行群間比較試験として行った。24週間の二重盲検期間を終了した被験者は群内で本剤162 mg/週の皮下投与群又はトシリズマブ8 mg/kg/4週の点滴静脈内投与群に割り付けられ、72週間非盲検下で投与した。

二重盲検期間では、MRA-SC群及びMRA-IV群とも631例に治験薬が投与された。MRA-SC群とMRA-IV群とは同様な有害事象プロファイルを示し、両群とも総じて忍容性が良好であった。MRA-SC群では投与部位反応の発現頻度は低く、その重症度は大部分が軽度であった。いずれの剤形でも、トシリズマブ点滴静脈内投与と比較して予測できない有害事象や新規の有害事象は観察されなかった。本試験の本剤皮下投与で観察された有害事象プロファイルと臨床検査値の変化は、RA患者を対象とした過去の試験のものと一致した。

非盲検下の投与には1135例が移行し、MRA-SC群に710例、MRA-IV群に425例がそれぞれ再割付けされた。本剤を皮下投与したときの長期安全性プロファイルは、総じてトシリズマブ点

滴静脈内投与と同様であった。投与部位反応は皮下投与後に認められたが、その発現頻度は低く、重症度はほとんどが軽度であった。新規の有害事象や予測できない有害事象は認められなかった。有害事象プロファイルと臨床検査値の変化は、本剤の RA 患者を対象としたこれまでの臨床試験でのものと同様であった。

重篤な有害事象の一覧を表 2.7.4.8-16 に示した。

2.7.4.5.9.4 RA 患者を対象とした第 III 相プラセボ対照二重盲検並行群間比較試験及びそれに続く非盲検延長試験 NA25220

(資料番号：5.3.5.4-6及び5.3.5.4-7)

本試験は、中等度～重度の活動性を有する RA 患者を対象に、DMARDs 併用下での本剤162 mg/週の皮下投与 (MRA-SC 群) のプラセボ皮下投与 (プラセボ群) に対する優越性を検討する24週間の二重盲検並行群間比較試験として行った。24週間の二重盲検期間を終了した被験者は各群内でオートインジェクター製剤を用いる群 (以降, AI) 群, 又はプレフィルドシリンジ製剤を用いる群 (以降, PFS 群) に割り付けられ, 24週から96週までは非盲検下で, 本剤162 mg を2週に1回皮下投与した。

また, 12週から48週までの間に腫脹関節数と圧痛関節数の投与開始前からの改善頻度が20%未満であった場合には, MRA-SC 群又はプラセボ群に割り付けられた被験者ともに, 本剤162 mg を週1回皮下投与する救済治療 (escape therapy) に移行した。そのような被験者は, 本試験が終了するまで, 非盲検下で投与を受けた。

二重盲検期間では, 438例に本剤が (ただしこの内1例は投与後未観察のため安全性集団から除外), 218例にプラセボが投与された。本剤の2週に1回皮下投与は, 有害事象のプロファイルから総じて忍容性が良好であり, その有害事象のプロファイルはトシリズマブ点滴静脈内投与の既知の安全性プロファイルと一致していた。また, 臨床的に意味のある新しい安全性シグナルは観察されなかった。総じて, 多くは軽度であった投与部位反応を含めて, 注目すべき有害事象は, プラセボ群よりも MRA-SC 群の方が発現頻度が高かった。

非盲検下の投与には, 453例の被験者が移行し, 二重盲検期間中に本剤の投与を受けた338例中, 168例は AI 群に, 他の170例は PFS 群に再割付けされた。また, 二重盲検期間中にプラセボの投与を受けた119例の内, 59例は AI 群に, 他の60例は PFS 群に再割付けされた。本剤皮下投与の長期安全性プロファイルは, 二重盲検期間での安全性プロファイルと同様であった。PFS 製剤と AI 製剤の忍容性は総じて良好であり, プラセボから本剤に切り替えた群の安全性は, 最初に MRA-SC 群に割り付けられた被験者の安全性と同程度であった。

本剤を毎週皮下投与した救済治療の安全性プロファイルと臨床検査値の変化は, 感染のわずかな増加を除き, 本剤の2週に1回皮下投与と同様であった。この結果から, 2週に1回の投与と週1回の投与は, いずれも安全であり, 忍容性は良好であることが示唆された。

重篤な有害事象の一覧を表 2.7.4.8-17 に示した。

2.7.4.6 市販後データ

本邦において, トシリズマブは点滴静注用製剤として2005年4月11日に「キャッスルマン病に伴う諸症状及び検査所見 (C 反応性タンパク高値, フィブリノーゲン高値, 赤血球沈降速度亢進, ヘモグロビン低値, アルブミン低値, 全身倦怠感) の改善。ただし, リンパ節の摘除が適応とならない患者に限る。」の効能・効果により製造販売承認を取得した。その後, 2008年4月16日に「関節リウマチ (関節の構造的損傷の防止を含む) 」, 多関節に活動性を有する若年性特発性関節炎 (以降, pJIA) 及び全身型若年性特発性関節炎 (以降, sJIA) の効能・効果の追加承認を取得し, いずれも再審査期間が終了している。トシリズマブの皮下注製剤については, 「関節リウマチ (関節の構造的損傷の防止を含む) 」の効能・効果にて, 2013年3月25日に製造販売承認を取得し, 現在再審査期間中である。

本邦においては、表 2.7.4.6-1 のとおり、製造販売後調査を実施した。これらの製造販売後調査結果は、再審査申請資料又は新医療用医薬品安全性定期報告書として提出済みであり、いずれの製造販売後調査においても、安全性及び有効性上、新たな問題点は認められなかった。

表 2.7.4.6-1 本邦で実施した製造販売後調査

実施要綱 No	調査種別	対象疾患	症例数	観察期間	調査実施期間	剤型
ML19367	特定使用成績調査（長期・全例）	キャッスルマン病	安全性解析対象症例：384例 有効性解析対象症例：354例	3年	2005年6月～2015年4月	IV
ML21939	特定使用成績調査（全例調査）	RA	安全性解析対象症例：7908例 有効性解析対象症例：6597例	6か月	2008年4月～2012年1月	IV
		pJIA	安全性解析対象症例：178例 有効性解析対象症例：145例	6か月	2008年4月～2012年1月	IV
ML21940	特定使用成績調査（全例調査）	sJIA	安全性解析対象症例：417例 有効性解析対象症例：253例	1年	2008年4月～2014年2月	IV
ML21943	特定使用成績調査（長期フォローアップ調査）	RA	安全性解析対象症例：5573例 有効性解析対象症例：なし	3年	2008年4月～2013年4月	IV
ACT1101	特定使用成績調査	RA	安全性解析対象症例：839例 有効性解析対象症例：763例	1年	2012年1月～2014年9月	IV
ACT1301	使用成績調査	RA	安全性解析対象症例：1003例 有効性解析対象症例：785例	6か月	2013年7月～2016年2月	SC

2.7.4.6.1 新医療用医薬品安全性定期報告書（皮下注第6回，調査単位期間：2015年4月11日～2016年4月10日）

[5.3.6-1]

最新の安全性定期報告書（皮下注第6回，調査単位期間：2015年4月11日～2016年4月10日）について概要を記載する。

2.7.4.6.1.1 通常の医薬品安全性監視活動

(1) 国内で集積された副作用・感染症例報告からの検討

当該調査単位期間中に総合機構に報告した副作用・感染症は348例571件であり、その内訳は、肺炎23件、間質性肺疾患18件、白血球数減少16件、蜂巣炎及びニューモシスチス・イロペチイ肺炎各13件、非定型マイコバクテリア感染12件等であった。また、XXXXXXXXXX及びその他安全性に係わる事項の検討を行った結果、現在の集積状況において本剤との直接的な因果性は示唆されなかったことから、現時点では添付文書改訂等の新たな安全確保措置の必要はないと判断した。

(2) 重要な特定されたリスク，重要な潜在的リスク及び重要な不足情報について

当該調査単位期間までに総合機構に報告した重篤な副作用に関し、2015年6月19日に総合機構へ提出済みの医薬品リスク管理計画書（以降，J-RMP）に定める「重要な特定されたリスク」，「重要な潜在的リスク」及び「重要な不足情報」について検討を行った。

重要な不足情報の「高齢者への投与」，及び「キャッスルマン病の病態及び IL-6作用抑制による影響」については、本剤における追加の安全性監視計画として実施してきた製造販売後調査結果に基づき、削除することが可能であると考え、その方針にて安全性定期報告書の提出及び再審査申請している。

その他の安全性検討事項については、現時点では J-RMP の改訂及び添付文書改訂等の新たな

な安全確保措置の必要はないと判断した。

表 2.7.4.6.1.1-1 安全性検討事項の重篤な副作用の報告件数*

安全性検討事項	当該調査単位期間までに総合機構に報告した重篤な副作用	
重要な特定されたリスク	重篤な感染症	712例1108件
	腸管穿孔	96例128件
	アナフィラキシー等の重篤な過敏症 (Infusion Reaction, 投与時反応を含む)	56例60件
重要な潜在的リスク	好中球減少に伴う感染症	好中球減少あるいは白血球減少として75例82件 この内、感染症発現に影響した可能性が否定できないのは7例
	血小板減少に伴う重篤な出血関連事象	血小板減少として27例27件 この内、出血関連事象を同時期に発現していたのは5例
	肝機能異常	67例78件 この内、重篤な肝機能異常を発現した5例7件中、肝臓疾患を発現していた報告はなし
	脂質検査値上昇に伴う心血管・脳血管事象	2例2件 この内、心血管・脳血管事象を発現していた報告はなし
	悪性腫瘍	168例191件
	脱髄関連疾患	2例2件
	Immunogenicity	特記すべき報告なし
	CYPs enzyme normalization	特記すべき報告なし
	間質性肺疾患	86例91件
	心障害	62例73件
	重要な不足情報	マクロファージ活性化症候群
高齢者への投与		高齢者における治療経験が集積され、本剤の有効性・安全性に与える新たな懸念は認められなかったことから高齢者への投与については、重要な不足情報から削除することが可能であると考えた
ワクチンの接種		特記すべき報告なし
B型肝炎ウイルスの再活性化		4例6件
胸膜炎		21例21件
注射部位反応		報告なし
	キャスルマン病の病態及びIL-6作用抑制による影響	製造販売後調査（実施要綱 No. ML19367）で検討し、当該安全性検討事項については削除する方針にて再審査申請を行った

CYP：シトクロム

*アクテムラ皮下注承認以降、当該調査単位期間までに総合機構に報告した件数。

(3) 研究報告及び外国での措置報告からの検討

当該調査単位期間中に、総合機構に報告した研究報告はなく、措置報告は1報であった。措置報告を行った1報は、Roche社によりサウジアラビアでの皮下注製剤の承認に伴い、Dear Healthcare Provider (DHCP) letterが発出されたものであった。本内容は、トシリズマブの安全性プロファイルの内容を周知するためのものであり、すでにCDS等で注意喚起を行っている内容である。現行の国内添付文書においても同様の内容について注意喚起を行っており、新たな知見は得られていないことから、添付文書改訂等の更なる安全対策が必要なものではなかった。

2.7.4.6.1.2 追加の医薬品安全性監視活動

今回の調査単位期間に終了したSC製剤におけるRA患者を対象とした使用成績調査

(ACT1301)において、新たな有効性・安全性上の懸念点は認められていないことから、当該安全性監視活動の実施状況を終了とする J-RMP の改訂方針について総合機構に相談した。

2.7.4.6.1.3 リスク最小化計画実施結果について

本剤の J-RMP に基づき実施した各リスク最小化活動については、2015年4月10日をもって、アクテムラ点滴静注用におけるキャッスルマン病の再審査期間が満了したことを受け、キャッスルマン病の使用条件を以下のとおり変更し、2015年6月19日に総合機構に J-RMP の変更届を提出した。

- 1). 施設制限から「特定使用成績調査（全例調査）に協力・契約可能な施設である」を削除
- 2). 医師制限から「特定使用成績調査（全例調査）に協力が可能である医師」を削除
- 3). 施設制限及び医師制限から特定使用成績調査（全例調査）の実施要綱に基づき実施していた適正使用に関する確認書の取得を終了したため、記載を削除
- 4). 流通制限から「施設で1例目の症例が適格である」を削除
- 5). キャッスルマン病症例の副作用収集状況についてのウェブサイト更新を終了

また、2016年3月25日付のアクテムラ点滴静注用における RA, pJIA, sJIA の再審査結果通知の受領に伴い、RA, pJIA, sJIA の使用条件を変更し、医療関係者及び患者への情報提供資料について改訂する予定で総合機構と相談した。

その他のリスク最小化計画については、見直しを行う必要はなかった。

2.7.4.6.2 PBRER からの安全性情報

[5.3.6-2]

Periodic Benefit-Risk Evaluation Report（以降、PBRER）/ Periodic Safety Update Report（以降、PSUR）のデータロック時点（2016年4月10日）での概要及び検討結果を以下に示した。

2.7.4.6.2.1 PBRER の概要

本文書は、tocilizumab (Actemra®/RoActemra®/RO4877533) に関して作成された第7回定期的ベネフィット・リスク評価報告 [Periodic Benefit-Risk Evaluation Report (PBRER)] / 第15回定期的安全性最新報告 [Periodic Safety Update Report (PSUR)] である。本文書ではこれ以降、本報告書を PBRER と称する。本 PBRER () は、tocilizumab のベネフィット・リスクバランスについて包括的で簡明かつ批判的な分析を行い、ベネフィット及びリスクに関する新たな情報を累積データに取り入れている。

本 PBRER の報告対象期間は、2015年10月11日から2016年4月10日まで、データロックポイント（以降、DLP）は2016年4月10日である。いずれかの国で Roche 並びに中外製薬が治験依頼者として初めて tocilizumab の臨床試験実施の認可を受けた日（DIBD）は1997年4月28日であり、IBD は2005年4月11日である。

本 PBRER には、Roche 及びそのビジネスパートナー（日本の中外製薬、

から入手された、臨床、非臨床、科学的なデータ、及び tocilizumab のベネフィット・リスクプロファイルに関するその他のソースに由来するデータの解析結果が記載されている。安全性情報等交換契約に基づき、Roche は tocilizumab のグローバル安全性データベースを管理しており、本報告書内の関連する箇所では marketing authorization holder（以降、MAH）と表記される。

- 適応症

Tocilizumab は中外製薬と共同開発され、成人における中等度から重度の活動性 RA、小児における活動性の sJIA 及び pJIA に加え、巨細胞性動脈炎や高安動脈炎、全身性硬化症を含む他

の適応症の治療薬として、世界的に研究されている。また、多発性骨髄腫、全身性エリテマトーデス、強直性脊椎炎及びクローン病の患者についても研究が行われていたが、これらの適応症に対する tocilizumab の開発は現在行われていない。

Tocilizumab は Actemra[®]及び RoActemra[®]として販売されている。2014年3月6日付の現行の CDS [] (本報告対象期間開始時及び終了時に有効)に記載されているとおり、tocilizumab は成人における中等度から高度の活動性の RA、2歳以上の患者における活動性 sJIA、及び2歳以上の患者における活動性 pJIA を適応症として承認されている。更にインドと日本では、キャッスルマン病の適応も承認されている。

- 臨床開発プログラム

本 PBRER の報告対象期間中に、tocilizumab を治験薬とする企業主導介入臨床試験4件が終了し、中外製薬主導試験3件を含む35件が継続中であった。

- 世界の製造販売承認状況

2005年4月11日、キャッスルマン病に対する治療の適応で日本において世界で初めて販売が承認されてから本 PBRER の報告対象期間の終了(2016年4月10日)までに、tocilizumab は世界100カ国を超える国々で承認されている。

- 使用患者数

DIBD(1997年4月28日)から本 PBRER の DLP までの間に治験薬として tocilizumab を投与された累積治験被験者数(IV 製剤と SC 製剤の合計)は、[]例([]患者年)である。

IBD(2005年4月11日)から2016年4月10日までの間に市販されている tocilizumab を投与された患者は、計[]名([]患者年)と推定される。

- 安全性上の理由で施行された措置(臨床試験)

本報告対象期間中に tocilizumab の臨床試験における使用に際して、安全性上の理由で施行された措置はなかった。

- 安全性上の理由で施行された措置(市販後)

追加のリスク最小化策の導入

- オーストラリアでは、2016年1月21日に Actemra[®] SC 製剤が承認及び発売され、ローカルの追加のリスク最小化策を行うことについて、以下のとおり合意が得られた。Roche は「重篤な過敏症反応」に対して、教材を用いたリスク最小化策を施行することに同意し、医療従事者向け及び患者向けパンフレットの使用を提案する。オーストラリア版の教材は EU 版のものと類似しているため、Roche は EU における成果指標の解析結果に基づき、教材の有効性を証明することを提案する。

- Roche Brazil では、現地の規制要件に従い、RMP の一環として、RA(IV 及び SC)及び sJIA に関する教材の改編又は更新を行った。

- イタリアでは、2015年5月19日に技術的なエラー(患者アラートカードの作成不備)が検出されたが、イタリア保健当局(AIFA)の協力を得て2015年6月24日に是正された。その後、修正済みの教材が医療従事者に配布された。

医療従事者又は治験責任医師への安全性関連通知「Dear Healthcare Professional Communications」、 「Dear Investigator Letters」及び「To Whom it may Concern letter」等

- イスラエルでは、Actemra[®]の添付文書の更新に関する医療従事者向けの通知が送付された。この通知には、最新版の添付文書への変更点(前回版との比較により示している)、特に薬物動態・薬理プロファイルについて記載されていた。添付文書中の安全性に関する情報に変更はなかった。この医療従事者への通知の目的は、登録された製品の添付文書に重要な変更があった場合は、その都度医療従事者(薬剤師及び医師)に通知しなければならないという、現地の規制に従うことであった。

台湾添付文書の更新

- 本 PBRER の報告対象期間に先立ち、tocilizumab IV 製剤の台湾添付文書が2015年7月22日に更新され、tocilizumab の副作用として、スティーブンス・ジョンソン症候群(SJS)が新た

に追加された。Tocilizumab SC 製剤の台湾添付文書が2015年10月23日に更新され、SJS に関する記載が追加された。

- 2016年2月には、台湾中外製薬股份有限公司から各施設宛に、tocilizumab IV 製剤の台湾添付文書第6.0版のSJSに関する変更点について記載した「Dear Doctor Letter」及び「Package Insert Revision Information (添付文書改訂情報)」が通常的安全性活動として送付された。
- 2016年2月19日には、台湾 FDA が、tocilizumab SC 製剤の新たな添付文書(第2.0版)を承認した。この更新には、一次包装材料の変更(ガラスシリンジからプラスチックシリンジへの変更)と、2015年11月11日付で変更申請していたウイルス再活性化に関する項目の「B型肝炎ウイルス再活性化についての情報」が含まれた。当時、tocilizumab SC 製剤は台湾では販売されていなかったため、本改訂について薬事関連手続きは必要とされなかった。

韓国添付文書の更新

- 2016年3月15日に、tocilizumab IV 製剤の韓国添付文書が更新された。新たな適応症として、sJIA 及び pJIA が用法・用量とともに追加され、これらの適応症に対する本剤の使用方法が追記された。

本 PBRER の報告対象期間中に、安全性上の理由に基づき、MAH 又は保健当局によって実施されたその他の措置(リスクマネジメント活動を含む)はなかった。

- 安全性参照情報の変更

本 PBRER は、安全性参照情報として、本報告対象期間開始時及び本 PBRER の DLP の時点で有効であった tocilizumab の CDS [REDACTED] (2014年3月6日付)を使用している。本報告対象期間中、tocilizumab の CDS に対する変更はなかった。

- シグナル及びリスクの評価

本報告期間中に四つのシグナル(「黒色腫」、「消化管穿孔」、「傷害、中毒および処置合併症」及び「薬効欠如」)が特定された。

- 黒色腫のシグナルは本調査期間中に否定され、評価終了となった。MAH は、黒色腫に関する医薬品安全性評価報告書(以降、DSR) [REDACTED] に対するファーマコビジランス・リスク・アセスメント委員会(PRAC)評価報告書を、本 PBRER の報告対象期間中である2015年10月27日に受理した。PRAC の DSR [REDACTED] 評価報告書の結論において、国/地域、年齢及び性別による層別 Observed versus Expected Analysis (OE 解析)を示し更なる評価をするよう要請された。これを受けて、MAH は2015年11月15日に同シグナルの再検討を開始し、DSR 第2報(2016年5月31日付 [REDACTED])を作成し、本 PBRER とともに提出する。黒色腫に関する DSR [REDACTED] の結論は臨床試験及び市販後使用における標準化罹患比に基づいている。一般集団と比較して黒色腫のリスク上昇を示唆する証拠は発見されなかった。

例外はオーストラリアで、一般集団と比較して算出された標準化発現比は3.71 (95%CI: 2.16,5.93)であった。しかし、この結果は生物学的製剤未投与 RA 患者と同程度であり、オーストラリアでは、生物学的製剤未投与 RA 患者における黒色腫の背景リスクが一般集団と比較して上昇しているとされている。MAH は現時点での製品の添付文書の変更は不要と結論付けた。

- 消化管穿孔は本 PBRER ([REDACTED]) の報告対象期間中に否定されたシグナルに分類された。消化管穿孔は tocilizumab の既知の副作用である。同シグナルは同リスクの重篤度及び頻度を更に調査するため2015年9月27日に MAH により検討が開始された。本報告対象期間中に DSR [REDACTED] が最終化され、同シグナルは2015年11月3日に評価終了となった。同 DSR の概要は前回の PBRER ([REDACTED]) で述べたため本報告書には再度記載しない。

DSR [REDACTED] に対する PRAC の最終評価報告書(EMA/H/C/PSUSA/00002980/201510の手順による)において、Rapporteur は DSR [REDACTED] が GA30111試験に関連しているとみなして同 DSR の結論を妥当であるとみなした。

MAH は消化管穿孔のシグナルの評価終了を承認し、DSR [REDACTED] は GA30111試験を参照したことを断言し、通常的安全性監視手順により消化管穿孔の発現を監視していく。

- Tocilizumab に対する薬効欠如のシグナルは、本 PBRER の最新情報報告期間中に否定され、評価終了となった。DSR [] は、曝露者数が増加している状況において、薬効欠如の報告率は一定に保たれていると結論づけた。MAH は同シグナルを2016年4月28日に否定し、評価が終了した。
- 本報告対象期間中の2016年4月8日に、器官別大分類「傷害、中毒および処置合併症」の件数が増加していることを示す数値的シグナルが通常のシグナル検出手順において特定された。この数値的シグナルの主な要因は有害事象を伴わない投薬過誤であることが特定された。検討において MAH は、曝露に関する報告率は安定しており、現時点では対応不要であると結論付けた。同シグナルは次の報告対象期間における確定的レビューのために MAH により暫定的に評価継続とされ、本件及びその進捗状況は次の報告対象期間中に提示する。

PBRER ([]) (報告対象期間：2015年4月11日～10月10日) で示された WA29049試験の結果に基づき、MAH は EU-RMP から重要な潜在的リスクの好中球減少症及び潜在的リスクの感染症を削除することを提案した。PRAC は同 PBRER ([]) を EMEA/H/C/PSUSA/00002980/201510の手順に従ってレビューし、最終評価報告書(2016年5月13日付)の中で重要な潜在的リスクの「好中球減少症及び感染症の潜在的リスク」を削除するという MAH の提案を支持した。重要な潜在的リスクの「好中球減少症及び感染症の潜在的リスク」は次回の EU-RMP 改訂の際に EU-RMP から削除する。

本 PBRER の報告対象期間中に新たに特定されたリスクはなかった。Tocilizumab の安全性プロファイルは、初回製造販売承認取得時と比較してほとんど変化していない。臨床試験の結果は市販後に観察された安全性プロファイルと一致している。CDS には、tocilizumab の安全性プロファイルと、承認された各適応症における tocilizumab の使用に伴うリスクが適切に記載されている。

- ベネフィット・リスク評価

Tocilizumab (RoActemra[®]/Actemra[®]) の RA (IV 又は SC 製剤)、sJIA、pJIA 及びキャッスルマン病の治療におけるベネフィット・リスクプロファイルに変更はなく、プロファイルは依然として良好である。

- 総合的な結論

MAH は、本 PBRER の報告対象期間中に得られた関連データ、すなわち臨床試験、市販後調査、既刊文献及びその他の情報源から得られたデータについて評価を実施した。市販後調査データに対する安全性評価の結果は、臨床試験データにおいて観察された安全性プロファイルと一致していた。Tocilizumab の RA (IV 又は SC 製剤)、sJIA、pJIA 及びキャッスルマン病 (IV 製剤) の治療におけるベネフィット・リスクプロファイルに変更はなく、プロファイルは依然として良好である。現時点では、CDS のさらなる改訂又は追加の措置は不要である。PRAC の支持を得たことにより、重要な潜在的リスクの「好中球減少症及び感染症の潜在的リスク」は EU-RMP の今後作成する版から削除する。

2.7.4.6.2.2 PBRER からの検討結果

本報告期間中に入手した情報を検討した結果、新たな安全性シグナルを示す有害事象は認められず、トシリズマブの安全性プロファイルに影響するような重大な新しい知見はなかった。

2.7.4.7 参考文献

- 1) Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7.

- 2) Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41(1):15-23.

2.7.4.8 付録

表 2.7.4.8-1	安全性評価例の被験者背景 (MRA632JP 試験)	107
表 2.7.4.8-2	安全性評価例の被験者背景 (WA28119試験)	110
表 2.7.4.8-3	治験薬に対する副作用発現例数 (%) (WA28119試験-二重盲検期間)	111
表 2.7.4.8-4	観察期間あたりの事象別有害事象発現件数 (Events /100 PYs, MRA632JP 試験-二重盲検期間)	120
表 2.7.4.8-5	観察期間あたりの事象別有害事象発現件数 (Events /100 PYs, MRA632JP 試験-全期間の本剤全投与例)	123
表 2.7.4.8-6	重症度別の事象別有害事象発現例数 (MRA632JP 試験-二重盲検期間)	127
表 2.7.4.8-7	重症度別の事象別有害事象発現例数 (MRA632JP 試験-全期間の本剤全投与例)	132
表 2.7.4.8-8	重症度別の事象別有害事象発現例数 (WA28119試験-二重盲検期間)	138
表 2.7.4.8-9	投与開始後初めて発現した有害事象の発現時期 (MRA632JP 試験-全期間の本剤全投与例)	188
表 2.7.4.8-10	投与開始後初めて発現した有害事象の発現時期 (WA28119試験-二重盲検期間)	198
表 2.7.4.8-11	重篤な有害事象一覧 (MRA632JP 試験-二重盲検期間)	228
表 2.7.4.8-12	重篤な有害事象一覧 (MRA632JP 試験-全期間)	230
表 2.7.4.8-13	重篤な有害事象一覧 (WA28119試験-二重盲検期間)	233
表 2.7.4.8-14	死亡例一覧 (MRA229JP 試験-二重盲検期間と非盲検期間を併せた期間)	245
表 2.7.4.8-15	重篤な有害事象一覧 (MRA229JP 試験-二重盲検期間と非盲検期間を併せた期間)	246
表 2.7.4.8-16	重篤な有害事象一覧 (WA22762試験)	261
表 2.7.4.8-17	重篤な有害事象一覧 (NA25220試験)	287
表 2.7.4.8-18	臨床検査値の CTCAE によるシフトテーブル (MRA632JP 試験-二重盲検期間)	306
表 2.7.4.8-19	臨床検査値の CTCAE によるシフトテーブル (MRA632JP 試験-全期間の本剤全投与例)	335
表 2.7.4.8-20	臨床検査値の CTCAE によるシフトテーブル (WA28119試験-二重盲検期間)	364
表 2.7.4.8-21	年齢別有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)	369
表 2.7.4.8-22	年齢別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)	370
表 2.7.4.8-23	性別有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)	374
表 2.7.4.8-24	性別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)	375
表 2.7.4.8-25	初回投与前の体重別有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)	379
表 2.7.4.8-26	初回投与前の体重別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)	380

表 2.7.4.8-27	体重別有害事象の発現状況の要約 (WA28119試験-二重盲検期間)	384
表 2.7.4.8-28	治験薬投与開始時の副腎皮質ステロイド投与量別, 有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)	392
表 2.7.4.8-29	治験薬投与開始時の副腎皮質ステロイド投与量別, 有害事象発現例数 (MRA632JP 試験-全期間の本剤全投与例)	393
表 2.7.4.8-30	副腎皮質ステロイドによると考えられる有害事象発現例数 (WA28119試験-二重盲検期間)	397

表 2.7.4.8-1 安全性評価例の被験者背景 (MRA632JP 試験)

dmt01_sp Demographic Data
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Sex		
n	18	18
Male	3 (16.7%)	2 (11.1%)
Female	15 (83.3%)	16 (88.9%)
Age (years)		
n	18	18
mean	30.8	31.1
std	13.1	18.1
min	17	13
median	27.0	26.5
max	68	66
Age (years) Category		
n	18	18
< 18	2 (11.1%)	4 (22.2%)
18 -< 65	15 (83.3%)	12 (66.7%)
65 -	1 (5.6%)	2 (11.1%)
Weight (kg) at Randomized		
n	18	18
mean	59.73	55.04
std	14.67	15.87
min	39.4	32.9
median	57.90	53.05
max	99.7	97.4
Height (cm) at Screening		
n	18	18
mean	162.8	157.9
std	6.8	8.1
min	152	139
median	161.0	160.0
max	177	169
BMI (kg/m**2) at Randomized		
n	18	18
mean	22.58	21.79
std	5.64	4.69
min	15.4	15.2
median	21.26	20.80
max	39.0	34.1
HLA-B39		
n	18	18
NO	18 (100.0%)	18 (100.0%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_sp.out
 21DEC2015 21:12

dmt01_sp Demographic Data
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
HLA-B52		
n	18	18
YES	13 (72.2%)	7 (38.9%)
NO	5 (27.8%)	11 (61.1%)
Exposure to Corticosteroids (mg/kg Equivalent to Prednisolone) at Randomization		
n	18	18
mean	0.52	0.57
std	0.16	0.19
min	0.4	0.4
median	0.45	0.50
max	0.9	1.0
Exposure to Corticosteroids Category (mg/kg Equivalent to Prednisolone) at Randomization		
n	18	18
< 0.6	14 (77.8%)	13 (72.2%)
0.6 -< 0.8	2 (11.1%)	2 (11.1%)
0.8 -	2 (11.1%)	3 (16.7%)
Pregnancy Test		
n	14	12
NEGATIVE	14 (100.0%)	12 (100.0%)
Takayasu Arteritis Classification		
n	18	18
I	2 (11.1%)	2 (11.1%)
IIA	3 (16.7%)	2 (11.1%)
IIB	5 (27.8%)	3 (16.7%)
III	1 (5.6%)	3 (16.7%)
V	7 (38.9%)	8 (44.4%)
Disease Duration of Takayasu arteritis (years)		
n	18	18
mean	3.57	6.46
std	4.03	7.37
min	0.1	0.4
median	2.89	3.33
max	16.5	22.8
Prior Treatment: Surgery		
n	18	18
YES	1 (5.6%)	5 (27.8%)
NO	17 (94.4%)	13 (72.2%)
Prior Treatment: Biologics		
n	18	18
YES	2 (11.1%)	0
NO	16 (88.9%)	18 (100.0%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_sp.out
 21DEC2015 21:12

dmt01_sp Demographic Data
 Protocol: MRA632JP
 Analysis: SAFETY

	PLACEBO (N=18)	MRA-SC 162mg/w (N=18)
Prior Treatment: DMARDs/Immunosuppressant		
n	18	18
YES	13 (72.2%)	12 (66.7%)
NO	5 (27.8%)	6 (33.3%)

Percentages are based on n (number of valid values).

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/dmt01.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/dmt01_sp.out
 21DEC2015 21:12

Page 3 of 3

[5.3.5.1-1 表 15.1-8を再掲]

表 2.7.4.8-2 安全性評価例の被験者背景 (WA28119試験)

Summary of Demographic Characteristics, All Patients Population
Protocol: WA28119

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age (years)				
n	50	51	100	50
Mean (SD)	69.3 (8.1)	67.8 (7.7)	69.5 (8.5)	69.4 (8.2)
Median	70.5	68.0	71.0	71.0
Min - Max	52 - 83	52 - 84	51 - 85	53 - 91
Age group (years)				
n	50	51	100	50
< 65 years	16 (32.0%)	17 (33.3%)	32 (32.0%)	17 (34.0%)
>= 65 years	34 (68.0%)	34 (66.7%)	68 (68.0%)	33 (66.0%)
Sex				
n	50	51	100	50
Male	12 (24.0%)	14 (27.5%)	22 (22.0%)	15 (30.0%)
Female	38 (76.0%)	37 (72.5%)	78 (78.0%)	35 (70.0%)
Ethnicity				
n	50	51	100	50
Hispanic or Latino	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
Not Hispanic or Latino	49 (98.0%)	49 (96.1%)	96 (96.0%)	46 (92.0%)
Not Reported	0	1 (2.0%)	2 (2.0%)	2 (4.0%)
Unknown	1 (2.0%)	0	0	1 (2.0%)
Race				
n	50	51	100	50
Asian	0	0	0	1 (2.0%)
Black or African American	0	2 (3.9%)	1 (1.0%)	0
Other	0	0	1 (1.0%)	1 (2.0%)
White	50 (100.0%)	49 (96.1%)	97 (97.0%)	47 (94.0%)
Unknown	0	0	1 (1.0%)	1 (2.0%)
Weight (kg)				
n	50	51	100	49
Mean (SD)	70.12 (15.83)	73.13 (15.34)	69.82 (13.82)	70.84 (16.09)
Median	66.65	70.60	67.50	69.20
Min - Max	47.7 - 120.0	48.5 - 108.0	48.0 - 105.0	46.4 - 124.1
Height (cm)				
n	50	51	100	49
Mean (SD)	164.70 (9.51)	167.86 (8.45)	163.90 (10.08)	165.33 (9.09)
Median	162.80	167.00	163.00	167.70
Min - Max	139.7 - 188.0	153.0 - 191.0	125.3 - 187.0	139.0 - 184.0
BMI (kg/m2)				
n	50	51	100	49
Mean (SD)	25.70 (4.46)	25.80 (4.13)	25.97 (4.42)	25.99 (6.15)
Median	24.92	25.35	25.62	24.80
Min - Max	18.0 - 40.1	18.3 - 36.0	18.1 - 38.6	17.8 - 53.4
Smoking History				
n	50	51	100	49
Never	35 (70.0%)	29 (56.9%)	57 (57.0%)	28 (57.1%)
Current	7 (14.0%)	9 (17.6%)	13 (13.0%)	5 (10.2%)
Previous	8 (16.0%)	13 (25.5%)	30 (30.0%)	16 (32.7%)

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_dm.sas / Output:
/opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_dm_AP.out
11JUL2016 21:21 (PDRD)

表 2.7.4.8-3 治験薬に対する副作用発現例数 (%) (WA28119試験-二重盲検期間)

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Overall total number of patients with at least one adverse event	21 (42.0%)	18 (35.3%)	52 (52.0%)	26 (53.1%)
Overall total number of events	59	83	127	51
感染症および寄生虫症				
Total number of patients with at least one adverse event	15 (30.0%)	13 (25.5%)	32 (32.0%)	15 (30.6%)
Total number of events	25	41	57	16
鼻咽頭炎	1 (2.0%)	4 (7.8%)	7 (7.0%)	2 (4.1%)
上気道感染	3 (6.0%)	3 (5.9%)	3 (3.0%)	2 (4.1%)
気管支炎	2 (4.0%)	3 (5.9%)	4 (4.0%)	0
口腔ヘルペス	2 (4.0%)	2 (3.9%)	2 (2.0%)	2 (4.1%)
膀胱炎	1 (2.0%)	1 (2.0%)	6 (6.0%)	0
帯状疱疹	0	2 (3.9%)	3 (3.0%)	2 (4.1%)
鼻炎	0	3 (5.9%)	3 (3.0%)	1 (2.0%)
尿路感染	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
副鼻腔炎	0	0	2 (2.0%)	2 (4.1%)
喉頭炎	0	1 (2.0%)	2 (2.0%)	0
皮膚真菌感染	0	0	3 (3.0%)	0
せつ	1 (2.0%)	1 (2.0%)	0	0
下気道感染	0	1 (2.0%)	1 (1.0%)	0
気道感染	0	1 (2.0%)	0	1 (2.0%)
結膜炎	1 (2.0%)	0	1 (1.0%)	0
丹毒	1 (2.0%)	0	1 (1.0%)	0
肺炎	0	0	1 (1.0%)	1 (2.0%)
ウイルス感染	0	0	0	1 (2.0%)
ウイルス性鼻咽頭炎	0	0	1 (1.0%)	0
ウイルス性気道感染	1 (2.0%)	0	0	0
ウイルス性上気道感染	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 120CT2016 18:53

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
ヘモフィルス性肺炎	0	0	1 (1.0%)	0
ヘルペスウイルス感染	1 (2.0%)	0	0	0
胃腸炎	0	0	1 (1.0%)	0
咽頭炎	0	1 (2.0%)	0	0
陰部帯状疱疹	0	1 (2.0%)	0	0
外陰腔真菌感染	1 (2.0%)	0	0	0
感染性胆管炎	0	0	0	1 (2.0%)
感染性腸炎	0	1 (2.0%)	0	0
感染性皮膚潰瘍	1 (2.0%)	0	0	0
気管炎	0	0	1 (1.0%)	0
憩室炎	0	1 (2.0%)	0	0
限局性感染	1 (2.0%)	0	0	0
口角口唇炎	1 (2.0%)	0	0	0
口腔カンジダ症	1 (2.0%)	0	0	0
歯周炎	0	1 (2.0%)	0	0
歯肉炎	0	0	1 (1.0%)	0
歯膿瘍	1 (2.0%)	0	0	0
消化管感染	1 (2.0%)	0	0	0
腎盂腎炎	1 (2.0%)	0	0	0
爪囲炎	0	0	1 (1.0%)	0
爪真菌症	0	1 (2.0%)	0	0
膿疱性皮疹	0	1 (2.0%)	0	0
敗血症	0	0	1 (1.0%)	0
肺感染	1 (2.0%)	0	0	0
毛包炎	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

Page 2 of 9

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
胃腸障害				
Total number of patients with at least one adverse event	6 (12.0%)	3 (5.9%)	4 (4.0%)	4 (8.2%)
Total number of events	7	6	4	4
下痢	1 (2.0%)	2 (3.9%)	0	0
胃炎	0	0	2 (2.0%)	0
口内乾燥	0	0	1 (1.0%)	1 (2.0%)
嘔吐	0	1 (2.0%)	0	1 (2.0%)
胃腸出血	0	0	0	1 (2.0%)
胃腸障害	0	0	0	1 (2.0%)
鼓腸	1 (2.0%)	0	0	0
口内炎	1 (2.0%)	0	0	0
歯痛	0	1 (2.0%)	0	0
消化不良	1 (2.0%)	0	0	0
舌潰瘍	0	1 (2.0%)	0	0
大腸炎	0	0	1 (1.0%)	0
腹腔内血腫	1 (2.0%)	0	0	0
腹部膨満	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
臨床検査				
Total number of patients with at least one adverse event	1 (2.0%)	3 (5.9%)	10 (10.0%)	3 (6.1%)
Total number of events	1	4	16	9
アラニンアミノトランスフェラーゼ増加	1 (2.0%)	0	3 (3.0%)	2 (4.1%)
肝酵素上昇	0	2 (3.9%)	3 (3.0%)	0
アスパラギン酸アミノトランスフェラーゼ増加	0	0	3 (3.0%)	1 (2.0%)
補体成分C3減少	0	0	3 (3.0%)	1 (2.0%)
低比重リボ蛋白増加	0	2 (3.9%)	0	1 (2.0%)
補体成分C4減少	0	0	2 (2.0%)	1 (2.0%)
トランスアミナーゼ上昇	0	0	1 (1.0%)	0
血小板数減少	0	0	0	1 (2.0%)
好中球数減少	0	0	0	1 (2.0%)
白血球数減少	0	0	0	1 (2.0%)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	3 (5.9%)	7 (7.0%)	4 (8.2%)
Total number of events	1	6	7	4
脱毛症	0	2 (3.9%)	1 (1.0%)	2 (4.1%)
発疹	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
多汗症	0	0	2 (2.0%)	0
そう痒症	0	1 (2.0%)	0	0
光線角化症	0	1 (2.0%)	0	0
紅斑	0	0	1 (1.0%)	0
湿疹	0	1 (2.0%)	0	0
皮膚炎	0	0	1 (1.0%)	0
皮膚乾燥	0	0	1 (1.0%)	0
皮膚灼熱感	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
神経系障害				
Total number of patients with at least one adverse event	3 (6.0%)	4 (7.8%)	5 (5.0%)	2 (4.1%)
Total number of events	6	7	6	2
浮動性めまい	1 (2.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
頭痛	2 (4.0%)	1 (2.0%)	2 (2.0%)	0
錯感覚	0	2 (3.9%)	0	0
感覚鈍麻	0	0	1 (1.0%)	0
起立不耐性	0	0	1 (1.0%)	0
傾眠	1 (2.0%)	0	0	0
健忘	0	0	0	1 (2.0%)
失神	1 (2.0%)	0	0	0
片頭痛	1 (2.0%)	0	0	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	3 (6.0%)	0	4 (4.0%)	4 (8.2%)
Total number of events	3	0	7	6
無力症	2 (4.0%)	0	0	1 (2.0%)
注射部位疼痛	1 (2.0%)	0	0	1 (2.0%)
末梢性浮腫	0	0	1 (1.0%)	1 (2.0%)
悪寒	0	0	1 (1.0%)	0
胸痛	0	0	1 (1.0%)	0
倦怠感	0	0	1 (1.0%)	0
注射部位そう痒感	0	0	0	1 (2.0%)
注射部位血腫	0	0	1 (1.0%)	0
注射部位紅斑	0	0	0	1 (2.0%)
注射部位蕁麻疹	0	0	0	1 (2.0%)
疲労	0	0	1 (1.0%)	0
冷感	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
呼吸器、胸郭および縦隔障害 Total number of patients with at least one adverse event	3 (6.0%)	4 (7.8%)	4 (4.0%)	0
Total number of events	4	6	5	0
口腔咽頭痛	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
咳嗽	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
咽頭紅斑	0	1 (2.0%)	0	0
湿性咳嗽	0	1 (2.0%)	0	0
鼻の炎症	1 (2.0%)	0	0	0
労作性呼吸困難	0	1 (2.0%)	0	0
筋骨格系および結合組織障害 Total number of patients with at least one adverse event	3 (6.0%)	1 (2.0%)	4 (4.0%)	2 (4.1%)
Total number of events	3	2	6	3
関節痛	0	0	1 (1.0%)	1 (2.0%)
筋肉痛	1 (2.0%)	0	0	1 (2.0%)
背部痛	0	0	2 (2.0%)	0
顎痛	0	0	1 (1.0%)	0
関節腫脹	0	0	1 (1.0%)	0
筋骨格痛	1 (2.0%)	0	0	0
骨粗鬆症	0	0	1 (1.0%)	0
四肢痛	1 (2.0%)	0	0	0
腱痛	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

Page 6 of 9

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	5 (5.0%)	1 (2.0%)
Total number of events	3	0	8	2
好中球減少症	0	0	3 (3.0%)	1 (2.0%)
白血球減少症	0	0	3 (3.0%)	0
リンパ球減少症	1 (2.0%)	0	1 (1.0%)	0
リンパ節症	1 (2.0%)	0	0	0
血小板減少症	0	0	0	1 (2.0%)
代謝および栄養障害				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	3 (3.0%)	1 (2.0%)
Total number of events	2	4	3	1
高コレステロール血症	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
ビタミンD欠乏	1 (2.0%)	0	0	0
高脂血症	0	0	1 (1.0%)	0
食欲減退	0	0	1 (1.0%)	0
低カリウム血症	0	1 (2.0%)	0	0
葉酸欠乏	1 (2.0%)	0	0	0
血管障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	1 (1.0%)	3 (6.1%)
Total number of events	0	2	1	3
高血圧	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
ほてり	0	0	0	1 (2.0%)
拡張期高血圧	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

Page 7 of 9

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
心臓障害				
Total number of patients with at least one adverse event	1 (2.0%)	2 (3.9%)	1 (1.0%)	0
Total number of events	1	2	1	0
動悸	1 (2.0%)	0	1 (1.0%)	0
不整脈	0	1 (2.0%)	0	0
慢性心不全	0	1 (2.0%)	0	0
腎および尿路障害				
Total number of patients with at least one adverse event	0	2 (3.9%)	1 (1.0%)	0
Total number of events	0	2	2	0
尿意切迫	0	2 (3.9%)	0	0
排尿困難	0	0	1 (1.0%)	0
眼障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	0	0
Total number of events	2	0	0	0
眼瞼炎	1 (2.0%)	0	0	0
緑内障	1 (2.0%)	0	0	0
精神障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	1 (1.0%)	0
Total number of events	0	1	1	0
初期不眠症	0	0	1 (1.0%)	0
抑うつ気分を伴う適応障害	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

t_ae_pt_relt_sp Adverse Events Related to TCZ (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
耳および迷路障害 Total number of patients with at least one adverse event	1 (2.0%)	0	0	0
Total number of events	1	0	0	0
回転性めまい	1 (2.0%)	0	0	0
傷害、中毒および処置合併症 Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
注射に伴う反応	0	0	1 (1.0%)	0
生殖系および乳房障害 Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
勃起不全	0	0	1 (1.0%)	0
免疫系障害 Total number of patients with at least one adverse event	0	0	0	1 (2.0%)
Total number of events	0	0	0	1
過敏症	0	0	0	1 (2.0%)
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） Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
辺縁帯リンパ腫	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 Percentages are based on N in the column headings.
 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_pt_relt.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_pt_relt_sp.out
 12OCT2016 18:53

表 2.7.4.8-4 観察期間あたりの事象別有害事象発現件数 (Events /100 PYs, MRA632JP 試験-二重盲検期間)

aepyB_sp Adverse Events (Event /Patient-Year) -Double Blind Period
 Protocol: MRA LVV
 Analysis: SAFETY

Body System/ Adverse Event	Placebo N=18 Event (E/100PY)	MRA-SC 162mg/W N=18 Event (E/100PY)
Total Exposure Period (Patient-years)	5.9	7.9
ALL BODY SYSTEMS		
Total Pts with at Least one AE	11	14
Total Number of AEs	32 (541.6)	46 (581.4)
感染症および寄生虫症		
Total Pts With at Least one AE	6	9
鼻咽頭炎	3 (50.8)	11 (139.0)
上気道感染	0	4 (50.6)
胃腸炎	0	2 (25.3)
咽頭炎	0	2 (25.3)
麦粒腫	0	2 (25.3)
癩風	1 (16.9)	1 (12.6)
カンピロバクター胃腸炎	0	1 (12.6)
気管支炎	1 (16.9)	0
口腔ヘルペス	0	1 (12.6)
帯状疱疹	1 (16.9)	0
膀胱炎	0	1 (12.6)
Total Number of AEs	6 (101.6)	25 (316.0)
胃腸障害		
Total Pts With at Least one AE	5	3
悪心	0	1 (12.6)
胃腸の炎症	0	1 (12.6)
下痢	1 (16.9)	0
出血性胃潰瘍	1 (16.9)	0
上腹部痛	1 (16.9)	0
舌出血	1 (16.9)	0
腸炎	1 (16.9)	0
腹痛	0	1 (12.6)
嘔吐	1 (16.9)	0
Total Number of AEs	6 (101.6)	3 (37.9)
皮膚および皮下組織障害		
Total Pts With at Least one AE	1	6
ざ瘡	1 (16.9)	1 (12.6)
そう痒症	0	1 (12.6)
寒冷蕁麻疹	0	1 (12.6)
結節性紅斑	0	1 (12.6)
多形紅斑	0	1 (12.6)
点状出血	0	1 (12.6)
皮下出血	0	1 (12.6)
皮脂欠乏性湿疹	1 (16.9)	0
皮膚乾燥	0	1 (12.6)
Total Number of AEs	2 (33.9)	8 (101.1)
眼障害		
Total Pts With at Least one AE	2	1
白内障	1 (16.9)	1 (12.6)
眼脂	1 (16.9)	0
Total Number of AEs	2 (33.9)	1 (12.6)

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepyB.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/aepyB_sp.out
 21JUN2016 11:57

aepyB_sp Adverse Events (Event /Patient-Year) -Double Blind Period
 Protocol: MRA LVV
 Analysis: SAFETY

Body System/ Adverse Event	Placebo N=18 Event (E/100PY)	MRA-SC 162mg/W N=18 Event (E/100PY)
呼吸器、胸郭および縦隔障害		
Total Pts With at Least one AE	3	0
口腔咽頭痛	2 (33.9)	0
喀血	2 (33.9)	0
Total Number of AEs	4 (67.7)	0
神経系障害		
Total Pts With at Least one AE	1	2
感覚鈍麻	0	1 (12.6)
傾眠	0	1 (12.6)
頭痛	1 (16.9)	0
Total Number of AEs	1 (16.9)	2 (25.3)
臨床検査		
Total Pts With at Least one AE	2	1
体重増加	2 (33.9)	0
アラニンアミノトランスフェラーゼ増加	0	1 (12.6)
γ-グルタミルトランスフェラーゼ増加	1 (16.9)	0
血中クレアチニン増加	1 (16.9)	0
血中フィブリノゲン増加	1 (16.9)	0
Total Number of AEs	5 (84.6)	1 (12.6)
精神障害		
Total Pts With at Least one AE	1	1
不安	0	1 (12.6)
不眠症	1 (16.9)	0
Total Number of AEs	1 (16.9)	1 (12.6)
一般・全身障害および投与部位の状態		
Total Pts With at Least one AE	1	0
胸痛	1 (16.9)	0
Total Number of AEs	1 (16.9)	0
肝胆道系障害		
Total Pts With at Least one AE	1	0
肝機能異常	1 (16.9)	0
Total Number of AEs	1 (16.9)	0
筋骨格系および結合組織障害		
Total Pts With at Least one AE	0	1
筋肉痛	0	1 (12.6)
頸部痛	0	1 (12.6)
四肢痛	0	1 (12.6)
Total Number of AEs	0	3 (37.9)
血液およびリンパ系障害		
Total Pts With at Least one AE	1	0
貧血	1 (16.9)	0
Total Number of AEs	1 (16.9)	0
血管障害		
Total Pts With at Least one AE	1	0
出血性ショック	1 (16.9)	0
Total Number of AEs	1 (16.9)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepyB.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/aepyB_sp.out
 21JUN2016 11:57

aepyB_sp Adverse Events (Event /Patient-Year) -Double Blind Period
 Protocol: MRA LVV
 Analysis: SAFETY

Body System/ Adverse Event	Placebo N=18 Event (E/100PY)	MRA-SC 162mg/W N=18 Event (E/100PY)
傷害、中毒および処置合併症		
Total Pts With at Least one AE	0	1
肋骨骨折	0	1 (12.6)
Total Number of AEs	0	1 (12.6)
代謝および栄養障害		
Total Pts With at Least one AE	0	1
食欲減退	0	1 (12.6)
Total Number of AEs	0	1 (12.6)
内分泌障害		
Total Pts With at Least one AE	1	0
ステロイド離脱症候群	1 (16.9)	0
Total Number of AEs	1 (16.9)	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.

E/100PY : rate of Adverse Events per 100 Patient-years.

Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepyB.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/aepyB_sp.out
 21JUN2016 11:57

表 2.7.4.8-5 観察期間あたりの事象別有害事象発現件数 (Events /100 PYs, MRA632JP 試験-全期間の本剤全投与例)

aepy_mt_sp Adverse Events (Event /Patient-Year)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Body System/ Adverse Event	MRA-SC 162mg/W Total N=36 Event (E/100PY)
Total Exposure Period (Patient-years)	46.0
ALL BODY SYSTEMS	
Total Pts with at Least one AE	34
Total Number of AEs	247 (536.6)
感染症および寄生虫症	
Total Pts With at Least one AE	31
鼻咽頭炎	36 (78.2)
上気道感染	18 (39.1)
咽頭炎	11 (23.9)
胃腸炎	7 (15.2)
感染性腸炎	5 (10.9)
口腔ヘルペス	4 (8.7)
膀胱炎	4 (8.7)
麦粒腫	3 (6.5)
インフルエンザ	2 (4.3)
外陰部腔カンジダ症	2 (4.3)
副鼻腔炎	2 (4.3)
せつ	1 (2.2)
ウイルス性腸炎	1 (2.2)
カンピロバクター胃腸炎	1 (2.2)
ヘモフィルス性肺炎	1 (2.2)
β溶血性レンサ球菌感染	1 (2.2)
急性腎盂腎炎	1 (2.2)
歯冠周囲炎	1 (2.2)
歯周炎	1 (2.2)
食道カンジダ症	1 (2.2)
爪囲炎	1 (2.2)
尿路感染	1 (2.2)
肺炎	1 (2.2)
皮膚真菌感染	1 (2.2)
鼻炎	1 (2.2)
毛包炎	1 (2.2)
癬風	1 (2.2)
Total Number of AEs	110 (239.0)
胃腸障害	
Total Pts With at Least one AE	16
悪心	4 (8.7)
下痢	4 (8.7)
口内炎	3 (6.5)
腹痛	3 (6.5)
齦歯	3 (6.5)
口唇炎	2 (4.3)
腹部不快感	2 (4.3)
胃腸の炎症	1 (2.2)
過敏性腸症候群	1 (2.2)
歯肉痛	1 (2.2)
腸炎	1 (2.2)
便秘	1 (2.2)
Total Number of AEs	26 (56.5)

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepy.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aepy_mt_sp.out
 12JAN2017 17:14

aepy_mt_sp Adverse Events (Event /Patient-Year)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Body System/ Adverse Event	MRA-SC 162mg/W Total N=36 Event (E/100PY)
皮膚および皮下組織障害	
Total Pts With at Least one AE	16
皮下出血	4 (8.7)
ざ瘡	3 (6.5)
湿疹	2 (4.3)
発疹	2 (4.3)
皮膚乾燥	2 (4.3)
蕁麻疹	2 (4.3)
そう痒症	1 (2.2)
寒冷蕁麻疹	1 (2.2)
結節性紅斑	1 (2.2)
多形紅斑	1 (2.2)
脱毛症	1 (2.2)
点状出血	1 (2.2)
皮膚剥脱	1 (2.2)
嵌入爪	1 (2.2)
Total Number of AEs	23 (50.0)
筋骨格系および結合組織障害	
Total Pts With at Least one AE	11
背部痛	5 (10.9)
筋肉痛	4 (8.7)
四肢痛	2 (4.3)
顎関節症候群	1 (2.2)
関節痛	1 (2.2)
筋骨格痛	1 (2.2)
頸部痛	1 (2.2)
足底筋膜炎	1 (2.2)
椎間板突出	1 (2.2)
変形性関節症	1 (2.2)
Total Number of AEs	18 (39.1)
神経系障害	
Total Pts With at Least one AE	9
失神寸前の状態	3 (6.5)
頭痛	3 (6.5)
感覚鈍麻	2 (4.3)
緊張性頭痛	2 (4.3)
傾眠	1 (2.2)
坐骨神経痛	1 (2.2)
複合性局所疼痛症候群	1 (2.2)
Total Number of AEs	13 (28.2)
傷害、中毒および処置合併症	
Total Pts With at Least one AE	7
挫傷	3 (6.5)
肋骨骨折	2 (4.3)
処置による疼痛	1 (2.2)
節足動物刺傷	1 (2.2)
足骨折	1 (2.2)
Total Number of AEs	8 (17.4)

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepy.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aepy_mt_sp.out
 12JAN2017 17:14

aepy_mt_sp Adverse Events (Event /Patient-Year)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Body System/ Adverse Event	MRA-SC 162mg/W Total N=36 Event (E/100PY)
眼障害	
Total Pts With at Least one AE	6
アレルギー性結膜炎	1 (2.2)
眼乾燥	1 (2.2)
眼瞼炎	1 (2.2)
眼瞼発疹	1 (2.2)
視力障害	1 (2.2)
囊下白内障	1 (2.2)
白内障	1 (2.2)
Total Number of AEs	7 (15.2)
呼吸器、胸郭および縦隔障害	
Total Pts With at Least one AE	6
肺梗塞	2 (4.3)
咳嗽	1 (2.2)
気縦隔症	1 (2.2)
声帯肥厚	1 (2.2)
鼻出血	1 (2.2)
喀血	1 (2.2)
Total Number of AEs	7 (15.2)
血液およびリンパ系障害	
Total Pts With at Least one AE	5
鉄欠乏性貧血	4 (8.7)
貧血	1 (2.2)
Total Number of AEs	5 (10.9)
精神障害	
Total Pts With at Least one AE	5
不眠症	3 (6.5)
うつ病	1 (2.2)
パニック障害	1 (2.2)
不安	1 (2.2)
Total Number of AEs	6 (13.0)
臨床検査	
Total Pts With at Least one AE	5
アラニンアミノトランスフェラーゼ増加	3 (6.5)
アスパラギン酸アミノトランスフェラーゼ	2 (4.3)
γ-グルタミルトランスフェラーゼ増加	1 (2.2)
胸部X線異常	1 (2.2)
胸部コンピュータ断層撮影異常	1 (2.2)
白血球数減少	1 (2.2)
Total Number of AEs	9 (19.6)
一般・全身障害および投与部位の状態	
Total Pts With at Least one AE	3
注射部位出血	2 (4.3)
胸痛	1 (2.2)
疼痛	1 (2.2)
Total Number of AEs	4 (8.7)
肝胆道系障害	
Total Pts With at Least one AE	2
肝機能異常	2 (4.3)
Total Number of AEs	2 (4.3)

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepy.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aepy_mt_sp.out
 12JAN2017 17:14

aepy_mt_sp Adverse Events (Event /Patient-Year)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Body System/ Adverse Event	MRA-SC 162mg/W Total N=36 Event (E/100PY)
腎および尿路障害	
Total Pts With at Least one AE	2
緊張性膀胱	1 (2.2)
血尿	1 (2.2)
Total Number of AEs	2 (4.3)
生殖系および乳房障害	
Total Pts With at Least one AE	2
月経困難症	1 (2.2)
産褥期乳汁分泌増加	1 (2.2)
卵巣嚢胞	1 (2.2)
Total Number of AEs	3 (6.5)
代謝および栄養障害	
Total Pts With at Least one AE	2
脂質異常症	1 (2.2)
食欲減退	1 (2.2)
Total Number of AEs	2 (4.3)
内分泌障害	
Total Pts With at Least one AE	1
ステロイド離脱症候群	1 (2.2)
Total Number of AEs	1 (2.2)
免疫系障害	
Total Pts With at Least one AE	1
造影剤アレルギー	1 (2.2)
Total Number of AEs	1 (2.2)

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 E/100PY : rate of Adverse Events per 100 Patient-years.
 Multiple occurrences of the same adverse event in one individual counted respectively.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aepy.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aepy_mt_sp.out
 12JAN2017 17:14

表 2.7.4.8-6 重症度別の事象別有害事象発現例数 (MRA632JP 試験-二重盲検期間)

aet03_sp Adverse Events by Intensity
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PLACEBO (N=18)			
	Total	MILD	MODERATE	SEVERE
- Any adverse events -	11 (61.1%)	6 (33.3%)	4 (22.2%)	1 (5.6%)
感染症および寄生虫症				
- Overall -	6 (33.3%)	5 (27.8%)	1 (5.6%)	0
鼻咽頭炎	3 (16.7%)	3 (16.7%)	0	0
癩風	1 (5.6%)	1 (5.6%)	0	0
気管支炎	1 (5.6%)	0	1 (5.6%)	0
带状疱疹	1 (5.6%)	1 (5.6%)	0	0
胃腸障害				
- Overall -	5 (27.8%)	2 (11.1%)	2 (11.1%)	1 (5.6%)
下痢	1 (5.6%)	1 (5.6%)	0	0
出血性胃潰瘍	1 (5.6%)	0	0	1 (5.6%)
上腹部痛	1 (5.6%)	0	1 (5.6%)	0
舌出血	1 (5.6%)	1 (5.6%)	0	0
腸炎	1 (5.6%)	0	1 (5.6%)	0
嘔吐	1 (5.6%)	1 (5.6%)	0	0
皮膚および皮下組織障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
ざ瘡	1 (5.6%)	1 (5.6%)	0	0
皮脂欠乏性湿疹	1 (5.6%)	1 (5.6%)	0	0
眼障害				
- Overall -	2 (11.1%)	1 (5.6%)	1 (5.6%)	0
白内障	1 (5.6%)	0	1 (5.6%)	0
眼脂	1 (5.6%)	1 (5.6%)	0	0
呼吸器、胸郭および縦隔障害				
- Overall -	3 (16.7%)	3 (16.7%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Percentages are based on N.
 Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
 Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet03.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet03_sp.out
 28DEC2015 18:16
 Page 1 of 5

aet03_sp Adverse Events by Intensity
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PLACEBO (N=18)			
	Total	MILD	MODERATE	SEVERE
口腔咽頭痛	2 (11.1%)	2 (11.1%)	0	0
咯血	1 (5.6%)	1 (5.6%)	0	0
神経系障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
頭痛	1 (5.6%)	1 (5.6%)	0	0
精神障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
不眠症	1 (5.6%)	1 (5.6%)	0	0
臨床検査				
- Overall -	2 (11.1%)	2 (11.1%)	0	0
体重増加	2 (11.1%)	2 (11.1%)	0	0
γ-グルタミルトランスフェラーゼ増加	1 (5.6%)	1 (5.6%)	0	0
血中クレアチニン増加	1 (5.6%)	1 (5.6%)	0	0
血中フィブリノゲン増加	1 (5.6%)	1 (5.6%)	0	0
一般・全身障害および投与部位の状態				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
胸痛	1 (5.6%)	1 (5.6%)	0	0
肝胆道系障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
肝機能異常	1 (5.6%)	1 (5.6%)	0	0
血液およびリンパ系障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
貧血	1 (5.6%)	1 (5.6%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Percentages are based on N.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet03.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet03_sp.out
 28DEC2015 18:16
 Page 2 of 5

aet03_sp Adverse Events by Intensity
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	PLACEBO (N=18)			
	Total	MILD	MODERATE	SEVERE
血管障害				
- Overall -	1 (5.6%)	0	0	1 (5.6%)
出血性ショック	1 (5.6%)	0	0	1 (5.6%)
内分泌障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
ステロイド離脱症候群	1 (5.6%)	1 (5.6%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Percentages are based on N.
 Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
 Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet03.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet03_sp.out
 28DEC2015 18:16
 Page 3 of 5

aet03_sp Adverse Events by Intensity
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/w (N=18)			
	Total	MILD	MODERATE	SEVERE
- Any adverse events -	14 (77.8%)	13 (72.2%)	1 (5.6%)	0
感染症および寄生虫症				
- Overall -	9 (50.0%)	9 (50.0%)	0	0
咽頭炎	6 (33.3%)	6 (33.3%)	0	0
上気道感染	3 (16.7%)	3 (16.7%)	0	0
胃腸炎	2 (11.1%)	2 (11.1%)	0	0
咽頭炎	2 (11.1%)	2 (11.1%)	0	0
癩風	1 (5.6%)	1 (5.6%)	0	0
カンピロバクター胃腸炎	1 (5.6%)	1 (5.6%)	0	0
口腔ヘルペス	1 (5.6%)	1 (5.6%)	0	0
麦粒腫	1 (5.6%)	1 (5.6%)	0	0
膀胱炎	1 (5.6%)	1 (5.6%)	0	0
胃腸障害				
- Overall -	3 (16.7%)	3 (16.7%)	0	0
悪心	1 (5.6%)	1 (5.6%)	0	0
胃腸の炎症	1 (5.6%)	1 (5.6%)	0	0
腹痛	1 (5.6%)	1 (5.6%)	0	0
皮膚および皮下組織障害				
- Overall -	6 (33.3%)	6 (33.3%)	0	0
ざ瘡	1 (5.6%)	1 (5.6%)	0	0
そう痒症	1 (5.6%)	1 (5.6%)	0	0
寒冷尋麻疹	1 (5.6%)	1 (5.6%)	0	0
結節性紅斑	1 (5.6%)	1 (5.6%)	0	0
多形紅斑	1 (5.6%)	1 (5.6%)	0	0
点状出血	1 (5.6%)	1 (5.6%)	0	0
皮下出血	1 (5.6%)	1 (5.6%)	0	0
皮膚乾燥	1 (5.6%)	1 (5.6%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Percentages are based on N.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet03.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet03_sp.out
 28DEC2015 18:16
 Page 4 of 5

aet03_sp Adverse Events by Intensity
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/w (N=18)			
	Total	MILD	MODERATE	SEVERE
眼障害				
- Overall -	1 (5.6%)	0	1 (5.6%)	0
白内障	1 (5.6%)	0	1 (5.6%)	0
神経系障害				
- Overall -	2 (11.1%)	2 (11.1%)	0	0
感覚鈍麻	1 (5.6%)	1 (5.6%)	0	0
傾眠	1 (5.6%)	1 (5.6%)	0	0
精神障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
不安	1 (5.6%)	1 (5.6%)	0	0
筋骨格系および結合組織障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
筋肉痛	1 (5.6%)	1 (5.6%)	0	0
頸部痛	1 (5.6%)	1 (5.6%)	0	0
四肢痛	1 (5.6%)	1 (5.6%)	0	0
傷害、中毒および処置合併症				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
肋骨骨折	1 (5.6%)	1 (5.6%)	0	0
代謝および栄養障害				
- Overall -	1 (5.6%)	1 (5.6%)	0	0
食欲減退	1 (5.6%)	1 (5.6%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Percentages are based on N.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aet03.sas / Output:
 /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aet03_sp.out
 28DEC2015 18:16
 Page 5 of 5

[5.3.5.1-1 表 15.3.1-5を再掲]

表 2.7.4.8-7 重症度別の事象別有害事象発現例数 (MRA632JP 試験-全期間の本剤全投与例)

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
- Any adverse events -	34 (94.4%)	22 (61.1%)	10 (27.8%)	2 (5.6%)
感染症および寄生虫症				
- Overall -	31 (86.1%)	25 (69.4%)	5 (13.9%)	1 (2.8%)
鼻咽頭炎	18 (50.0%)	18 (50.0%)	0	0
咽頭炎	7 (19.4%)	6 (16.7%)	1 (2.8%)	0
上気道感染	7 (19.4%)	6 (16.7%)	1 (2.8%)	0
胃腸炎	5 (13.9%)	5 (13.9%)	0	0
感染性腸炎	4 (11.1%)	3 (8.3%)	1 (2.8%)	0
口腔ヘルペス	3 (8.3%)	3 (8.3%)	0	0
膀胱炎	3 (8.3%)	3 (8.3%)	0	0
インフルエンザ	2 (5.6%)	2 (5.6%)	0	0
外陰部腔カンジダ症	2 (5.6%)	2 (5.6%)	0	0
副鼻腔炎	2 (5.6%)	2 (5.6%)	0	0
せつ	1 (2.8%)	0	1 (2.8%)	0
ウイルス性腸炎	1 (2.8%)	0	1 (2.8%)	0
カンピロバクター胃腸炎	1 (2.8%)	1 (2.8%)	0	0
ヘモフィルス性肺炎	1 (2.8%)	0	1 (2.8%)	0
β溶血性レンサ球菌感染	1 (2.8%)	1 (2.8%)	0	0
急性腎盂腎炎	1 (2.8%)	0	0	1 (2.8%)
歯冠周囲炎	1 (2.8%)	1 (2.8%)	0	0
歯周炎	1 (2.8%)	1 (2.8%)	0	0
食道カンジダ症	1 (2.8%)	1 (2.8%)	0	0
爪囲炎	1 (2.8%)	1 (2.8%)	0	0
尿路感染	1 (2.8%)	1 (2.8%)	0	0
肺炎	1 (2.8%)	0	1 (2.8%)	0
麦粒腫	1 (2.8%)	1 (2.8%)	0	0
皮膚真菌感染	1 (2.8%)	1 (2.8%)	0	0
鼻炎	1 (2.8%)	1 (2.8%)	0	0
毛包炎	1 (2.8%)	1 (2.8%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN201717:04
 Page 1 of 6

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
癩風	1 (2.8%)	1 (2.8%)	0	0
胃腸障害				
- Overall -	16 (44.4%)	15 (41.7%)	1 (2.8%)	0
下痢	4 (11.1%)	4 (11.1%)	0	0
悪心	3 (8.3%)	3 (8.3%)	0	0
腹痛	3 (8.3%)	3 (8.3%)	0	0
齦歯	3 (8.3%)	2 (5.6%)	1 (2.8%)	0
口唇炎	2 (5.6%)	2 (5.6%)	0	0
口内炎	2 (5.6%)	2 (5.6%)	0	0
腹部不快感	2 (5.6%)	2 (5.6%)	0	0
胃腸の炎症	1 (2.8%)	1 (2.8%)	0	0
過敏性腸症候群	1 (2.8%)	1 (2.8%)	0	0
歯肉痛	1 (2.8%)	1 (2.8%)	0	0
腸炎	1 (2.8%)	1 (2.8%)	0	0
便秘	1 (2.8%)	1 (2.8%)	0	0
皮膚および皮下組織障害				
- Overall -	16 (44.4%)	16 (44.4%)	0	0
ざ瘡	3 (8.3%)	3 (8.3%)	0	0
皮下出血	3 (8.3%)	3 (8.3%)	0	0
湿疹	2 (5.6%)	2 (5.6%)	0	0
発疹	2 (5.6%)	2 (5.6%)	0	0
皮膚乾燥	2 (5.6%)	2 (5.6%)	0	0
蕁麻疹	2 (5.6%)	2 (5.6%)	0	0
そう痒症	1 (2.8%)	1 (2.8%)	0	0
寒冷蕁麻疹	1 (2.8%)	1 (2.8%)	0	0
結節性紅斑	1 (2.8%)	1 (2.8%)	0	0
多形紅斑	1 (2.8%)	1 (2.8%)	0	0
脱毛症	1 (2.8%)	1 (2.8%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN2017:04
 Page 2 of 6

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
点状出血	1 (2.8%)	1 (2.8%)	0	0
皮膚剥脱	1 (2.8%)	1 (2.8%)	0	0
嵌入爪	1 (2.8%)	1 (2.8%)	0	0
筋骨格系および結合組織障害 - Overall -	11 (30.6%)	10 (27.8%)	1 (2.8%)	0
筋肉痛	4 (11.1%)	4 (11.1%)	0	0
背部痛	4 (11.1%)	4 (11.1%)	0	0
四肢痛	2 (5.6%)	2 (5.6%)	0	0
顎関節症候群	1 (2.8%)	1 (2.8%)	0	0
関節痛	1 (2.8%)	1 (2.8%)	0	0
筋骨格痛	1 (2.8%)	1 (2.8%)	0	0
頸部痛	1 (2.8%)	1 (2.8%)	0	0
足底筋膜炎	1 (2.8%)	1 (2.8%)	0	0
椎間板突出	1 (2.8%)	1 (2.8%)	0	0
変形性関節症	1 (2.8%)	0	1 (2.8%)	0
神経系障害 - Overall -	9 (25.0%)	8 (22.2%)	0	1 (2.8%)
失神寸前の状態	3 (8.3%)	3 (8.3%)	0	0
頭痛	3 (8.3%)	3 (8.3%)	0	0
感覚鈍麻	2 (5.6%)	2 (5.6%)	0	0
緊張性頭痛	1 (2.8%)	1 (2.8%)	0	0
傾眠	1 (2.8%)	1 (2.8%)	0	0
坐骨神経痛	1 (2.8%)	1 (2.8%)	0	0
複合性局所疼痛症候群	1 (2.8%)	0	0	1 (2.8%)
傷害、中毒および処置合併症 - Overall -	7 (19.4%)	6 (16.7%)	1 (2.8%)	0
挫傷	3 (8.3%)	3 (8.3%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN201717:04
 Page 3 of 6

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
肋骨骨折	2 (5.6%)	1 (2.8%)	1 (2.8%)	0
処置による疼痛	1 (2.8%)	1 (2.8%)	0	0
節足動物刺傷	1 (2.8%)	1 (2.8%)	0	0
足骨折	1 (2.8%)	1 (2.8%)	0	0
眼障害				
- Overall -	6 (16.7%)	4 (11.1%)	2 (5.6%)	0
アレルギー性結膜炎	1 (2.8%)	1 (2.8%)	0	0
眼乾燥	1 (2.8%)	1 (2.8%)	0	0
眼瞼炎	1 (2.8%)	1 (2.8%)	0	0
眼瞼発疹	1 (2.8%)	1 (2.8%)	0	0
視力障害	1 (2.8%)	0	1 (2.8%)	0
嚥下白内障	1 (2.8%)	1 (2.8%)	0	0
白内障	1 (2.8%)	0	1 (2.8%)	0
呼吸器、胸郭および縦隔障害				
- Overall -	6 (16.7%)	5 (13.9%)	1 (2.8%)	0
肺梗塞	2 (5.6%)	1 (2.8%)	1 (2.8%)	0
咳嗽	1 (2.8%)	1 (2.8%)	0	0
気縦隔症	1 (2.8%)	1 (2.8%)	0	0
声帯肥厚	1 (2.8%)	1 (2.8%)	0	0
鼻出血	1 (2.8%)	1 (2.8%)	0	0
喀血	1 (2.8%)	1 (2.8%)	0	0
血液およびリンパ系障害				
- Overall -	5 (13.9%)	5 (13.9%)	0	0
鉄欠乏性貧血	4 (11.1%)	4 (11.1%)	0	0
貧血	1 (2.8%)	1 (2.8%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN2017:04
 Page 4 of 6

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
精神障害				
- Overall -	5 (13.9%)	5 (13.9%)	0	0
不眠症	3 (8.3%)	3 (8.3%)	0	0
うつ病	1 (2.8%)	1 (2.8%)	0	0
パニック障害	1 (2.8%)	1 (2.8%)	0	0
不安	1 (2.8%)	1 (2.8%)	0	0
臨床検査				
- Overall -	5 (13.9%)	5 (13.9%)	0	0
アラニンアミノトランスフェラーゼ増加	3 (8.3%)	3 (8.3%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	2 (5.6%)	0	0
γ-グルタミルトランスフェラーゼ増加	1 (2.8%)	1 (2.8%)	0	0
胸部X線異常	1 (2.8%)	1 (2.8%)	0	0
胸部コンピュータ断層撮影異常	1 (2.8%)	1 (2.8%)	0	0
白血球数減少	1 (2.8%)	1 (2.8%)	0	0
一般・全身障害および投与部位の状態				
- Overall -	3 (8.3%)	2 (5.6%)	1 (2.8%)	0
胸痛	1 (2.8%)	1 (2.8%)	0	0
注射部位出血	1 (2.8%)	1 (2.8%)	0	0
疼痛	1 (2.8%)	0	1 (2.8%)	0
肝胆道系障害				
- Overall -	2 (5.6%)	1 (2.8%)	1 (2.8%)	0
肝機能異常	2 (5.6%)	1 (2.8%)	1 (2.8%)	0
腎および尿路障害				
- Overall -	2 (5.6%)	2 (5.6%)	0	0
緊張性膀胱	1 (2.8%)	1 (2.8%)	0	0
血尿	1 (2.8%)	1 (2.8%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.

Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN2017:04
 Page 5 of 6

aet03_mt_sp Adverse Events by Greatest Intensity
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	MRA-SC 162mg/W Total (N=36)			
	Total	MILD	MODERATE	SEVERE
生殖系および乳房障害				
- Overall -	2 (5.6%)	2 (5.6%)	0	0
月経困難症	1 (2.8%)	1 (2.8%)	0	0
産褥期乳汁分泌増加	1 (2.8%)	1 (2.8%)	0	0
卵巣嚢胞	1 (2.8%)	1 (2.8%)	0	0
代謝および栄養障害				
- Overall -	2 (5.6%)	2 (5.6%)	0	0
脂質異常症	1 (2.8%)	1 (2.8%)	0	0
食欲減退	1 (2.8%)	1 (2.8%)	0	0
内分泌障害				
- Overall -	1 (2.8%)	1 (2.8%)	0	0
ステロイド離脱症候群	1 (2.8%)	1 (2.8%)	0	0
免疫系障害				
- Overall -	1 (2.8%)	1 (2.8%)	0	0
造影剤アレルギー	1 (2.8%)	1 (2.8%)	0	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
 Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03_mt_sp.out
 12JAN201717:04
 Page 6 of 6

[5.3.5.1-7 表 11.3-8を再掲]

表 2.7.4.8-8 重症度別の事象別有害事象発現例数 (WA28119試験-二重盲検期間)

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
- Any adverse events -	- Any Grade -	48 (96.0%)	47 (92.2%)	98 (98.0%)	47 (95.9%)
	1	16 (32.0%)	20 (39.2%)	33 (33.0%)	16 (32.7%)
	2	20 (40.0%)	13 (25.5%)	39 (39.0%)	19 (38.8%)
	3	11 (22.0%)	13 (25.5%)	24 (24.0%)	11 (22.4%)
	4	1 (2.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
感染症および寄生虫症 - Overall -	- Any Grade -	38 (76.0%)	33 (64.7%)	75 (75.0%)	36 (73.5%)
	1	21 (42.0%)	17 (33.3%)	40 (40.0%)	19 (38.8%)
	2	14 (28.0%)	10 (19.6%)	26 (26.0%)	14 (28.6%)
	3	3 (6.0%)	6 (11.8%)	9 (9.0%)	3 (6.1%)
鼻咽頭炎	- Any Grade -	9 (18.0%)	13 (25.5%)	29 (29.0%)	12 (24.5%)
	1	6 (12.0%)	10 (19.6%)	24 (24.0%)	11 (22.4%)
	2	3 (6.0%)	3 (5.9%)	5 (5.0%)	1 (2.0%)
上気道感染	- Any Grade -	5 (10.0%)	7 (13.7%)	10 (10.0%)	6 (12.2%)
	1	3 (6.0%)	5 (9.8%)	9 (9.0%)	5 (10.2%)
	2	2 (4.0%)	2 (3.9%)	1 (1.0%)	1 (2.0%)
気管支炎	- Any Grade -	5 (10.0%)	5 (9.8%)	8 (8.0%)	4 (8.2%)
	1	3 (6.0%)	3 (5.9%)	4 (4.0%)	2 (4.1%)
	2	2 (4.0%)	2 (3.9%)	4 (4.0%)	2 (4.1%)
尿路感染	- Any Grade -	2 (4.0%)	4 (7.8%)	10 (10.0%)	4 (8.2%)
	1	0	1 (2.0%)	7 (7.0%)	3 (6.1%)
	2	2 (4.0%)	3 (5.9%)	2 (2.0%)	1 (2.0%)
	3	0	0	1 (1.0%)	0
胃腸炎	- Any Grade -	4 (8.0%)	4 (7.8%)	3 (3.0%)	4 (8.2%)
	1	2 (4.0%)	2 (3.9%)	1 (1.0%)	3 (6.1%)
	2	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	3	0	1 (2.0%)	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
鼻炎	- Any Grade -	2 (4.0%)	3 (5.9%)	6 (6.0%)	4 (8.2%)
	1	2 (4.0%)	3 (5.9%)	6 (6.0%)	2 (4.1%)
	3	0	0	0	2 (4.1%)
口腔ヘルペス	- Any Grade -	3 (6.0%)	2 (3.9%)	4 (4.0%)	5 (10.2%)
	1	3 (6.0%)	1 (2.0%)	4 (4.0%)	4 (8.2%)
	2	0	1 (2.0%)	0	1 (2.0%)
膀胱炎	- Any Grade -	2 (4.0%)	3 (5.9%)	7 (7.0%)	0
	1	1 (2.0%)	3 (5.9%)	3 (3.0%)	0
	2	1 (2.0%)	0	3 (3.0%)	0
結膜炎	- Any Grade -	4 (8.0%)	1 (2.0%)	4 (4.0%)	1 (2.0%)
	1	3 (6.0%)	1 (2.0%)	2 (2.0%)	0
	2	1 (2.0%)	0	2 (2.0%)	1 (2.0%)
副鼻腔炎	- Any Grade -	1 (2.0%)	2 (3.9%)	3 (3.0%)	4 (8.2%)
	1	0	1 (2.0%)	1 (1.0%)	3 (6.1%)
	2	1 (2.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
帯状疱疹	- Any Grade -	0	2 (3.9%)	5 (5.0%)	2 (4.1%)
	2	0	0	4 (4.0%)	2 (4.1%)
	3	0	2 (3.9%)	1 (1.0%)	0
咽頭炎	- Any Grade -	1 (2.0%)	3 (5.9%)	4 (4.0%)	0
	1	1 (2.0%)	1 (2.0%)	3 (3.0%)	0
	2	0	2 (3.9%)	1 (1.0%)	0
喉頭炎	- Any Grade -	0	2 (3.9%)	3 (3.0%)	1 (2.0%)
	1	0	2 (3.9%)	2 (2.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
歯肉炎	- Any Grade -	1 (2.0%)	2 (3.9%)	2 (2.0%)	0
	1	0	2 (3.9%)	2 (2.0%)	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
ウイルス性胃腸炎	- Any Grade -	0	1 (2.0%)	3 (3.0%)	0
	1	0	1 (2.0%)	2 (2.0%)	0
	2	0	0	1 (1.0%)	0
下気道感染	- Any Grade -	0	1 (2.0%)	3 (3.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	1 (2.0%)	2 (2.0%)	0
歯膿瘍	- Any Grade -	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
	1	2 (4.0%)	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
消化管感染	- Any Grade -	1 (2.0%)	0	3 (3.0%)	0
	1	1 (2.0%)	0	3 (3.0%)	0
	2	0	0	0	0
丹毒	- Any Grade -	1 (2.0%)	0	2 (2.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	1 (2.0%)	0	1 (1.0%)	0
膿疱性皮疹	- Any Grade -	0	2 (3.9%)	2 (2.0%)	0
	1	0	2 (3.9%)	2 (2.0%)	0
	2	0	0	0	0
麦粒腫	- Any Grade -	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	0
	2	2 (4.0%)	0	0	1 (2.0%)
皮膚真菌感染	- Any Grade -	0	0	4 (4.0%)	0
	1	0	0	4 (4.0%)	0
	2	0	0	0	0
インフルエンザ	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	2 (2.0%)	0
	2	0	0	0	0
ウイルス性上気道感染	- Any Grade -	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
	1	1 (2.0%)	0	1 (1.0%)	0
	2	0	0	0	1 (2.0%)
外陰部腔カンジダ症	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
外陰腔真菌感染	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
気道感染	- Any Grade -	0	2 (3.9%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	0
	2	0	0	0	1 (2.0%)
	3	0	1 (2.0%)	0	0
口腔カンジダ症	- Any Grade -	1 (2.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	2 (2.0%)	0
歯感染	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
歯周炎	- Any Grade -	1 (2.0%)	2 (3.9%)	0	0
	1	1 (2.0%)	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
爪囲炎	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
爪真菌症	- Any Grade -	0	2 (3.9%)	1 (1.0%)	0
	1	0	2 (3.9%)	1 (1.0%)	0
肺炎	- Any Grade -	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	3	1 (2.0%)	0	1 (1.0%)	0
蜂巣炎	- Any Grade -	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
	2	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	1 (2.0%)
せつ	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	1 (2.0%)	0	0	0
ウイルス感染	- Any Grade -	0	0	0	2 (4.1%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
ヘルペスウイルス感染	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
眼部単純ヘルペス	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	0
限局性感染	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	3	1 (2.0%)	0	0	0
口腔真菌感染	- Any Grade -	0	0	0	2 (4.1%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
腎盂腎炎	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
	3	0	0	1 (1.0%)	0
創傷感染	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
皮膚カンジダ	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
毛包炎	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	1 (1.0%)	0
腔感染	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
ウイルス性咽頭炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
ウイルス性気道感染	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
ウイルス性迷路炎	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
サイトメガロウイルス感染	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
ヘモフィルス性肺炎	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
陰部帯状疱疹	- Any Grade -	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
外陰部腫炎	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
感染性小腸結腸炎	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
感染性胆管炎	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
感染性腸炎	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
感染性皮膚潰瘍	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
気管炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
憩室炎	- Any Grade -	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
口角口唇炎	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
口腔膿瘍	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
細菌性眼感染	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
歯髄炎	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
耳感染	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
真菌感染	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
真菌性喉頭炎	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
水痘帯状疱疹ウイルス感染	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
単純ヘルペス	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
中咽頭カンジダ症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
中耳炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
乳房蜂巣炎	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
乳様突起炎	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
尿路性敗血症	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
膿尿	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
敗血症	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
肺感染	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
白癬感染	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
皮膚感染	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
皮膚細菌感染	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
慢性副鼻腔炎	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
迷路炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
咬傷感染	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
筋骨格系および結合組織障害 - Overall -	- Any Grade -	34 (68.0%)	32 (62.7%)	63 (63.0%)	28 (57.1%)
	1	19 (38.0%)	22 (43.1%)	42 (42.0%)	19 (38.8%)
	2	12 (24.0%)	8 (15.7%)	16 (16.0%)	6 (12.2%)
	3	2 (4.0%)	2 (3.9%)	5 (5.0%)	3 (6.1%)
	4	1 (2.0%)	0	0	0
関節痛	- Any Grade -	11 (22.0%)	8 (15.7%)	13 (13.0%)	8 (16.3%)
	1	7 (14.0%)	8 (15.7%)	10 (10.0%)	5 (10.2%)
	2	3 (6.0%)	0	3 (3.0%)	2 (4.1%)
	3	0	0	0	1 (2.0%)
	4	1 (2.0%)	0	0	0
背部痛	- Any Grade -	7 (14.0%)	10 (19.6%)	14 (14.0%)	7 (14.3%)
	1	4 (8.0%)	8 (15.7%)	8 (8.0%)	4 (8.2%)
	2	3 (6.0%)	2 (3.9%)	6 (6.0%)	2 (4.1%)
	3	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
筋骨格痛	- Any Grade -	5 (10.0%)	2 (3.9%)	12 (12.0%)	6 (12.2%)
	1	4 (8.0%)	2 (3.9%)	9 (9.0%)	5 (10.2%)
	2	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
四肢痛	- Any Grade -	5 (10.0%)	5 (9.8%)	8 (8.0%)	5 (10.2%)
	1	3 (6.0%)	2 (3.9%)	6 (6.0%)	5 (10.2%)
	2	2 (4.0%)	3 (5.9%)	2 (2.0%)	0
筋肉痛	- Any Grade -	4 (8.0%)	4 (7.8%)	9 (9.0%)	4 (8.2%)
	1	3 (6.0%)	4 (7.8%)	8 (8.0%)	3 (6.1%)
	2	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
筋痙縮	- Any Grade -	6 (12.0%)	4 (7.8%)	4 (4.0%)	6 (12.2%)
	1	6 (12.0%)	4 (7.8%)	4 (4.0%)	3 (6.1%)
	2	0	0	0	3 (6.1%)
変形性関節症	- Any Grade -	3 (6.0%)	4 (7.8%)	7 (7.0%)	2 (4.1%)
	1	1 (2.0%)	1 (2.0%)	5 (5.0%)	2 (4.1%)
	2	2 (4.0%)	2 (3.9%)	1 (1.0%)	0
頸部痛	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	2 (4.0%)	4 (7.8%)	6 (6.0%)	1 (2.0%)
	2	1 (2.0%)	4 (7.8%)	5 (5.0%)	1 (2.0%)
滑液包炎	- Any Grade -	0	0	1 (1.0%)	0
	1	2 (4.0%)	1 (2.0%)	1 (1.0%)	4 (8.2%)
	2	0	0	0	3 (6.1%)
顎痛	- Any Grade -	2 (4.0%)	0	3 (3.0%)	1 (2.0%)
	1	2 (4.0%)	0	3 (3.0%)	1 (2.0%)
	2	0	0	0	1 (2.0%)
筋骨格硬直	- Any Grade -	1 (2.0%)	0	4 (4.0%)	1 (2.0%)
	1	1 (2.0%)	0	4 (4.0%)	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 9 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
骨粗鬆症	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
	1	0	1 (2.0%)	0	2 (4.1%)
	2	0	0	1 (1.0%)	0
	3	1 (2.0%)	0	0	0
脊椎痛	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
腱炎	- Any Grade -	1 (2.0%)	0	4 (4.0%)	0
	1	1 (2.0%)	0	4 (4.0%)	0
関節炎	- Any Grade -	0	0	3 (3.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
筋力低下	- Any Grade -	2 (4.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	2 (2.0%)	0
	2	1 (2.0%)	0	0	0
骨減少症	- Any Grade -	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
	1	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
関節硬直	- Any Grade -	1 (2.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	2 (2.0%)	0
関節腫脹	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
筋骨格系胸痛	- Any Grade -	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
	2	0	0	1 (1.0%)	0
肩回旋筋腱板症候群	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
四肢不快感	- Any Grade -	2 (4.0%)	0	1 (1.0%)	0
	1	2 (4.0%)	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
線維筋痛	- Any Grade -	2 (4.0%)	1 (2.0%)	0	0
	1	2 (4.0%)	0	0	0
	3	0	1 (2.0%)	0	0
側腹部痛	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
足底筋膜炎	- Any Grade -	1 (2.0%)	0	2 (2.0%)	0
	1	0	0	1 (1.0%)	0
	2	1 (2.0%)	0	1 (1.0%)	0
ミオパチー	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
筋緊張	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
斜頸	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
椎間板突出	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	0	1 (1.0%)	0
	- Any Grade -	0	0	2 (2.0%)	0
変形性脊椎症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
腱痛	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	0
腱付着部症	- Any Grade -	0	2 (3.9%)	0	0
	1	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
単径部痛	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	0
	3	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
シェーグレン症候群	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
リウマトイド結節	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
関節可動域低下	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
関節周囲炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
関節障害	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
筋硬化症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
筋骨格不快感	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
筋攣縮	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
頸部脊柱管狭窄症	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
骨端症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
出血性関節症	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
脊柱管狭窄症	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
脊椎炎	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
弾発指	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
軟骨痛	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
腱鞘炎	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
神経系障害 - Overall -	- Any Grade -	23 (46.0%)	22 (43.1%)	43 (43.0%)	22 (44.9%)
	1	19 (38.0%)	16 (31.4%)	32 (32.0%)	14 (28.6%)
	2	2 (4.0%)	5 (9.8%)	8 (8.0%)	7 (14.3%)
	3	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
	4	0	0	0	1 (2.0%)
頭痛	- Any Grade -	16 (32.0%)	12 (23.5%)	27 (27.0%)	10 (20.4%)
	1	15 (30.0%)	12 (23.5%)	22 (22.0%)	7 (14.3%)
	2	1 (2.0%)	0	4 (4.0%)	3 (6.1%)
	3	0	0	1 (1.0%)	0
浮動性めまい	- Any Grade -	6 (12.0%)	8 (15.7%)	6 (6.0%)	10 (20.4%)
	1	6 (12.0%)	7 (13.7%)	6 (6.0%)	8 (16.3%)
	2	0	1 (2.0%)	0	2 (4.1%)
錯感覚	- Any Grade -	5 (10.0%)	4 (7.8%)	4 (4.0%)	2 (4.1%)
	1	4 (8.0%)	3 (5.9%)	4 (4.0%)	2 (4.1%)
	2	0	1 (2.0%)	0	0
	3	1 (2.0%)	0	0	0
感覚鈍麻	- Any Grade -	2 (4.0%)	0	3 (3.0%)	1 (2.0%)
	1	1 (2.0%)	0	2 (2.0%)	1 (2.0%)
	2	1 (2.0%)	0	1 (1.0%)	0
坐骨神経痛	- Any Grade -	2 (4.0%)	0	2 (2.0%)	2 (4.1%)
	1	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
	2	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
振戦	- Any Grade -	3 (6.0%)	3 (5.9%)	0	0
	1	3 (6.0%)	2 (3.9%)	0	0
	2	0	1 (2.0%)	0	0
傾眠	- Any Grade -	1 (2.0%)	0	2 (2.0%)	1 (2.0%)
	1	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
失神	- Any Grade -	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
	1	1 (2.0%)	0	0	0
	2	0	1 (2.0%)	0	0
片頭痛	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	1 (2.0%)	0	1 (1.0%)	0
知覚過敏	- Any Grade -	1 (2.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
健忘	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	1 (1.0%)	0
構語障害	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
	2	0	0	0	0
手根管症候群	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	0
	2	0	0	0	1 (2.0%)
ジスキネジア	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	1 (2.0%)	0	0
ヘルペス後神経痛	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 14 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
意識消失	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
異常感覚	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
一過性脳虚血発作	- Any Grade -	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
感覚障害	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
起立不耐性	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
蟻走感	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
血栓性脳卒中	- Any Grade -	0	0	0	1 (2.0%)
	4	0	0	0	1 (2.0%)
三叉神経痛	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
灼熱感	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
神経痛	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
神経変性障害	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
脊髄性跛行症	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
足根管症候群	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
多発ニューロパチー	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
注意力障害	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
平衡障害	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
味覚異常	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
味覚消失	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
肋間神経痛	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
嗜眠	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
一般・全身障害および投与部位の状態 - Overall -	- Any Grade -	21 (42.0%)	14 (27.5%)	37 (37.0%)	25 (51.0%)
	1	13 (26.0%)	12 (23.5%)	26 (26.0%)	20 (40.8%)
	2	8 (16.0%)	2 (3.9%)	9 (9.0%)	5 (10.2%)
	3	0	0	2 (2.0%)	0
	4	0	0	0	0
末梢性浮腫	- Any Grade -	8 (16.0%)	6 (11.8%)	16 (16.0%)	12 (24.5%)
	1	7 (14.0%)	5 (9.8%)	13 (13.0%)	10 (20.4%)
	2	1 (2.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
疲労	- Any Grade -	8 (16.0%)	3 (5.9%)	8 (8.0%)	5 (10.2%)
	1	6 (12.0%)	2 (3.9%)	7 (7.0%)	4 (8.2%)
	2	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
無力症	- Any Grade -	5 (10.0%)	0	5 (5.0%)	3 (6.1%)
	1	3 (6.0%)	0	3 (3.0%)	3 (6.1%)
	2	2 (4.0%)	0	2 (2.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 16 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
発熱	- Any Grade -	2 (4.0%)	2 (3.9%)	1 (1.0%)	2 (4.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
	2	1 (2.0%)	1 (2.0%)	0	0
非心臓性胸痛	- Any Grade -	1 (2.0%)	3 (5.9%)	1 (1.0%)	2 (4.1%)
	1	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
	2	0	1 (2.0%)	0	1 (2.0%)
末梢腫脹	- Any Grade -	0	2 (3.9%)	4 (4.0%)	1 (2.0%)
	1	0	1 (2.0%)	3 (3.0%)	1 (2.0%)
	2	0	1 (2.0%)	1 (1.0%)	0
倦怠感	- Any Grade -	1 (2.0%)	0	3 (3.0%)	0
	1	0	0	3 (3.0%)	0
	2	1 (2.0%)	0	0	0
インフルエンザ様疾患	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	2	0	0	0	0
胸痛	- Any Grade -	0	0	1 (1.0%)	2 (4.1%)
	1	0	0	1 (1.0%)	2 (4.1%)
	2	0	0	0	0
腫脹	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	0	0	2 (2.0%)	0
嚢胞	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
浮腫	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
	2	0	0	0	0
悪寒	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	0	0	0	0
空腹	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
	2	0	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
注射部位そう痒感	- Any Grade -	0	0	0	2 (4.1%)
	1	0	0	0	2 (4.1%)
注射部位血腫	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
注射部位反応	- Any Grade -	0	0	0	2 (4.1%)
	1	0	0	0	2 (4.1%)
注射部位疼痛	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	1 (2.0%)	0	0	0
熱感	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
歩行障害	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	2 (2.0%)	0
冷感	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	2 (2.0%)	0
疼痛	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
異常感	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
胸部不快感	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
重力性浮腫	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
注射部位紅斑	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
注射部位出血	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
注射部位内出血	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
注射部位蕁麻疹	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
不快感	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
歩行不能	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
薬物不耐性	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
腋窩痛	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
皮膚および皮下組織障害 - Overall -	- Any Grade -	17 (34.0%)	17 (33.3%)	33 (33.0%)	25 (51.0%)
	1	15 (30.0%)	16 (31.4%)	27 (27.0%)	19 (38.8%)
	2	2 (4.0%)	1 (2.0%)	6 (6.0%)	5 (10.2%)
	3	0	0	0	1 (2.0%)
脱毛症	- Any Grade -	3 (6.0%)	5 (9.8%)	5 (5.0%)	7 (14.3%)
	1	3 (6.0%)	5 (9.8%)	4 (4.0%)	4 (8.2%)
	2	0	0	1 (1.0%)	3 (6.1%)
発疹	- Any Grade -	4 (8.0%)	2 (3.9%)	7 (7.0%)	5 (10.2%)
	1	4 (8.0%)	2 (3.9%)	7 (7.0%)	4 (8.2%)
	3	0	0	0	1 (2.0%)
そう痒症	- Any Grade -	1 (2.0%)	1 (2.0%)	2 (2.0%)	4 (8.2%)
	1	1 (2.0%)	1 (2.0%)	2 (2.0%)	4 (8.2%)
紅斑	- Any Grade -	1 (2.0%)	2 (3.9%)	3 (3.0%)	1 (2.0%)
	1	0	2 (3.9%)	2 (2.0%)	1 (2.0%)
	2	1 (2.0%)	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
湿疹	- Any Grade -	2 (4.0%)	2 (3.9%)	2 (2.0%)	0
	1	2 (4.0%)	2 (3.9%)	2 (2.0%)	0
寝汗	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
多汗症	- Any Grade -	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
	1	1 (2.0%)	1 (2.0%)	3 (3.0%)	0
	2	1 (2.0%)	0	0	0
斑状出血	- Any Grade -	1 (2.0%)	3 (5.9%)	0	2 (4.1%)
	1	1 (2.0%)	2 (3.9%)	0	2 (4.1%)
	2	0	1 (2.0%)	0	0
皮膚乾燥	- Any Grade -	0	0	2 (2.0%)	3 (6.1%)
	1	0	0	2 (2.0%)	2 (4.1%)
	2	0	0	0	1 (2.0%)
ざ瘡	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
アレルギー性皮膚炎	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
乾癬	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
紅斑性皮疹	- Any Grade -	0	0	1 (1.0%)	2 (4.1%)
	1	0	0	1 (1.0%)	2 (4.1%)
皮膚炎	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
皮膚疼痛	- Any Grade -	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
	1	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
顔面腫脹	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
光線過敏性反応	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	0
	2	0	0	0	1 (2.0%)
光線角化症	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
全身性皮疹	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	0	0	0	0
蕁麻疹	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	0	0
	2	0	0	1 (1.0%)	0
ざ瘡様皮膚炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	0	0
そう痒性皮疹	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	0	0	0	0
びまん性脱毛症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	0	0
一過性棘融解性皮膚症	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	2	0	0	0	0
間擦疹	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	2	0	0	0	0
結節性紅斑	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	0	0
脂腺障害	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	0
水疱	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	0
接触性皮膚炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 21 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
全身性そう痒症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
爪線状隆起	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
点状出血	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
斑状皮疹	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
皮膚亀裂	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
皮膚灼熱感	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
皮膚腫脹	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
皮膚出血	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
皮膚障害	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
皮膚病変	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
嵌入爪	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
胃腸障害 - Overall -	- Any Grade -	19 (38.0%)	15 (29.4%)	36 (36.0%)	18 (36.7%)
	1	12 (24.0%)	8 (15.7%)	27 (27.0%)	14 (28.6%)
	2	6 (12.0%)	7 (13.7%)	7 (7.0%)	4 (8.2%)
	3	1 (2.0%)	0	2 (2.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
下痢	- Any Grade -	8 (16.0%)	5 (9.8%)	12 (12.0%)	3 (6.1%)
	1	7 (14.0%)	4 (7.8%)	10 (10.0%)	3 (6.1%)
	2	1 (2.0%)	1 (2.0%)	0	0
	3	0	0	2 (2.0%)	0
悪心	- Any Grade -	5 (10.0%)	4 (7.8%)	8 (8.0%)	2 (4.1%)
	1	4 (8.0%)	2 (3.9%)	6 (6.0%)	2 (4.1%)
	2	1 (2.0%)	2 (3.9%)	2 (2.0%)	0
上腹部痛	- Any Grade -	3 (6.0%)	4 (7.8%)	3 (3.0%)	3 (6.1%)
	1	0	2 (3.9%)	3 (3.0%)	2 (4.1%)
	2	3 (6.0%)	2 (3.9%)	0	1 (2.0%)
嘔吐	- Any Grade -	2 (4.0%)	3 (5.9%)	2 (2.0%)	2 (4.1%)
	1	1 (2.0%)	1 (2.0%)	2 (2.0%)	2 (4.1%)
	2	1 (2.0%)	2 (3.9%)	0	0
便秘	- Any Grade -	3 (6.0%)	4 (7.8%)	0	1 (2.0%)
	1	3 (6.0%)	2 (3.9%)	0	0
	2	0	2 (3.9%)	0	1 (2.0%)
胃食道逆流性疾患	- Any Grade -	2 (4.0%)	1 (2.0%)	2 (2.0%)	2 (4.1%)
	1	1 (2.0%)	0	1 (1.0%)	2 (4.1%)
	2	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
腹痛	- Any Grade -	2 (4.0%)	2 (3.9%)	3 (3.0%)	0
	1	2 (4.0%)	2 (3.9%)	3 (3.0%)	0
胃炎	- Any Grade -	0	1 (2.0%)	2 (2.0%)	2 (4.1%)
	1	0	1 (2.0%)	1 (1.0%)	2 (4.1%)
	2	0	0	1 (1.0%)	0
鼓腸	- Any Grade -	2 (4.0%)	2 (3.9%)	1 (1.0%)	0
	1	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
	2	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 23 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
口腔内潰瘍形成	- Any Grade -	0	2 (3.9%)	3 (3.0%)	0
	1	0	1 (2.0%)	3 (3.0%)	0
	2	0	1 (2.0%)	0	0
口内乾燥	- Any Grade -	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
	1	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
歯痛	- Any Grade -	0	2 (3.9%)	3 (3.0%)	0
	1	0	1 (2.0%)	2 (2.0%)	0
	2	0	1 (2.0%)	1 (1.0%)	0
消化不良	- Any Grade -	4 (8.0%)	1 (2.0%)	0	0
	1	3 (6.0%)	1 (2.0%)	0	0
	2	1 (2.0%)	0	0	0
痔核	- Any Grade -	2 (4.0%)	1 (2.0%)	0	1 (2.0%)
	1	2 (4.0%)	1 (2.0%)	0	1 (2.0%)
腹部膨満	- Any Grade -	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
	1	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
アフタ性潰瘍	- Any Grade -	0	0	1 (1.0%)	2 (4.1%)
	1	0	0	0	1 (2.0%)
	2	0	0	1 (1.0%)	1 (2.0%)
胃腸障害	- Any Grade -	2 (4.0%)	0	0	1 (2.0%)
	1	2 (4.0%)	0	0	1 (2.0%)
歯肉痛	- Any Grade -	1 (2.0%)	1 (2.0%)	0	1 (2.0%)
	1	1 (2.0%)	1 (2.0%)	0	1 (2.0%)
びらん性胃炎	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	1 (2.0%)	0	0	0
下腹部痛	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	1 (2.0%)	1 (2.0%)	0	0
歯の知覚過敏	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
舌苔	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
大腸炎	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	1 (1.0%)	0
腹部不快感	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
便意切迫	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
齦歯	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
垂イレウス	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
胃酸過多	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
胃腸出血	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
過敏性腸症候群	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
憩室	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
口腔粘膜水疱形成	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
口内炎	- Any Grade -	1 (2.0%)	0	0	0
	3	1 (2.0%)	0	0	0
歯の脱落	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
歯肉退縮	- Any Grade - 2	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
歯肉潰瘍	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
消化管運動障害	- Any Grade - 1	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
食道痙攣	- Any Grade - 2	0 0	0 0	0 0	1 (2.0%) 1 (2.0%)
舌痛	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
舌潰瘍	- Any Grade - 1	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
大腸ポリープ	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0
腸憩室	- Any Grade - 2	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
腹腔内血腫	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0
変色便	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0
嚥下障害	- Any Grade - 1	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
肛門出血	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 040CT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
呼吸器、胸郭および縦隔障害 - Overall -	- Any Grade -	16 (32.0%)	17 (33.3%)	22 (22.0%)	11 (22.4%)
	1	12 (24.0%)	14 (27.5%)	16 (16.0%)	5 (10.2%)
	2	3 (6.0%)	2 (3.9%)	4 (4.0%)	4 (8.2%)
	3	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
	4	0	0	1 (1.0%)	0
口腔咽頭痛	- Any Grade -	5 (10.0%)	8 (15.7%)	7 (7.0%)	4 (8.2%)
	1	4 (8.0%)	8 (15.7%)	6 (6.0%)	3 (6.1%)
	2	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
咳嗽	- Any Grade -	7 (14.0%)	3 (5.9%)	6 (6.0%)	3 (6.1%)
	1	5 (10.0%)	3 (5.9%)	6 (6.0%)	3 (6.1%)
	2	2 (4.0%)	0	0	0
呼吸困難	- Any Grade -	1 (2.0%)	3 (5.9%)	3 (3.0%)	4 (8.2%)
	1	1 (2.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
	2	0	1 (2.0%)	1 (1.0%)	3 (6.1%)
鼻出血	- Any Grade -	4 (8.0%)	0	3 (3.0%)	1 (2.0%)
	1	4 (8.0%)	0	3 (3.0%)	1 (2.0%)
労作性呼吸困難	- Any Grade -	3 (6.0%)	1 (2.0%)	1 (1.0%)	0
	1	2 (4.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	1 (2.0%)	0	0
アレルギー性鼻炎	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
胸膜痛	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
肺塞栓症	- Any Grade -	0	0	2 (2.0%)	0
	2	0	0	1 (1.0%)	0
	4	0	0	1 (1.0%)	0
発声障害	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 27 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
鼻茸	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	0
	2	0	0	0	1 (2.0%)
鼻漏	- Any Grade -	0	0	0	2 (4.1%)
	2	0	0	0	1 (2.0%)
	3	0	0	0	1 (2.0%)
喘息	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	1 (2.0%)	0	0	0
	3	0	1 (2.0%)	0	0
カタル	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
	3	0	0	0	0
咽頭紅斑	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
間質性肺疾患	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	0	0
逆流性喉頭炎	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
胸水	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	3	0	0	0	0
好酸球性気管支炎	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	3	0	0	0	0
湿性咳嗽	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	2	0	0	0	0
睡眠時無呼吸症候群	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	0
肺臓炎	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	2	0	0	0	0
鼻の炎症	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	3	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 28 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
鼻潰瘍	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
慢性閉塞性肺疾患	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
喘鳴	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
眼障害 - Overall -	- Any Grade -	15 (30.0%)	14 (27.5%)	18 (18.0%)	13 (26.5%)
	1	13 (26.0%)	8 (15.7%)	14 (14.0%)	9 (18.4%)
	2	2 (4.0%)	3 (5.9%)	4 (4.0%)	3 (6.1%)
	3	0	3 (5.9%)	0	1 (2.0%)
白内障	- Any Grade -	3 (6.0%)	5 (9.8%)	5 (5.0%)	1 (2.0%)
	1	2 (4.0%)	0	4 (4.0%)	1 (2.0%)
	2	1 (2.0%)	3 (5.9%)	1 (1.0%)	0
	3	0	2 (3.9%)	0	0
眼乾燥	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
霧視	- Any Grade -	2 (4.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
	1	2 (4.0%)	1 (2.0%)	2 (2.0%)	0
結膜出血	- Any Grade -	0	0	0	1 (2.0%)
	1	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
眼充血	- Any Grade -	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
	1	2 (4.0%)	1 (2.0%)	1 (1.0%)	0
眼瞼炎	- Any Grade -	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
緑内障	- Any Grade -	2 (4.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	1 (2.0%)
眼そう痒症	- Any Grade -	0	0	0	2 (4.1%)
	1	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
眼痛	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
眼部不快感	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	1 (2.0%)	1 (2.0%)	0	0
視力障害	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
視力低下	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
複視	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	1 (2.0%)	0	0	0
	2	0	1 (2.0%)	0	0
流涙増加	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
核性白内障	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
眼の異物感	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
眼の炎症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
眼球乾燥症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
眼出血	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
眼精疲労	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
眼部腫脹	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
虚血性視神経症	- Any Grade -	0	0	0	1 (2.0%)
	3	0	0	0	1 (2.0%)
強膜炎	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
高眼圧症	- Any Grade -	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
硝子体剥離	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
閃輝暗点	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
虹彩炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
虹彩毛様体炎	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
網膜剥離	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
傷害、中毒および処置合併症 - Overall -	- Any Grade -	10 (20.0%)	14 (27.5%)	26 (26.0%)	10 (20.4%)
	1	5 (10.0%)	10 (19.6%)	12 (12.0%)	7 (14.3%)
	2	5 (10.0%)	3 (5.9%)	11 (11.0%)	3 (6.1%)
	3	0	1 (2.0%)	3 (3.0%)	0
転倒	- Any Grade -	2 (4.0%)	2 (3.9%)	7 (7.0%)	2 (4.1%)
	1	1 (2.0%)	2 (3.9%)	3 (3.0%)	1 (2.0%)
	2	1 (2.0%)	0	4 (4.0%)	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
挫傷	- Any Grade -	0	2 (3.9%)	4 (4.0%)	2 (4.1%)
	1	0	2 (3.9%)	3 (3.0%)	2 (4.1%)
	2	0	0	1 (1.0%)	0
裂傷	- Any Grade -	1 (2.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
節足動物咬傷	- Any Grade -	0	2 (3.9%)	2 (2.0%)	0
	1	0	2 (3.9%)	2 (2.0%)	0
	2	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
骨挫傷	- Any Grade -	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
	3	0	0	1 (1.0%)	0
創傷	- Any Grade -	0	2 (3.9%)	1 (1.0%)	0
	1	0	2 (3.9%)	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
肋骨骨折	- Any Grade -	2 (4.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
アルコール中毒	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	2	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	0
歯牙破折	- Any Grade -	0	0	2 (2.0%)	0
	2	0	0	2 (2.0%)	0
	3	0	0	1 (1.0%)	0
手骨折	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	0	1 (1.0%)	0
	3	0	0	0	0
処置によるめまい	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	2	1 (2.0%)	0	0	1 (2.0%)
	3	0	0	0	0
上顎炎	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
肉離れ	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
半月板損傷	- Any Grade -	0	0	1 (1.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	0
	2	0	0	0	1 (2.0%)
腱断裂	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	2	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	0
靭帯捻挫	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
サンバーン	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
ストレス骨折	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
外傷性血腫	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
眼内異物	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
眼窩周囲血腫	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
顔面損傷	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
筋損傷	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
筋断裂	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
腰椎骨折	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
四肢損傷	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
術後創合併症	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
脊椎圧迫骨折	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
足骨折	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
損傷	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
注射に伴う反応	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
頭部損傷	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
軟部組織損傷	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
熱傷	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
皮下血腫	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
皮膚化学熱傷	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
血管障害	- Overall -	13 (26.0%)	9 (17.6%)	23 (23.0%)	13 (26.5%)
	1	11 (22.0%)	5 (9.8%)	7 (7.0%)	8 (16.3%)
	2	1 (2.0%)	2 (3.9%)	11 (11.0%)	2 (4.1%)
	3	1 (2.0%)	2 (3.9%)	5 (5.0%)	3 (6.1%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
高血圧	- Any Grade -	4 (8.0%)	4 (7.8%)	12 (12.0%)	6 (12.2%)
	1	3 (6.0%)	1 (2.0%)	4 (4.0%)	3 (6.1%)
	2	0	2 (3.9%)	5 (5.0%)	2 (4.1%)
血腫	3	1 (2.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
	- Any Grade -	3 (6.0%)	1 (2.0%)	5 (5.0%)	3 (6.1%)
	1	3 (6.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
側頭動脈炎	2	0	0	4 (4.0%)	0
	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	3	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
高血圧クリーゼ	- Any Grade -	0	1 (2.0%)	2 (2.0%)	0
	2	0	1 (2.0%)	0	0
	3	0	0	2 (2.0%)	0
深部静脈血栓症	- Any Grade -	0	0	3 (3.0%)	0
	2	0	0	3 (3.0%)	0
	- Any Grade -	2 (4.0%)	0	1 (1.0%)	0
低血圧	1	2 (4.0%)	0	1 (1.0%)	0
	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
ほてり	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
レイノー現象	1	1 (2.0%)	0	1 (1.0%)	0
	- Any Grade -	0	2 (3.9%)	0	0
	2	0	2 (3.9%)	0	0
血栓性静脈炎	- Any Grade -	1 (2.0%)	1 (2.0%)	0	0
	1	1 (2.0%)	1 (2.0%)	0	0
	- Any Grade -	0	0	0	1 (2.0%)
末梢冷感	1	0	0	0	1 (2.0%)
	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
リンパうっ滞	- Any Grade -	0	0	0	0
	1	0	0	0	1 (2.0%)
	- Any Grade -	0	1 (2.0%)	0	0
拡張期高血圧	1	0	1 (2.0%)	0	0
	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
顎筋跛行	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
乾性壊疽	- Any Grade -	0	0	0	1 (2.0%)
	3	0	0	0	1 (2.0%)
間欠性跛行	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
鎖骨下動脈狭窄	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
潮紅	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
表在性血栓性静脈炎	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
末梢血管障害	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
末梢動脈狭窄	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
臨床検査 - Overall -	- Any Grade -	9 (18.0%)	8 (15.7%)	23 (23.0%)	7 (14.3%)
	1	8 (16.0%)	3 (5.9%)	14 (14.0%)	4 (8.2%)
	2	1 (2.0%)	3 (5.9%)	9 (9.0%)	3 (6.1%)
	3	0	1 (2.0%)	0	0
	4	0	1 (2.0%)	0	0
アラニンアミノトランスフェラーゼ増加	- Any Grade -	2 (4.0%)	0	5 (5.0%)	2 (4.1%)
	1	2 (4.0%)	0	3 (3.0%)	2 (4.1%)
	2	0	0	2 (2.0%)	0
眼圧上昇	- Any Grade -	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
	1	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
アスパラギン酸アミノトランスフェラーゼ増加	- Any Grade -	1 (2.0%)	0	4 (4.0%)	1 (2.0%)
	1	1 (2.0%)	0	2 (2.0%)	1 (2.0%)
	2	0	0	2 (2.0%)	0
肝酵素上昇	- Any Grade -	0	2 (3.9%)	4 (4.0%)	0
	1	0	0	3 (3.0%)	0
	2	0	1 (2.0%)	1 (1.0%)	0
体重増加	- Any Grade -	1 (2.0%)	0	3 (3.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	0
	2	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
補体成分 C 3 減少	- Any Grade -	0	0	3 (3.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
血圧上昇	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	0	2 (2.0%)	0
体温上昇	- Any Grade -	0	2 (3.9%)	0	1 (2.0%)
	1	0	2 (3.9%)	0	1 (2.0%)
	2	0	2 (3.9%)	0	1 (2.0%)
低比重リポ蛋白増加	- Any Grade -	0	2 (3.9%)	0	1 (2.0%)
	1	0	2 (3.9%)	0	1 (2.0%)
	2	0	2 (3.9%)	0	1 (2.0%)
補体成分 C 4 減少	- Any Grade -	0	0	2 (2.0%)	1 (2.0%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	0	0	1 (1.0%)	0
血中クレアチンホスホキナーゼ増加	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
体重減少	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 37 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
トランスアミナーゼ上昇	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
ビタミンB12減少	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0
ヘモグロビン減少	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
血小板数減少	- Any Grade - 1	0 0	0 0	0 0	1 (2.0%) 1 (2.0%)
血中カリウム異常	- Any Grade - 2	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
血中カリウム減少	- Any Grade - 3	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
血中クレアチニン増加	- Any Grade - 2	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
血中ビリルビン増加	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
血中甲状腺刺激ホルモン減少	- Any Grade - 1	0 0	0 0	1 (1.0%) 1 (1.0%)	0 0
血中尿酸増加	- Any Grade - 2	0 0	1 (2.0%) 1 (2.0%)	0 0	0 0
好中球数減少	- Any Grade - 2	0 0	0 0	0 0	1 (2.0%) 1 (2.0%)
白血球数減少	- Any Grade - 1	0 0	0 0	0 0	1 (2.0%) 1 (2.0%)
白血球数増加	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0
平均赤血球容積増加	- Any Grade - 1	1 (2.0%) 1 (2.0%)	0 0	0 0	0 0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
精神障害	- Any Grade -	13 (26.0%)	8 (15.7%)	12 (12.0%)	8 (16.3%)
- Overall -	1	11 (22.0%)	6 (11.8%)	9 (9.0%)	4 (8.2%)
	2	1 (2.0%)	1 (2.0%)	2 (2.0%)	4 (8.2%)
	3	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
不眠症	- Any Grade -	4 (8.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
	1	4 (8.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
不安	- Any Grade -	6 (12.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
	1	5 (10.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
	3	1 (2.0%)	0	1 (1.0%)	0
うつ病	- Any Grade -	3 (6.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
	1	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
	2	1 (2.0%)	0	0	2 (4.1%)
睡眠障害	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	3 (6.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	2	0	0	0	2 (4.1%)
抑うつ気分	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	0	0
	2	0	0	1 (1.0%)	0
ストレス	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
易刺激性	- Any Grade -	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
緊張	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
激越	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
錯乱状態	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 39 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
失見当識	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
初期不眠症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
身体症状症	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
精神状態変化	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
抑うつ気分を伴う適応障害	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
代謝および栄養障害 - Overall -	- Any Grade -	4 (8.0%)	7 (13.7%)	10 (10.0%)	7 (14.3%)
	1	2 (4.0%)	1 (2.0%)	7 (7.0%)	4 (8.2%)
	2	2 (4.0%)	5 (9.8%)	3 (3.0%)	2 (4.1%)
	3	0	0	0	1 (2.0%)
	4	0	1 (2.0%)	0	0
高コレステロール血症	- Any Grade -	0	1 (2.0%)	2 (2.0%)	3 (6.1%)
	1	0	0	2 (2.0%)	1 (2.0%)
	2	0	1 (2.0%)	0	2 (4.1%)
低カリウム血症	- Any Grade -	0	3 (5.9%)	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	2 (3.9%)	0	0
	4	0	1 (2.0%)	0	0
糖尿病	- Any Grade -	2 (4.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	2 (2.0%)	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 40 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
低ナトリウム血症	- Any Grade -	0	1 (2.0%)	1 (1.0%)	1 (2.0%)
	2	0	1 (2.0%)	1 (1.0%)	0
	3	0	0	0	1 (2.0%)
食欲減退	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	1 (1.0%)	0
2型糖尿病	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
ビタミンD欠乏	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
高血糖	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
高脂血症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
高尿酸血症	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
食欲亢進	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
痛風	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
低血糖	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
鉄欠乏	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
葉酸欠乏	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 41 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
耳および迷路障害	- Any Grade -	6 (12.0%)	6 (11.8%)	7 (7.0%)	4 (8.2%)
- Overall -	1	5 (10.0%)	6 (11.8%)	7 (7.0%)	3 (6.1%)
	2	1 (2.0%)	0	0	1 (2.0%)
回転性めまい	- Any Grade -	3 (6.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
	1	3 (6.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
耳痛	- Any Grade -	1 (2.0%)	0	2 (2.0%)	2 (4.1%)
	1	1 (2.0%)	0	2 (2.0%)	2 (4.1%)
耳鳴	- Any Grade -	1 (2.0%)	2 (3.9%)	0	1 (2.0%)
	1	1 (2.0%)	2 (3.9%)	0	0
	2	0	0	0	1 (2.0%)
頭位性回転性めまい	- Any Grade -	0	2 (3.9%)	2 (2.0%)	0
	1	0	2 (3.9%)	2 (2.0%)	0
聴力低下	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
耳不快感	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
前庭障害	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
難聴	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
両耳難聴	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 42 of 50

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
心臓障害	- Any Grade -	6 (12.0%)	6 (11.8%)	8 (8.0%)	3 (6.1%)
- Overall -	1	3 (6.0%)	2 (3.9%)	4 (4.0%)	2 (4.1%)
	2	2 (4.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	3	1 (2.0%)	2 (3.9%)	3 (3.0%)	0
	4	0	1 (2.0%)	0	0
動悸	- Any Grade -	4 (8.0%)	2 (3.9%)	2 (2.0%)	2 (4.1%)
	1	3 (6.0%)	1 (2.0%)	2 (2.0%)	1 (2.0%)
	2	0	1 (2.0%)	0	1 (2.0%)
	3	1 (2.0%)	0	0	0
上室性頻脈	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	3	0	0	1 (1.0%)	0
心房細動	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	2 (2.0%)	0
大動脈弁狭窄	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
	3	0	1 (2.0%)	0	0
頻脈	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
	3	0	0	1 (1.0%)	0
慢性心不全	- Any Grade -	0	2 (3.9%)	0	0
	3	0	1 (2.0%)	0	0
	4	0	1 (2.0%)	0	0
狭心症	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
徐脈	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
心血管障害	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
心不全	- Any Grade -	0	1 (2.0%)	0	0
	4	0	1 (2.0%)	0	0
心房頻脈	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
僧帽弁閉鎖不全症	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
頻脈性不整脈	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
不整脈	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
腎および尿路障害 - Overall -	- Any Grade -	4 (8.0%)	6 (11.8%)	7 (7.0%)	0
	1	4 (8.0%)	2 (3.9%)	4 (4.0%)	0
	2	0	3 (5.9%)	3 (3.0%)	0
	4	0	1 (2.0%)	0	0
排尿困難	- Any Grade -	2 (4.0%)	1 (2.0%)	3 (3.0%)	0
	1	2 (4.0%)	0	2 (2.0%)	0
	2	0	1 (2.0%)	1 (1.0%)	0
尿意切迫	- Any Grade -	0	2 (3.9%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	1 (1.0%)	0
頻尿	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	1 (2.0%)	0	0
血尿	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
腎機能障害	- Any Grade -	0	1 (2.0%)	0	0
	4	0	1 (2.0%)	0	0
腎虚血	- Any Grade -	0	1 (2.0%)	0	0
	2	0	1 (2.0%)	0	0
腎嚢胞	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
腎不全	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
多尿	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
尿失禁	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
慢性腎臓病	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
血液およびリンパ系障害 - Overall -	- Any Grade -	4 (8.0%)	1 (2.0%)	8 (8.0%)	1 (2.0%)
	1	1 (2.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
	2	2 (4.0%)	0	1 (1.0%)	0
	3	1 (2.0%)	0	3 (3.0%)	0
	4	0	0	1 (1.0%)	0
好中球減少症	- Any Grade -	0	0	4 (4.0%)	1 (2.0%)
	1	0	0	2 (2.0%)	1 (2.0%)
	3	0	0	1 (1.0%)	0
	4	0	0	1 (1.0%)	0
白血球減少症	- Any Grade -	0	0	4 (4.0%)	0
	1	0	0	2 (2.0%)	0
	3	0	0	2 (2.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
貧血	- Any Grade -	2 (4.0%)	0	2 (2.0%)	0
	1	1 (2.0%)	0	2 (2.0%)	0
	3	1 (2.0%)	0	0	0
リンパ球減少症	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	2	1 (2.0%)	0	0	0
白血球増加症	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	1	0	1 (2.0%)	0	0
	2	0	0	1 (1.0%)	0
リンパ節症	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	2	0	0	0	0
血小板減少症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
	3	0	0	1 (1.0%)	0
貪食細胞性組織球症	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
	3	0	0	0	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） - Overall -	- Any Grade -	3 (6.0%)	3 (5.9%)	2 (2.0%)	3 (6.1%)
	1	2 (4.0%)	2 (3.9%)	1 (1.0%)	3 (6.1%)
	3	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
大腸腺腫	- Any Grade -	1 (2.0%)	0	0	1 (2.0%)
	1	1 (2.0%)	0	0	1 (2.0%)
	3	0	0	0	0
アクロコルドン	- Any Grade -	1 (2.0%)	0	0	0
	1	1 (2.0%)	0	0	0
	3	0	0	0	0
メラノサイト性母斑	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0
悪性黒色腫	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
	3	0	1 (2.0%)	0	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
脂漏性角化症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
消化器の良性新生物	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
神経腫	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
腎新生物	- Any Grade -	1 (2.0%)	0	0	0
	3	1 (2.0%)	0	0	0
乳癌	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0
辺縁帯リンパ腫	- Any Grade -	0	0	1 (1.0%)	0
	3	0	0	1 (1.0%)	0
卵巣腺腫	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
生殖系および乳房障害 - Overall -	- Any Grade -	0	2 (3.9%)	5 (5.0%)	3 (6.1%)
	1	0	1 (2.0%)	2 (2.0%)	2 (4.1%)
	2	0	1 (2.0%)	3 (3.0%)	1 (2.0%)
前立腺炎	- Any Grade -	0	1 (2.0%)	1 (1.0%)	0
	2	0	1 (2.0%)	1 (1.0%)	0
陰部そう痒症	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
女性化乳房	- Any Grade -	0	0	0	1 (2.0%)
	2	0	0	0	1 (2.0%)
直腸瘤	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
乳房圧痛	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
乳房痛	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
不正子宮出血	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
勃起不全	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
腔出血	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
腔分泌物	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
免疫系障害 - Overall -	- Any Grade -	3 (6.0%)	2 (3.9%)	2 (2.0%)	3 (6.1%)
	1	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
	2	1 (2.0%)	1 (2.0%)	0	0
	3	1 (2.0%)	0	1 (1.0%)	1 (2.0%)
薬物過敏症	- Any Grade -	1 (2.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	1	0	0	0	1 (2.0%)
	2	0	1 (2.0%)	0	0
	3	1 (2.0%)	0	1 (1.0%)	0
季節性アレルギー	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
節足動物咬傷アレルギー	- Any Grade -	0	1 (2.0%)	0	1 (2.0%)
	1	0	1 (2.0%)	0	1 (2.0%)
過敏症	- Any Grade -	0	0	0	1 (2.0%)
	3	0	0	0	1 (2.0%)
続発性免疫不全症	- Any Grade -	1 (2.0%)	0	0	0
	2	1 (2.0%)	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
内分泌障害					
- Overall -	- Any Grade -	1 (2.0%)	2 (3.9%)	6 (6.0%)	0
	1	1 (2.0%)	1 (2.0%)	4 (4.0%)	0
	2	0	1 (2.0%)	2 (2.0%)	0
クッシング様症状	- Any Grade -	0	2 (3.9%)	1 (1.0%)	0
	1	0	1 (2.0%)	1 (1.0%)	0
	2	0	1 (2.0%)	0	0
甲状腺機能低下症	- Any Grade -	0	0	2 (2.0%)	0
	1	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
甲状腺腫	- Any Grade -	1 (2.0%)	0	1 (1.0%)	0
	1	1 (2.0%)	0	1 (1.0%)	0
クッシング症候群	- Any Grade -	0	0	1 (1.0%)	0
	1	0	0	1 (1.0%)	0
副腎機能不全	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
外科および内科処置					
- Overall -	- Any Grade -	3 (6.0%)	1 (2.0%)	1 (1.0%)	1 (2.0%)
	1	2 (4.0%)	1 (2.0%)	0	1 (2.0%)
	2	0	0	1 (1.0%)	0
	3	1 (2.0%)	0	0	0
白内障手術	- Any Grade -	2 (4.0%)	0	0	0
	1	2 (4.0%)	0	0	0
股関節形成	- Any Grade -	1 (2.0%)	0	0	0
	3	1 (2.0%)	0	0	0
抜歯	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.
 All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

t_ae_ctc_sp Adverse Events by Highest NCI CTCAE Grade (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

MedDRA System Organ Class MedDRA Preferred Term	Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
皮膚新生物切除	- Any Grade -	0	0	0	1 (2.0%)
	1	0	0	0	1 (2.0%)
縫合	- Any Grade -	0	1 (2.0%)	0	0
	1	0	1 (2.0%)	0	0
製品の問題 - Overall -	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
医療機器破損	- Any Grade -	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
 To the SOC Overall row counts, a patient contributes once for each grade for which at least one AE with the corresponding highest grade is reported.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_ctc.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_ctc_sp.out
 04OCT2016 17:52

Page 50 of 50

[5.3.5.3-1 表 2.4-6を再掲]

表 2.7.4.8-9 投与開始後初めて発現した有害事象の発現時期
(MRA632JP 試験-全期間の本剤全投与例)

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
No. of Pts treated in each period	36	36	35	32	32	31	24	16	8	3
ALL BODY SYSTEMS										
Total Pts with at Least one AE	34 (94.4)	24 (66.7)	21 (60.0)	17 (53.1)	14 (43.8)	13 (41.9)	13 (54.2)	9 (56.3)	3 (37.5)	2 (66.7)
Total Number of AEs	201	47	38	27	25	26	19	13	4	2
感染症および寄生虫症										
Total Pts With at Least one AE	31 (86.1)	17 (47.2)	10 (28.6)	7 (21.9)	10 (31.3)	3 (9.7)	5 (20.8)	3 (18.8)	1 (12.5)	1 (33.3)
鼻咽頭炎	18 (50.0)	6 (16.7)	6 (17.1)	-	2 (6.3)	1 (3.2)	1 (4.2)	1 (6.3)	1 (12.5)	-
咽頭炎	7 (19.4)	3 (8.3)	1 (2.9)	-	2 (6.3)	-	-	1 (6.3)	-	-
上気道感染	7 (19.4)	4 (11.1)	-	2 (6.3)	1 (3.1)	-	-	-	-	-
胃腸炎	5 (13.9)	1 (2.8)	2 (5.7)	1 (3.1)	1 (3.1)	-	-	-	-	-
感染性腸炎	4 (11.1)	-	1 (2.9)	1 (3.1)	1 (3.1)	-	-	-	1 (12.5)	-
口腔ヘルペス	3 (8.3)	-	1 (2.9)	1 (3.1)	-	-	1 (4.2)	-	-	-
膀胱炎	3 (8.3)	2 (5.6)	-	1 (3.1)	-	-	-	-	-	-
インフルエンザ	2 (5.6)	-	-	-	-	-	1 (4.2)	1 (6.3)	-	-
外陰部腔カンジダ症	2 (5.6)	2 (5.6)	-	-	-	-	-	-	-	-
副鼻腔炎	2 (5.6)	-	-	1 (3.1)	-	1 (3.2)	-	-	-	-
せつ	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
ウイルス性腸炎	1 (2.8)	-	-	-	-	-	-	-	-	1 (33.3)
カンピロバクター胃腸炎	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
ヘモフィルス性肺炎	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
β溶血性レンサ球菌感染	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
急性腎盂腎炎	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
歯冠周囲炎	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-

Multiple occurrences of the same AE in one individual counted only once in new onset period.
Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
歯周炎	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
食道カンジダ症	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
爪囲炎	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
尿路感染	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
肺炎	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
麦粒腫	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
皮膚真菌感染	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
鼻炎	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
毛包炎	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
癬風	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
Total Number of AEs	70	22	13	8	11	3	6	4	2	1

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
胃腸障害										
Total Pts With at Least one AE	16 (44.4)	5 (13.9)	3 (8.6)	3 (9.4)	2 (6.3)	3 (9.7)	2 (8.3)	2 (12.5)	0	1 (33.3)
下痢	4 (11.1)	1 (2.8)	-	-	-	1 (3.2)	1 (4.2)	1 (6.3)	-	-
悪心	3 (8.3)	1 (2.8)	-	1 (3.1)	-	1 (3.2)	-	-	-	-
腹痛	3 (8.3)	1 (2.8)	-	1 (3.1)	1 (3.1)	-	-	-	-	-
黴菌	3 (8.3)	-	-	1 (3.1)	-	1 (3.2)	1 (4.2)	-	-	-
口唇炎	2 (5.6)	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-
口内炎	2 (5.6)	-	-	1 (3.1)	-	-	-	1 (6.3)	-	-
腹部不快感	2 (5.6)	-	1 (2.9)	-	1 (3.1)	-	-	-	-	-
胃腸の炎症	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
過敏性腸症候群	1 (2.8)	-	-	-	-	-	-	-	-	1 (33.3)
歯肉痛	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
腸炎	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
便秘	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
Total Number of AEs	24	6	3	4	3	3	2	2	0	1

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
皮膚および皮下組織障害										
Total Pts With at Least one AE	16 (44.4)	4 (11.1)	3 (8.6)	4 (12.5)	2 (6.3)	4 (12.9)	2 (8.3)	0	0	0
ざ瘡	3 (8.3)	1 (2.8)	-	-	-	2 (6.5)	-	-	-	-
皮下出血	3 (8.3)	1 (2.8)	1 (2.9)	-	1 (3.1)	-	-	-	-	-
湿疹	2 (5.6)	-	-	-	-	1 (3.2)	1 (4.2)	-	-	-
発疹	2 (5.6)	-	1 (2.9)	1 (3.1)	-	-	-	-	-	-
皮膚乾燥	2 (5.6)	-	-	1 (3.1)	1 (3.1)	-	-	-	-	-
蕁麻疹	2 (5.6)	-	-	1 (3.1)	-	1 (3.2)	-	-	-	-
そう痒症	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
寒冷蕁麻疹	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
結節性紅斑	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
多形紅斑	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
脱毛症	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
点状出血	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
皮膚剥脱	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
嵌入爪	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
Total Number of AEs	22	5	4	4	2	5	2	0	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
筋骨格系および結合組織障害										
Total Pts With at Least one AE	11 (30.6)	1 (2.8)	2 (5.7)	3 (9.4)	3 (9.4)	3 (9.7)	3 (12.5)	0	0	0
筋肉痛	4 (11.1)	1 (2.8)	-	1 (3.1)	1 (3.1)	1 (3.2)	-	-	-	-
背部痛	4 (11.1)	-	1 (2.9)	-	-	1 (3.2)	2 (8.3)	-	-	-
四肢痛	2 (5.6)	-	-	2 (6.3)	-	-	-	-	-	-
顎関節症候群	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
関節痛	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
筋骨格痛	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
頸部痛	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
足底筋膜炎	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
椎間板突出	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
変形性関節症	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
Total Number of AEs	17	1	2	4	4	3	3	0	0	0
神経系障害										
Total Pts With at Least one AE	9 (25.0)	2 (5.6)	4 (11.4)	1 (3.1)	0	1 (3.2)	2 (8.3)	1 (6.3)	0	0
失神寸前の状態	3 (8.3)	1 (2.8)	-	-	-	1 (3.2)	1 (4.2)	-	-	-
頭痛	3 (8.3)	-	1 (2.9)	1 (3.1)	-	-	-	1 (6.3)	-	-
感覚鈍麻	2 (5.6)	-	1 (2.9)	-	-	-	1 (4.2)	-	-	-
緊張性頭痛	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
傾眠	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
坐骨神経痛	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
複合性局所疼痛症候群	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
Total Number of AEs	12	2	4	1	0	2	2	1	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

Page 5 of 10

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
傷害、中毒および処置合併症										
Total Pts With at Least one AE	7 (19.4)	0	0	2 (6.3)	1 (3.1)	1 (3.2)	1 (4.2)	2 (12.5)	1 (12.5)	0
挫傷	3 (8.3)	-	-	1 (3.1)	1 (3.1)	1 (3.2)	-	-	-	-
肋骨骨折	2 (5.6)	-	-	1 (3.1)	-	-	1 (4.2)	-	-	-
処置による疼痛	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
節足動物刺傷	1 (2.8)	-	-	-	-	-	-	-	1 (12.5)	-
足骨折	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
Total Number of AEs	8	0	0	2	1	1	1	2	1	0
眼障害										
Total Pts With at Least one AE	6 (16.7)	1 (2.8)	1 (2.9)	1 (3.1)	1 (3.1)	2 (6.5)	0	1 (6.3)	0	0
アレルギー性結膜炎	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
眼乾燥	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
眼瞼炎	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
眼瞼発疹	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
視力障害	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
囊下白内障	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
白内障	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
Total Number of AEs	7	1	1	1	1	2	0	1	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
呼吸器、胸郭および縦隔障害										
Total Pts With at Least one AE	6 (16.7)	1 (2.8)	1 (2.9)	0	3 (9.4)	1 (3.2)	1 (4.2)	0	0	0
肺梗塞	2 (5.6)	-	1 (2.9)	-	-	1 (3.2)	-	-	-	-
咳嗽	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
気縦隔症	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
声帯肥厚	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
鼻出血	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
喀血	1 (2.8)	-	-	-	1 (3.1)	-	-	-	-	-
Total Number of AEs	7	1	1	0	3	1	1	0	0	0
血液およびリンパ系障害										
Total Pts With at Least one AE	5 (13.9)	0	1 (2.9)	1 (3.1)	0	1 (3.2)	1 (4.2)	1 (6.3)	0	0
鉄欠乏性貧血	4 (11.1)	-	1 (2.9)	-	-	1 (3.2)	1 (4.2)	1 (6.3)	-	-
貧血	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
Total Number of AEs	5	0	1	1	0	1	1	1	0	0
精神障害										
Total Pts With at Least one AE	5 (13.9)	3 (8.3)	3 (8.6)	0	0	0	0	0	0	0
不眠症	3 (8.3)	1 (2.8)	2 (5.7)	-	-	-	-	-	-	-
うつ病	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
パニック障害	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
不安	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
Total Number of AEs	6	3	3	0	0	0	0	0	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
臨床検査										
Total Pts With at Least one AE	5 (13.9)	1 (2.8)	1 (2.9)	0	0	2 (6.5)	0	1 (6.3)	0	0
アラニンアミノトランスフェラーゼ増加	3 (8.3)	1 (2.8)	1 (2.9)	-	-	1 (3.2)	-	-	-	-
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6)	-	1 (2.9)	-	-	1 (3.2)	-	-	-	-
γ-グルタミルトランスフェラーゼ増加	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
胸部X線異常	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
胸部コンピュータ断層撮影異常	1 (2.8)	-	-	-	-	-	-	1 (6.3)	-	-
白血球数減少	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
Total Number of AEs	9	2	2	0	0	3	0	2	0	0
一般・全身障害および投与部位の状態										
Total Pts With at Least one AE	3 (8.3)	0	1 (2.9)	0	0	0	1 (4.2)	0	1 (12.5)	0
胸痛	1 (2.8)	-	-	-	-	-	1 (4.2)	-	-	-
注射部位出血	1 (2.8)	-	-	-	-	-	-	-	1 (12.5)	-
疼痛	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
Total Number of AEs	3	0	1	0	0	0	1	0	1	0
肝胆道系障害										
Total Pts With at Least one AE	2 (5.6)	1 (2.8)	0	0	0	1 (3.2)	0	0	0	0
肝機能異常	2 (5.6)	1 (2.8)	-	-	-	1 (3.2)	-	-	-	-
Total Number of AEs	2	1	0	0	0	1	0	0	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

Page 8 of 10

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
腎および尿路障害										
Total Pts With at Least one AE	2 (5.6)	1 (2.8)	0	1 (3.1)	0	0	0	0	0	0
緊張性膀胱	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
血尿	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
Total Number of AEs	2	1	0	1	0	0	0	0	0	0
生殖系および乳房障害										
Total Pts With at Least one AE	2 (5.6)	0	1 (2.9)	0	0	1 (3.2)	0	0	0	0
月経困難症	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
産褥期乳汁分泌増加	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
卵巣嚢胞	1 (2.8)	-	-	-	-	1 (3.2)	-	-	-	-
Total Number of AEs	3	0	2	0	0	1	0	0	0	0
代謝および栄養障害										
Total Pts With at Least one AE	2 (5.6)	1 (2.8)	0	1 (3.1)	0	0	0	0	0	0
脂質異常症	1 (2.8)	-	-	1 (3.1)	-	-	-	-	-	-
食欲減退	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
Total Number of AEs	2	1	0	1	0	0	0	0	0	0
内分泌障害										
Total Pts With at Least one AE	1 (2.8)	1 (2.8)	0	0	0	0	0	0	0	0
ステロイド離脱症候群	1 (2.8)	1 (2.8)	-	-	-	-	-	-	-	-
Total Number of AEs	1	1	0	0	0	0	0	0	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

aeperiod_mt_sp Adverse Events by Time Period (New Onset)
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-<60 No. (%)	Week60-<72 No. (%)	Week72-<84 No. (%)	Week84-<96 No. (%)	Week96-<108 No. (%)
免疫系障害										
Total Pts With at Least one AE	1 (2.8)	0	1 (2.9)	0	0	0	0	0	0	0
造影剤アレルギー	1 (2.8)	-	1 (2.9)	-	-	-	-	-	-	-
Total Number of AEs	1	0	1	0	0	0	0	0	0	0

Multiple occurrences of the same AE in one individual counted only once in new onset period.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeperiod.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeperiod_mt_sp.out
 17JAN2017 19:52

Page 10 of 10

[5.3.5.1-7 表 11.3-9を再掲]

表 2.7.4.8-10 投与開始後初めて発現した有害事象の発現時期 (WA28119試験-二重盲検期間)

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
No. of Pts treated in each period	50	50	49	46	43	41
ALL BODY SYSTEMS						
Total Pts with at Least one AE	48 (96.0)	43 (86.0)	40 (81.6)	29 (63.0)	30 (69.8)	15 (36.6)
Total Number of AEs	408	175	97	65	54	17
感染症および寄生虫症						
Total Pts With at Least one AE	38 (76.0)	16 (32.0)	15 (30.6)	7 (15.2)	12 (27.9)	7 (17.1)
鼻咽頭炎	9 (18.0)	1 (2.0)	4 (8.2)	1 (2.2)	2 (4.7)	1 (2.4)
気管支炎	5 (10.0)	-	2 (4.1)	2 (4.3)	1 (2.3)	-
上気道感染	5 (10.0)	2 (4.0)	-	1 (2.2)	1 (2.3)	1 (2.4)
胃腸炎	4 (8.0)	1 (2.0)	1 (2.0)	-	1 (2.3)	1 (2.4)
結膜炎	4 (8.0)	2 (4.0)	1 (2.0)	-	1 (2.3)	-
口腔ヘルペス	3 (6.0)	1 (2.0)	1 (2.0)	-	1 (2.3)	-
歯齦瘍	2 (4.0)	-	1 (2.0)	-	-	1 (2.4)
尿路感染	2 (4.0)	2 (4.0)	-	-	-	-
麦粒腫	2 (4.0)	-	1 (2.0)	-	1 (2.3)	-
鼻炎	2 (4.0)	-	1 (2.0)	-	1 (2.3)	-
膀胱炎	2 (4.0)	1 (2.0)	-	-	-	1 (2.4)
せつ	1 (2.0)	-	-	-	1 (2.3)	-
ウイルス性気道感染	1 (2.0)	-	-	1 (2.2)	-	-
ウイルス性上気道感染	1 (2.0)	-	-	1 (2.2)	-	-
ウイルス性迷路炎	1 (2.0)	-	1 (2.0)	-	-	-
ヘルペスウイルス感染	1 (2.0)	1 (2.0)	-	-	-	-
咽頭炎	1 (2.0)	1 (2.0)	-	-	-	-
外陰部腔炎	1 (2.0)	-	-	-	-	1 (2.4)
外陰腔真菌感染	1 (2.0)	-	-	1 (2.2)	-	-
感染性皮膚潰瘍	1 (2.0)	-	1 (2.0)	-	-	-
限局性感染	1 (2.0)	-	1 (2.0)	-	-	-
口角口唇炎	1 (2.0)	1 (2.0)	-	-	-	-
口腔カンジダ症	1 (2.0)	1 (2.0)	-	-	-	-
細菌性眼感染	1 (2.0)	-	1 (2.0)	-	-	-
菌感染	1 (2.0)	-	-	-	1 (2.3)	-
菌周炎	1 (2.0)	-	-	-	-	1 (2.4)
菌肉炎	1 (2.0)	-	1 (2.0)	-	-	-
消化管感染	1 (2.0)	-	-	-	1 (2.3)	-
腎盂腎炎	1 (2.0)	-	1 (2.0)	-	-	-
水痘帯状疱疹ウイルス感染	1 (2.0)	1 (2.0)	-	-	-	-
丹毒	1 (2.0)	-	-	-	1 (2.3)	-
膿尿	1 (2.0)	1 (2.0)	-	-	-	-
肺炎	1 (2.0)	1 (2.0)	-	-	-	-
肺感染	1 (2.0)	-	-	1 (2.2)	-	-
皮膚カンジダ	1 (2.0)	-	1 (2.0)	-	-	-
副鼻腔炎	1 (2.0)	-	-	-	1 (2.3)	-
腔感染	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	66	18	19	8	14	7

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	34 (68.0)	20 (40.0)	17 (34.7)	8 (17.4)	4 (9.3)	3 (7.3)
関節痛	11 (22.0)	2 (4.0)	5 (10.2)	2 (4.3)	2 (4.7)	-
背部痛	7 (14.0)	2 (4.0)	3 (6.1)	-	1 (2.3)	1 (2.4)
筋痙縮	6 (12.0)	3 (6.0)	2 (4.1)	1 (2.2)	-	-
筋骨格痛	5 (10.0)	1 (2.0)	2 (4.1)	1 (2.2)	1 (2.3)	-
四肢痛	5 (10.0)	2 (4.0)	2 (4.1)	-	-	1 (2.4)
筋肉痛	4 (8.0)	4 (8.0)	-	-	-	-
変形性関節症	3 (6.0)	2 (4.0)	-	-	1 (2.3)	-
顎痛	2 (4.0)	2 (4.0)	-	-	-	-
滑液包炎	2 (4.0)	1 (2.0)	1 (2.0)	-	-	-
筋力低下	2 (4.0)	1 (2.0)	-	-	1 (2.3)	-
頸部痛	2 (4.0)	-	2 (4.1)	-	-	-
四肢不快感	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
線維筋痛	2 (4.0)	-	-	1 (2.2)	-	1 (2.4)
ミオパチー	1 (2.0)	1 (2.0)	-	-	-	-
リウマトイド結節	1 (2.0)	-	-	1 (2.2)	-	-
関節可動域低下	1 (2.0)	-	1 (2.0)	-	-	-
関節硬直	1 (2.0)	-	1 (2.0)	-	-	-
筋骨格硬直	1 (2.0)	1 (2.0)	-	-	-	-
骨粗鬆症	1 (2.0)	-	1 (2.0)	-	-	-
脊椎痛	1 (2.0)	-	-	1 (2.2)	-	-
足底筋膜炎	1 (2.0)	1 (2.0)	-	-	-	-
弾弁指	1 (2.0)	-	1 (2.0)	-	-	-
椎間板突出	1 (2.0)	1 (2.0)	-	-	-	-
腱炎	1 (2.0)	-	1 (2.0)	-	-	-
単径部痛	1 (2.0)	-	1 (2.0)	-	-	-
Total Number of AEs	65	25	23	8	6	3
神経系障害						
Total Pts With at Least one AE	23 (46.0)	14 (28.0)	6 (12.2)	5 (10.9)	4 (9.3)	2 (4.9)
頭痛	16 (32.0)	6 (12.0)	5 (10.2)	2 (4.3)	2 (4.7)	1 (2.4)
浮動性めまい	6 (12.0)	5 (10.0)	-	1 (2.2)	-	-
錯感覚	5 (10.0)	3 (6.0)	-	1 (2.2)	1 (2.3)	-
振戦	3 (6.0)	1 (2.0)	-	2 (4.3)	-	-
感覚鈍麻	2 (4.0)	2 (4.0)	-	-	-	-
坐骨神経痛	2 (4.0)	1 (2.0)	1 (2.0)	-	-	-
失神	2 (4.0)	2 (4.0)	-	-	-	-
傾眠	1 (2.0)	1 (2.0)	-	-	-	-
知覚過敏	1 (2.0)	-	-	1 (2.2)	-	-
平衡障害	1 (2.0)	1 (2.0)	-	-	-	-
片頭痛	1 (2.0)	-	-	-	1 (2.3)	-
嗜眠	1 (2.0)	-	-	-	-	1 (2.4)
Total Number of AEs	41	22	6	7	4	2

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	21 (42.0)	12 (24.0)	6 (12.2)	1 (2.2)	6 (14.0)	0
疲労	8 (16.0)	2 (4.0)	2 (4.1)	-	4 (9.3)	-
末梢性浮腫	8 (16.0)	5 (10.0)	1 (2.0)	1 (2.2)	1 (2.3)	-
無力症	5 (10.0)	3 (6.0)	1 (2.0)	-	1 (2.3)	-
発熱	2 (4.0)	-	-	-	2 (4.7)	-
インフルエンザ様疾患	1 (2.0)	1 (2.0)	-	-	-	-
空腹	1 (2.0)	1 (2.0)	-	-	-	-
倦怠感	1 (2.0)	1 (2.0)	-	-	-	-
注射部位疼痛	1 (2.0)	-	1 (2.0)	-	-	-
熱感	1 (2.0)	-	1 (2.0)	-	-	-
非心臓性胸痛	1 (2.0)	1 (2.0)	-	-	-	-
疼痛	1 (2.0)	-	1 (2.0)	-	-	-
Total Number of AEs	30	14	7	1	8	0
胃腸障害						
Total Pts With at Least one AE	19 (38.0)	14 (28.0)	6 (12.2)	6 (13.0)	2 (4.7)	0
下痢	8 (16.0)	5 (10.0)	1 (2.0)	1 (2.2)	1 (2.3)	-
悪心	5 (10.0)	3 (6.0)	1 (2.0)	1 (2.2)	-	-
消化不良	4 (8.0)	2 (4.0)	2 (4.1)	-	-	-
上腹部痛	3 (6.0)	2 (4.0)	-	1 (2.2)	-	-
便秘	3 (6.0)	2 (4.0)	1 (2.0)	-	-	-
胃食道逆流性疾患	2 (4.0)	-	1 (2.0)	1 (2.2)	-	-
胃腸障害	2 (4.0)	-	2 (4.1)	-	-	-
鼓腸	2 (4.0)	2 (4.0)	-	-	-	-
口内乾燥	2 (4.0)	-	-	2 (4.3)	-	-
痔核	2 (4.0)	1 (2.0)	1 (2.0)	-	-	-
腹痛	2 (4.0)	2 (4.0)	-	-	-	-
腹部膨満	2 (4.0)	2 (4.0)	-	-	-	-
嘔吐	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
びらん性胃炎	1 (2.0)	-	-	1 (2.2)	-	-
下腹部痛	1 (2.0)	-	-	1 (2.2)	-	-
口内炎	1 (2.0)	1 (2.0)	-	-	-	-
歯の知覚過敏	1 (2.0)	1 (2.0)	-	-	-	-
歯肉痛	1 (2.0)	-	-	1 (2.2)	-	-
舌苔	1 (2.0)	-	1 (2.0)	-	-	-
大腸ポリープ	1 (2.0)	-	-	1 (2.2)	-	-
腹腔内血腫	1 (2.0)	-	-	-	1 (2.3)	-
変色便	1 (2.0)	1 (2.0)	-	-	-	-
便意切迫	1 (2.0)	1 (2.0)	-	-	-	-
肛門出血	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	50	27	10	11	2	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	17 (34.0)	8 (16.0)	8 (16.3)	2 (4.3)	0	1 (2.4)
発疹	4 (8.0)	1 (2.0)	2 (4.1)	-	-	1 (2.4)
脱毛症	3 (6.0)	1 (2.0)	2 (4.1)	-	-	-
湿疹	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
多汗症	2 (4.0)	1 (2.0)	1 (2.0)	-	-	-
ざ瘡	1 (2.0)	-	1 (2.0)	-	-	-
そう痒症	1 (2.0)	1 (2.0)	-	-	-	-
一過性棘融解性皮膚症	1 (2.0)	-	1 (2.0)	-	-	-
間擦疹	1 (2.0)	1 (2.0)	-	-	-	-
顔面腫脹	1 (2.0)	1 (2.0)	-	-	-	-
紅斑	1 (2.0)	-	1 (2.0)	-	-	-
寝汗	1 (2.0)	1 (2.0)	-	-	-	-
斑状出血	1 (2.0)	1 (2.0)	-	-	-	-
皮膚灼熱感	1 (2.0)	-	1 (2.0)	-	-	-
皮膚疼痛	1 (2.0)	-	1 (2.0)	-	-	-
蕁麻疹	1 (2.0)	-	-	1 (2.2)	-	-
Total Number of AEs	22	9	10	2	0	1
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	16 (32.0)	8 (16.0)	3 (6.1)	3 (6.5)	5 (11.6)	1 (2.4)
咳嗽	7 (14.0)	3 (6.0)	-	2 (4.3)	1 (2.3)	1 (2.4)
口腔咽頭痛	5 (10.0)	4 (8.0)	-	-	1 (2.3)	-
鼻出血	4 (8.0)	1 (2.0)	2 (4.1)	1 (2.2)	-	-
労作性呼吸困難	3 (6.0)	2 (4.0)	1 (2.0)	-	-	-
呼吸困難	1 (2.0)	-	-	-	1 (2.3)	-
肺炎	1 (2.0)	-	-	-	1 (2.3)	-
鼻の炎症	1 (2.0)	1 (2.0)	-	-	-	-
喘息	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	23	11	3	3	5	1
眼障害						
Total Pts With at Least one AE	15 (30.0)	7 (14.0)	4 (8.2)	5 (10.9)	0	0
白内障	3 (6.0)	-	2 (4.1)	1 (2.2)	-	-
眼充血	2 (4.0)	2 (4.0)	-	-	-	-
結膜出血	2 (4.0)	2 (4.0)	-	-	-	-
霧視	2 (4.0)	-	-	2 (4.3)	-	-
緑内障	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
眼乾燥	1 (2.0)	-	1 (2.0)	-	-	-
眼精疲労	1 (2.0)	1 (2.0)	-	-	-	-
眼部不快感	1 (2.0)	1 (2.0)	-	-	-	-
眼瞼炎	1 (2.0)	-	1 (2.0)	-	-	-
視力低下	1 (2.0)	-	-	1 (2.2)	-	-
複視	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	17	8	4	5	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
血管障害						
Total Pts With at Least one AE	13 (26.0)	7 (14.0)	3 (6.1)	2 (4.3)	3 (7.0)	2 (4.9)
高血圧	4 (8.0)	3 (6.0)	1 (2.0)	-	-	-
血腫	3 (6.0)	1 (2.0)	1 (2.0)	-	-	1 (2.4)
低血圧	2 (4.0)	-	-	1 (2.2)	1 (2.3)	-
ほてり	1 (2.0)	1 (2.0)	-	-	-	-
レイノー現象	1 (2.0)	-	-	-	-	1 (2.4)
顎筋跛行	1 (2.0)	1 (2.0)	-	-	-	-
間欠性跛行	1 (2.0)	-	-	-	1 (2.3)	-
鎖骨下動脈狭窄	1 (2.0)	-	-	-	1 (2.3)	-
側頭動脈炎	1 (2.0)	-	1 (2.0)	-	-	-
末梢血管障害	1 (2.0)	-	-	1 (2.2)	-	-
末梢冷感	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	17	7	3	2	3	2
精神障害						
Total Pts With at Least one AE	13 (26.0)	6 (12.0)	3 (6.1)	3 (6.5)	1 (2.3)	0
不安	6 (12.0)	2 (4.0)	2 (4.1)	2 (4.3)	-	-
不眠症	4 (8.0)	2 (4.0)	1 (2.0)	1 (2.2)	-	-
うつ病	3 (6.0)	1 (2.0)	1 (2.0)	-	1 (2.3)	-
睡眠障害	1 (2.0)	1 (2.0)	-	-	-	-
抑うつ気分	1 (2.0)	-	-	1 (2.2)	-	-
Total Number of AEs	15	6	4	4	1	0
傷害、中毒および処置合併症						
Total Pts With at Least one AE	10 (20.0)	3 (6.0)	1 (2.0)	3 (6.5)	3 (7.0)	1 (2.4)
転倒	2 (4.0)	-	1 (2.0)	1 (2.2)	-	-
肋骨骨折	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
眼内異物	1 (2.0)	1 (2.0)	-	-	-	-
四肢損傷	1 (2.0)	-	-	-	-	1 (2.4)
手骨折	1 (2.0)	-	-	1 (2.2)	-	-
術後創合併症	1 (2.0)	-	-	-	1 (2.3)	-
処置によるめまい	1 (2.0)	1 (2.0)	-	-	-	-
上顎炎	1 (2.0)	-	-	1 (2.2)	-	-
熱傷	1 (2.0)	-	-	-	1 (2.3)	-
裂傷	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	12	3	1	4	3	1
臨床検査						
Total Pts With at Least one AE	9 (18.0)	6 (12.0)	2 (4.1)	1 (2.2)	0	0
アラニンアミノトランスフェラーゼ増加	2 (4.0)	2 (4.0)	-	-	-	-
眼圧上昇	2 (4.0)	1 (2.0)	1 (2.0)	-	-	-
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.0)	1 (2.0)	-	-	-	-
ビタミンB12減少	1 (2.0)	-	1 (2.0)	-	-	-
体重減少	1 (2.0)	-	-	1 (2.2)	-	-
体重増加	1 (2.0)	1 (2.0)	-	-	-	-
白血球数増加	1 (2.0)	1 (2.0)	-	-	-	-
平均赤血球容積増加	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	10	7	2	1	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
耳および迷路障害						
Total Pts With at Least one AE	6 (12.0)	3 (6.0)	2 (4.1)	1 (2.2)	1 (2.3)	0
回転性めまい	3 (6.0)	1 (2.0)	-	1 (2.2)	1 (2.3)	-
耳痛	1 (2.0)	1 (2.0)	-	-	-	-
耳鳴	1 (2.0)	-	1 (2.0)	-	-	-
前庭障害	1 (2.0)	1 (2.0)	-	-	-	-
聴力低下	1 (2.0)	-	1 (2.0)	-	-	-
Total Number of AEs	7	3	2	1	1	0
心臓障害						
Total Pts With at Least one AE	6 (12.0)	4 (8.0)	1 (2.0)	1 (2.2)	0	0
動悸	4 (8.0)	3 (6.0)	1 (2.0)	-	-	-
狭心症	1 (2.0)	1 (2.0)	-	-	-	-
心血管障害	1 (2.0)	1 (2.0)	-	-	-	-
僧帽弁閉鎖不全症	1 (2.0)	-	-	1 (2.2)	-	-
頻脈	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	8	6	1	1	0	0
血液およびリンパ系障害						
Total Pts With at Least one AE	4 (8.0)	2 (4.0)	0	1 (2.2)	1 (2.3)	0
貧血	2 (4.0)	2 (4.0)	-	-	-	-
リンパ球減少症	1 (2.0)	-	-	1 (2.2)	-	-
リンパ節症	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	4	2	0	1	1	0
腎および尿路障害						
Total Pts With at Least one AE	4 (8.0)	1 (2.0)	1 (2.0)	2 (4.3)	1 (2.3)	0
排尿困難	2 (4.0)	1 (2.0)	-	1 (2.2)	-	-
血尿	1 (2.0)	-	-	1 (2.2)	-	-
腎嚢胞	1 (2.0)	-	-	-	1 (2.3)	-
尿失禁	1 (2.0)	-	1 (2.0)	-	-	-
Total Number of AEs	5	1	1	2	1	0
代謝および栄養障害						
Total Pts With at Least one AE	4 (8.0)	3 (6.0)	0	1 (2.2)	0	0
糖尿病	2 (4.0)	2 (4.0)	-	-	-	-
2型糖尿病	1 (2.0)	-	-	1 (2.2)	-	-
ビタミンD欠乏	1 (2.0)	1 (2.0)	-	-	-	-
葉酸欠乏	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	5	4	0	1	0	0
外科および内科処置						
Total Pts With at Least one AE	3 (6.0)	0	1 (2.0)	1 (2.2)	1 (2.3)	0
白内障手術	2 (4.0)	-	1 (2.0)	1 (2.2)	-	-
股関節形成	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	3	0	1	1	1	0
免疫系障害						
Total Pts With at Least one AE	3 (6.0)	2 (4.0)	0	0	1 (2.3)	0
季節性アレルギー	1 (2.0)	1 (2.0)	-	-	-	-
続発性免疫不全症	1 (2.0)	1 (2.0)	-	-	-	-
薬物過敏症	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	3	2	0	0	1	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 26 Week Prednisone Taper (N=50)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
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）						
Total Pts With at Least one AE	3 (6.0)	0	0	2 (4.3)	2 (4.7)	0
アコロルドン	1 (2.0)	-	-	-	1 (2.3)	-
腎新生物	1 (2.0)	-	-	-	1 (2.3)	-
大腸腺腫	1 (2.0)	-	-	1 (2.2)	-	-
乳癌	1 (2.0)	-	-	1 (2.2)	-	-
Total Number of AEs	4	0	0	2	2	0
内分泌障害						
Total Pts With at Least one AE	1 (2.0)	0	0	0	1 (2.3)	0
甲状腺腫	1 (2.0)	-	-	-	1 (2.3)	-
Total Number of AEs	1	0	0	0	1	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
No. of Pts treated in each period	51	51	47	47	46	46
ALL BODY SYSTEMS						
Total Pts with at Least one AE	47 (92.2)	41 (80.4)	34 (72.3)	28 (59.6)	30 (65.2)	13 (28.3)
Total Number of AEs	383	149	83	76	56	19
感染症および寄生虫症						
Total Pts With at Least one AE	33 (64.7)	19 (37.3)	13 (27.7)	7 (14.9)	16 (34.8)	4 (8.7)
鼻咽頭炎	13 (25.5)	7 (13.7)	2 (4.3)	-	4 (8.7)	-
上気道感染	7 (13.7)	2 (3.9)	1 (2.1)	-	1 (2.2)	3 (6.5)
気管支炎	5 (9.8)	-	1 (2.1)	3 (6.4)	1 (2.2)	-
胃腸炎	4 (7.8)	3 (5.9)	1 (2.1)	-	-	-
尿路感染	4 (7.8)	1 (2.0)	3 (6.4)	-	-	-
咽頭炎	3 (5.9)	-	1 (2.1)	1 (2.1)	1 (2.2)	-
鼻炎	3 (5.9)	1 (2.0)	-	2 (4.3)	-	-
膀胱炎	3 (5.9)	2 (3.9)	1 (2.1)	-	-	-
気道感染	2 (3.9)	-	1 (2.1)	-	1 (2.2)	-
口腔ヘルペス	2 (3.9)	-	1 (2.1)	-	1 (2.2)	-
喉頭炎	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
歯周炎	2 (3.9)	1 (2.0)	1 (2.1)	-	-	-
歯肉炎	2 (3.9)	-	-	2 (4.3)	-	-
带状疱疹	2 (3.9)	-	-	2 (4.3)	-	-
爪真菌症	2 (3.9)	-	2 (4.3)	-	-	-
膿疱性皮疹	2 (3.9)	2 (3.9)	-	-	-	-
副鼻腔炎	2 (3.9)	2 (3.9)	-	-	-	-
せつ	1 (2.0)	1 (2.0)	-	-	-	-
インフルエンザ	1 (2.0)	1 (2.0)	-	-	-	-
ウイルス性胃腸炎	1 (2.0)	-	-	-	1 (2.2)	-
サイトメガロウイルス感染	1 (2.0)	-	-	-	1 (2.2)	-
陰部带状疱疹	1 (2.0)	1 (2.0)	-	-	-	-
下気道感染	1 (2.0)	-	1 (2.1)	-	-	-
外陰腔真菌感染	1 (2.0)	-	-	1 (2.1)	-	-
感染性腸炎	1 (2.0)	-	-	-	1 (2.2)	-
眼部単純ヘルペス	1 (2.0)	1 (2.0)	-	-	-	-
憩室炎	1 (2.0)	-	-	-	-	1 (2.2)
結膜炎	1 (2.0)	1 (2.0)	-	-	-	-
歯感染	1 (2.0)	-	-	-	1 (2.2)	-
歯膿瘍	1 (2.0)	-	-	-	1 (2.2)	-
創傷感染	1 (2.0)	-	-	-	1 (2.2)	-
蜂巣炎	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	75	28	16	11	16	4

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	32 (62.7)	16 (31.4)	11 (23.4)	10 (21.3)	9 (19.6)	0
背部痛	10 (19.6)	4 (7.8)	1 (2.1)	2 (4.3)	3 (6.5)	-
関節痛	8 (15.7)	-	6 (12.8)	1 (2.1)	1 (2.2)	-
四肢痛	5 (9.8)	2 (3.9)	-	1 (2.1)	2 (4.3)	-
筋肉痛	4 (7.8)	1 (2.0)	2 (4.3)	1 (2.1)	-	-
筋痙縮	4 (7.8)	2 (3.9)	-	-	2 (4.3)	-
頸部痛	4 (7.8)	2 (3.9)	1 (2.1)	1 (2.1)	-	-
変形性関節症	4 (7.8)	2 (3.9)	1 (2.1)	1 (2.1)	-	-
筋骨格痛	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
腱付着部症	2 (3.9)	-	1 (2.1)	1 (2.1)	-	-
シェーグレン症候群	1 (2.0)	-	1 (2.1)	-	-	-
滑液包炎	1 (2.0)	1 (2.0)	-	-	-	-
筋骨格系胸痛	1 (2.0)	1 (2.0)	-	-	-	-
筋骨格不快感	1 (2.0)	-	1 (2.1)	-	-	-
筋攣縮	1 (2.0)	1 (2.0)	-	-	-	-
頸部脊柱管狭窄症	1 (2.0)	-	-	1 (2.1)	-	-
肩回旋筋腱板症候群	1 (2.0)	-	-	-	1 (2.2)	-
骨減少症	1 (2.0)	1 (2.0)	-	-	-	-
骨粗鬆症	1 (2.0)	-	1 (2.1)	-	-	-
脊椎痛	1 (2.0)	-	-	-	1 (2.2)	-
線維筋痛	1 (2.0)	1 (2.0)	-	-	-	-
側腹部痛	1 (2.0)	-	-	1 (2.1)	-	-
軟骨痛	1 (2.0)	-	-	1 (2.1)	-	-
腱鞘炎	1 (2.0)	-	-	1 (2.1)	-	-
腱痛	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	58	20	15	13	10	0
神経系障害						
Total Pts With at Least one AE	22 (43.1)	15 (29.4)	6 (12.8)	5 (10.6)	1 (2.2)	1 (2.2)
頭痛	12 (23.5)	7 (13.7)	2 (4.3)	2 (4.3)	1 (2.2)	-
浮動性めまい	8 (15.7)	5 (9.8)	2 (4.3)	-	-	1 (2.2)
錯感覚	4 (7.8)	3 (5.9)	-	1 (2.1)	-	-
振戦	3 (5.9)	2 (3.9)	1 (2.1)	-	-	-
ヘルペス後神経痛	1 (2.0)	-	-	1 (2.1)	-	-
一過性脳虚血発作	1 (2.0)	-	1 (2.1)	-	-	-
構語障害	1 (2.0)	1 (2.0)	-	-	-	-
失神	1 (2.0)	-	-	1 (2.1)	-	-
神経痛	1 (2.0)	-	1 (2.1)	-	-	-
片頭痛	1 (2.0)	-	-	1 (2.1)	-	-
味覚異常	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	34	19	7	6	1	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	17 (33.3)	9 (17.6)	4 (8.5)	5 (10.6)	0	3 (6.5)
口腔咽頭痛	8 (15.7)	5 (9.8)	2 (4.3)	1 (2.1)	-	-
咳嗽	3 (5.9)	-	-	2 (4.3)	-	1 (2.2)
呼吸困難	3 (5.9)	3 (5.9)	-	-	-	-
アレルギー性鼻炎	1 (2.0)	-	-	1 (2.1)	-	-
咽頭紅斑	1 (2.0)	1 (2.0)	-	-	-	-
逆流性喉頭炎	1 (2.0)	-	1 (2.1)	-	-	-
胸膜痛	1 (2.0)	1 (2.0)	-	-	-	-
湿性咳嗽	1 (2.0)	-	-	-	-	1 (2.2)
発声障害	1 (2.0)	-	-	-	-	1 (2.2)
労作性呼吸困難	1 (2.0)	-	1 (2.1)	-	-	-
喘息	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	22	10	4	5	0	3
皮膚および皮下組織障害						
Total Pts With at Least one AE	17 (33.3)	9 (17.6)	6 (12.8)	4 (8.5)	3 (6.5)	0
脱毛症	5 (9.8)	1 (2.0)	4 (8.5)	-	-	-
斑状出血	3 (5.9)	1 (2.0)	-	2 (4.3)	-	-
紅斑	2 (3.9)	-	1 (2.1)	-	1 (2.2)	-
湿疹	2 (3.9)	2 (3.9)	-	-	-	-
発疹	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
ざ瘡	1 (2.0)	1 (2.0)	-	-	-	-
そう痒症	1 (2.0)	1 (2.0)	-	-	-	-
そう痒性皮疹	1 (2.0)	1 (2.0)	-	-	-	-
アレルギー性皮膚炎	1 (2.0)	-	-	1 (2.1)	-	-
光線角化症	1 (2.0)	-	1 (2.1)	-	-	-
寝汗	1 (2.0)	1 (2.0)	-	-	-	-
多汗症	1 (2.0)	1 (2.0)	-	-	-	-
斑状皮疹	1 (2.0)	-	-	-	1 (2.2)	-
皮膚腫脹	1 (2.0)	-	1 (2.1)	-	-	-
皮膚障害	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	24	10	7	4	3	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
胃腸障害						
Total Pts With at Least one AE	15 (29.4)	10 (19.6)	5 (10.6)	4 (8.5)	5 (10.9)	3 (6.5)
下痢	5 (9.8)	1 (2.0)	1 (2.1)	2 (4.3)	-	1 (2.2)
悪心	4 (7.8)	1 (2.0)	-	-	3 (6.5)	-
上腹部痛	4 (7.8)	1 (2.0)	-	1 (2.1)	1 (2.2)	1 (2.2)
便秘	4 (7.8)	2 (3.9)	1 (2.1)	-	1 (2.2)	-
嘔吐	3 (5.9)	1 (2.0)	1 (2.1)	1 (2.1)	-	-
鼓腸	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
口腔内潰瘍形成	2 (3.9)	2 (3.9)	-	-	-	-
歯痛	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
腹痛	2 (3.9)	2 (3.9)	-	-	-	-
びらん性胃炎	1 (2.0)	-	1 (2.1)	-	-	-
胃炎	1 (2.0)	1 (2.0)	-	-	-	-
胃食道逆流性疾病	1 (2.0)	-	-	-	-	1 (2.2)
下腹部痛	1 (2.0)	-	1 (2.1)	-	-	-
憩室	1 (2.0)	-	-	-	1 (2.2)	-
歯肉痛	1 (2.0)	-	1 (2.1)	-	-	-
痔核	1 (2.0)	-	-	-	1 (2.2)	-
消化管運動障害	1 (2.0)	-	-	1 (2.1)	-	-
消化不良	1 (2.0)	1 (2.0)	-	-	-	-
舌潰瘍	1 (2.0)	1 (2.0)	-	-	-	-
嚥下障害	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	39	15	7	5	9	3
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	14 (27.5)	7 (13.7)	5 (10.6)	2 (4.3)	2 (4.3)	2 (4.3)
末梢性浮腫	6 (11.8)	4 (7.8)	1 (2.1)	-	1 (2.2)	-
疲労	3 (5.9)	1 (2.0)	1 (2.1)	-	1 (2.2)	-
非心臓性胸痛	3 (5.9)	-	1 (2.1)	2 (4.3)	-	-
発熱	2 (3.9)	-	1 (2.1)	-	1 (2.2)	-
末梢腫脹	2 (3.9)	-	-	-	-	2 (4.3)
インフルエンザ様疾患	1 (2.0)	-	-	-	1 (2.2)	-
悪寒	1 (2.0)	-	-	-	1 (2.2)	-
腫脹	1 (2.0)	1 (2.0)	-	-	-	-
注射部位血腫	1 (2.0)	1 (2.0)	-	-	-	-
嚢胞	1 (2.0)	1 (2.0)	-	-	-	-
腋窩痛	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	22	8	5	2	5	2

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
眼障害						
Total Pts With at Least one AE	14 (27.5)	6 (11.8)	2 (4.3)	6 (12.8)	2 (4.3)	0
白内障	5 (9.8)	1 (2.0)	1 (2.1)	2 (4.3)	1 (2.2)	-
眼の異物感	1 (2.0)	1 (2.0)	-	-	-	-
眼乾燥	1 (2.0)	1 (2.0)	-	-	-	-
眼充血	1 (2.0)	1 (2.0)	-	-	-	-
眼痛	1 (2.0)	1 (2.0)	-	-	-	-
眼部腫脹	1 (2.0)	1 (2.0)	-	-	-	-
眼部不快感	1 (2.0)	-	-	-	1 (2.2)	-
眼瞼炎	1 (2.0)	-	-	1 (2.1)	-	-
結膜出血	1 (2.0)	1 (2.0)	-	-	-	-
高眼圧症	1 (2.0)	1 (2.0)	-	-	-	-
閃輝暗点	1 (2.0)	-	-	1 (2.1)	-	-
複視	1 (2.0)	-	1 (2.1)	-	-	-
霧視	1 (2.0)	-	-	1 (2.1)	-	-
流涙増加	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	18	8	2	6	2	0
傷害、中毒および処置合併症						
Total Pts With at Least one AE	14 (27.5)	8 (15.7)	3 (6.4)	4 (8.5)	1 (2.2)	0
挫傷	2 (3.9)	1 (2.0)	1 (2.1)	-	-	-
節足動物咬傷	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
創傷	2 (3.9)	-	1 (2.1)	1 (2.1)	-	-
転倒	2 (3.9)	2 (3.9)	-	-	-	-
裂傷	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
アルコール中毒	1 (2.0)	1 (2.0)	-	-	-	-
サンバーン	1 (2.0)	1 (2.0)	-	-	-	-
筋損傷	1 (2.0)	-	-	1 (2.1)	-	-
骨挫傷	1 (2.0)	1 (2.0)	-	-	-	-
損傷	1 (2.0)	-	-	1 (2.1)	-	-
肉離れ	1 (2.0)	-	-	-	1 (2.2)	-
腱断裂	1 (2.0)	1 (2.0)	-	-	-	-
靭帯捻挫	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	18	9	3	5	1	0
血管障害						
Total Pts With at Least one AE	9 (17.6)	2 (3.9)	3 (6.4)	3 (6.4)	2 (4.3)	1 (2.2)
高血圧	4 (7.8)	1 (2.0)	2 (4.3)	-	-	1 (2.2)
血栓性静脈炎	2 (3.9)	-	-	1 (2.1)	1 (2.2)	-
拡張期高血圧	1 (2.0)	-	-	1 (2.1)	-	-
血腫	1 (2.0)	1 (2.0)	-	-	-	-
高血圧クリーゼ	1 (2.0)	-	-	1 (2.1)	-	-
側頭動脈炎	1 (2.0)	-	-	1 (2.1)	-	-
末梢動脈狭窄	1 (2.0)	-	-	-	1 (2.2)	-
末梢冷感	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	12	2	3	4	2	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48-> No. (%)
精神障害						
Total Pts With at Least one AE	8 (15.7)	2 (3.9)	3 (6.4)	2 (4.3)	0	2 (4.3)
不眠症	4 (7.8)	1 (2.0)	1 (2.1)	1 (2.1)	-	1 (2.2)
うつ病	1 (2.0)	-	1 (2.1)	-	-	-
易刺激性	1 (2.0)	1 (2.0)	-	-	-	-
睡眠障害	1 (2.0)	-	-	-	-	1 (2.2)
精神状態変化	1 (2.0)	1 (2.0)	-	-	-	-
不安	1 (2.0)	-	-	1 (2.1)	-	-
抑うつ気分を伴う適応障害	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	10	3	3	2	0	2
臨床検査						
Total Pts With at Least one AE	8 (15.7)	4 (7.8)	2 (4.3)	3 (6.4)	1 (2.2)	0
肝酵素上昇	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
眼圧上昇	2 (3.9)	2 (3.9)	-	-	-	-
体温上昇	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
低比重リポ蛋白増加	2 (3.9)	-	2 (4.3)	-	-	-
血中カリウム異常	1 (2.0)	-	-	1 (2.1)	-	-
血中カリウム減少	1 (2.0)	-	-	1 (2.1)	-	-
血中尿酸増加	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	11	4	2	4	1	0
代謝および栄養障害						
Total Pts With at Least one AE	7 (13.7)	4 (7.8)	3 (6.4)	0	0	0
低カリウム血症	3 (5.9)	2 (3.9)	1 (2.1)	-	-	-
高コレステロール血症	1 (2.0)	-	1 (2.1)	-	-	-
高尿酸血症	1 (2.0)	-	1 (2.1)	-	-	-
低ナトリウム血症	1 (2.0)	1 (2.0)	-	-	-	-
鉄欠乏	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	7	4	3	0	0	0
耳および迷路障害						
Total Pts With at Least one AE	6 (11.8)	3 (5.9)	1 (2.1)	1 (2.1)	2 (4.3)	0
耳鳴	2 (3.9)	1 (2.0)	1 (2.1)	-	-	-
頭位性回転性めまい	2 (3.9)	1 (2.0)	-	-	1 (2.2)	-
回転性めまい	1 (2.0)	-	-	1 (2.1)	-	-
耳不快感	1 (2.0)	1 (2.0)	-	-	-	-
難聴	1 (2.0)	-	-	-	1 (2.2)	-
Total Number of AEs	7	3	1	1	2	0
心臓障害						
Total Pts With at Least one AE	6 (11.8)	1 (2.0)	1 (2.1)	4 (8.5)	1 (2.2)	1 (2.2)
動悸	2 (3.9)	-	-	1 (2.1)	-	1 (2.2)
慢性心不全	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
上室性頻脈	1 (2.0)	-	-	-	1 (2.2)	-
心不全	1 (2.0)	-	1 (2.1)	-	-	-
大動脈弁狭窄	1 (2.0)	-	-	1 (2.1)	-	-
不整脈	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	8	1	1	4	1	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: PBO QW + 52 Week Prednisone Taper (N=51)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
腎および尿路障害						
Total Pts With at Least one AE	6 (11.8)	1 (2.0)	2 (4.3)	2 (4.3)	1 (2.2)	1 (2.2)
尿意切迫	2 (3.9)	-	-	1 (2.1)	1 (2.2)	-
腎機能障害	1 (2.0)	-	1 (2.1)	-	-	-
腎虚血	1 (2.0)	-	-	1 (2.1)	-	-
腎不全	1 (2.0)	-	-	-	-	1 (2.2)
排尿困難	1 (2.0)	1 (2.0)	-	-	-	-
頻尿	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	7	1	2	2	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)						
Total Pts With at Least one AE	3 (5.9)	0	0	0	2 (4.3)	1 (2.2)
メラノサイト性母斑	1 (2.0)	-	-	-	1 (2.2)	-
悪性黒色腫	1 (2.0)	-	-	-	1 (2.2)	-
消化器の良性新生物	1 (2.0)	-	-	-	-	1 (2.2)
Total Number of AEs	3	0	0	0	2	1
生殖系および乳房障害						
Total Pts With at Least one AE	2 (3.9)	1 (2.0)	1 (2.1)	0	0	0
前立腺炎	1 (2.0)	1 (2.0)	-	-	-	-
直腸瘤	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	2	1	1	0	0	0
内分泌障害						
Total Pts With at Least one AE	2 (3.9)	1 (2.0)	0	1 (2.1)	0	0
クッシング様症状	2 (3.9)	1 (2.0)	-	1 (2.1)	-	-
Total Number of AEs	2	1	0	1	0	0
免疫系障害						
Total Pts With at Least one AE	2 (3.9)	1 (2.0)	0	1 (2.1)	0	0
節足動物咬傷アレルギー	1 (2.0)	1 (2.0)	-	-	-	-
薬物過敏症	1 (2.0)	-	-	1 (2.1)	-	-
Total Number of AEs	2	1	0	1	0	0
外科および内科処置						
Total Pts With at Least one AE	1 (2.0)	0	1 (2.1)	0	0	0
縫合	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	1	0	1	0	0	0
血液およびリンパ系障害						
Total Pts With at Least one AE	1 (2.0)	1 (2.0)	0	0	0	0
白血球増加症	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	1	1	0	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
No. of Pts treated in each period	100	100	93	87	84	82
ALL BODY SYSTEMS						
Total Pts with at Least one AE	98 (98.0)	78 (78.0)	68 (73.1)	59 (67.8)	51 (60.7)	21 (25.6)
Total Number of AEs	713	279	170	137	93	34
感染症および寄生虫症						
Total Pts With at Least one AE	75 (75.0)	38 (38.0)	34 (36.6)	22 (25.3)	16 (19.0)	6 (7.3)
鼻咽頭炎	29 (29.0)	11 (11.0)	8 (8.6)	7 (8.0)	3 (3.6)	-
上気道感染	10 (10.0)	4 (4.0)	3 (3.2)	2 (2.3)	1 (1.2)	-
尿路感染	10 (10.0)	4 (4.0)	2 (2.2)	1 (1.1)	2 (2.4)	1 (1.2)
気管支炎	8 (8.0)	1 (1.0)	2 (2.2)	1 (1.1)	3 (3.6)	1 (1.2)
膀胱炎	7 (7.0)	4 (4.0)	3 (3.2)	-	-	-
鼻炎	6 (6.0)	3 (3.0)	1 (1.1)	1 (1.1)	-	1 (1.2)
帯状疱疹	5 (5.0)	1 (1.0)	2 (2.2)	-	2 (2.4)	-
咽頭炎	4 (4.0)	1 (1.0)	1 (1.1)	1 (1.1)	1 (1.2)	-
結膜炎	4 (4.0)	1 (1.0)	1 (1.1)	2 (2.3)	-	-
口腔ヘルペス	4 (4.0)	4 (4.0)	-	-	-	-
皮膚真菌感染	4 (4.0)	3 (3.0)	-	-	1 (1.2)	-
ウイルス性胃腸炎	3 (3.0)	1 (1.0)	1 (1.1)	-	-	1 (1.2)
胃腸炎	3 (3.0)	1 (1.0)	1 (1.1)	-	-	1 (1.2)
下気道感染	3 (3.0)	2 (2.0)	1 (1.1)	-	-	-
喉頭炎	3 (3.0)	1 (1.0)	-	1 (1.1)	-	1 (1.2)
消化管感染	3 (3.0)	1 (1.0)	2 (2.2)	-	-	-
副鼻腔炎	3 (3.0)	2 (2.0)	1 (1.1)	-	-	-
インフルエンザ	2 (2.0)	-	-	2 (2.3)	-	-
外陰部腔カンジダ症	2 (2.0)	-	1 (1.1)	-	1 (1.2)	-
口腔カンジダ症	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
歯肉炎	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
丹毒	2 (2.0)	-	2 (2.2)	-	-	-
爪囲炎	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
膿疱性皮膚疹	2 (2.0)	-	2 (2.2)	-	-	-
ウイルス性咽頭炎	1 (1.0)	-	-	-	1 (1.2)	-
ウイルス性上気道感染	1 (1.0)	-	-	1 (1.1)	-	-
ヘモフィルス性肺炎	1 (1.0)	-	-	1 (1.1)	-	-
ヘルペスウイルス感染	1 (1.0)	-	1 (1.1)	-	-	-
外陰腔真菌感染	1 (1.0)	1 (1.0)	-	-	-	-
感染性小腸結腸炎	1 (1.0)	-	-	1 (1.1)	-	-
眼部単純ヘルペス	1 (1.0)	1 (1.0)	-	-	-	-
気管炎	1 (1.0)	1 (1.0)	-	-	-	-
限局性感染	1 (1.0)	-	1 (1.1)	-	-	-
菌感染	1 (1.0)	-	1 (1.1)	-	-	-
菌膿瘍	1 (1.0)	-	-	-	1 (1.2)	-
耳感染	1 (1.0)	1 (1.0)	-	-	-	-
真菌感染	1 (1.0)	-	1 (1.1)	-	-	-
腎盂腎炎	1 (1.0)	-	-	1 (1.1)	-	-
創傷感染	1 (1.0)	-	-	1 (1.1)	-	-
単純ヘルペス	1 (1.0)	-	-	-	1 (1.2)	-
中耳炎	1 (1.0)	-	1 (1.1)	-	-	-
爪真菌症	1 (1.0)	-	-	-	-	1 (1.2)
乳房蜂巣炎	1 (1.0)	-	-	-	1 (1.2)	-
乳様突起炎	1 (1.0)	-	1 (1.1)	-	-	-
尿路性敗血症	1 (1.0)	-	-	-	1 (1.2)	-
敗血症	1 (1.0)	-	-	1 (1.1)	-	-
肺炎	1 (1.0)	1 (1.0)	-	-	-	-

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 04OCT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
麦粒腫	1 (1.0)	1 (1.0)	-	-	-	-
皮膚カンジダ	1 (1.0)	-	-	-	1 (1.2)	-
皮膚細菌感染	1 (1.0)	-	1 (1.1)	-	-	-
蜂巣炎	1 (1.0)	-	-	1 (1.1)	-	-
慢性副鼻腔炎	1 (1.0)	1 (1.0)	-	-	-	-
迷路炎	1 (1.0)	-	-	-	-	1 (1.2)
毛包炎	1 (1.0)	-	1 (1.1)	-	-	-
咬傷感染	1 (1.0)	-	1 (1.1)	-	-	-
Total Number of AEs	154	54	45	26	21	8
筋骨格系および結合組織障害						
Total Pts With at Least one AE	63 (63.0)	28 (28.0)	23 (24.7)	24 (27.6)	12 (14.3)	10 (12.2)
背部痛	14 (14.0)	8 (8.0)	2 (2.2)	-	2 (2.4)	2 (2.4)
関節痛	13 (13.0)	1 (1.0)	3 (3.2)	4 (4.6)	3 (3.6)	2 (2.4)
筋骨格痛	12 (12.0)	3 (3.0)	5 (5.4)	3 (3.4)	1 (1.2)	-
筋肉痛	9 (9.0)	2 (2.0)	4 (4.3)	2 (2.3)	-	1 (1.2)
四肢痛	8 (8.0)	2 (2.0)	3 (3.2)	1 (1.1)	2 (2.4)	-
変形性関節症	7 (7.0)	1 (1.0)	1 (1.1)	1 (1.1)	1 (1.2)	3 (3.7)
頸部痛	6 (6.0)	2 (2.0)	-	3 (3.4)	-	1 (1.2)
筋骨格硬直	4 (4.0)	1 (1.0)	-	2 (2.3)	1 (1.2)	-
筋痙縮	4 (4.0)	4 (4.0)	-	-	-	-
腱炎	4 (4.0)	2 (2.0)	-	1 (1.1)	1 (1.2)	-
顎痛	3 (3.0)	3 (3.0)	-	-	-	-
関節炎	3 (3.0)	-	2 (2.2)	1 (1.1)	-	-
関節硬直	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
関節腫脹	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
筋力低下	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
肩回旋筋腱板症候群	2 (2.0)	-	-	1 (1.1)	1 (1.2)	-
骨減少症	2 (2.0)	2 (2.0)	-	-	-	-
側腹部痛	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
足底筋膜炎	2 (2.0)	-	-	1 (1.1)	1 (1.2)	-
変形性脊椎症	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
ミオパチー	1 (1.0)	-	1 (1.1)	-	-	-
滑液包炎	1 (1.0)	1 (1.0)	-	-	-	-
関節周囲炎	1 (1.0)	-	-	1 (1.1)	-	-
関節障害	1 (1.0)	-	-	-	-	1 (1.2)
筋緊張	1 (1.0)	-	1 (1.1)	-	-	-
筋骨格系胸痛	1 (1.0)	-	1 (1.1)	-	-	-
骨粗鬆症	1 (1.0)	-	-	-	1 (1.2)	-
骨端症	1 (1.0)	-	1 (1.1)	-	-	-
四肢不快感	1 (1.0)	-	-	1 (1.1)	-	-
斜頸	1 (1.0)	1 (1.0)	-	-	-	-
出血性関節症	1 (1.0)	-	-	-	1 (1.2)	-
脊柱管狭窄症	1 (1.0)	-	-	-	-	1 (1.2)
脊椎炎	1 (1.0)	1 (1.0)	-	-	-	-
脊椎痛	1 (1.0)	-	-	1 (1.1)	-	-
椎間板突出	1 (1.0)	-	1 (1.1)	-	-	-
腱痛	1 (1.0)	-	1 (1.1)	-	-	-
Total Number of AEs	119	37	28	27	16	11

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
神経系障害						
Total Pts With at Least one AE	43 (43.0)	24 (24.0)	17 (18.3)	3 (3.4)	7 (8.3)	2 (2.4)
頭痛	27 (27.0)	16 (16.0)	8 (8.6)	2 (2.3)	1 (1.2)	-
浮動性めまい	6 (6.0)	4 (4.0)	1 (1.1)	-	1 (1.2)	-
錯感覚	4 (4.0)	-	1 (1.1)	1 (1.1)	2 (2.4)	-
感覚鈍麻	3 (3.0)	1 (1.0)	-	-	1 (1.2)	1 (1.2)
傾眠	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
坐骨神経痛	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
知覚過敏	2 (2.0)	-	1 (1.1)	-	1 (1.2)	-
片頭痛	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
ジスキネジア	1 (1.0)	-	1 (1.1)	-	-	-
異常感覚	1 (1.0)	-	1 (1.1)	-	-	-
起立不耐性	1 (1.0)	1 (1.0)	-	-	-	-
蟻走感	1 (1.0)	-	-	-	1 (1.2)	-
健忘	1 (1.0)	-	1 (1.1)	-	-	-
失神	1 (1.0)	-	1 (1.1)	-	-	-
灼熱感	1 (1.0)	-	1 (1.1)	-	-	-
手根管症候群	1 (1.0)	-	1 (1.1)	-	-	-
神経変性障害	1 (1.0)	-	1 (1.1)	-	-	-
多発ニューロパチー	1 (1.0)	-	-	-	-	1 (1.2)
肋間神経痛	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	59	26	20	3	8	2
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	37 (37.0)	20 (20.0)	8 (8.6)	12 (13.8)	2 (2.4)	3 (3.7)
末梢性浮腫	16 (16.0)	4 (4.0)	3 (3.2)	8 (9.2)	-	1 (1.2)
疲労	8 (8.0)	6 (6.0)	1 (1.1)	-	1 (1.2)	-
無力症	5 (5.0)	2 (2.0)	1 (1.1)	2 (2.3)	-	-
末梢腫脹	4 (4.0)	2 (2.0)	1 (1.1)	-	-	1 (1.2)
倦怠感	3 (3.0)	3 (3.0)	-	-	-	-
腫脹	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
嚢胞	2 (2.0)	-	1 (1.1)	-	-	1 (1.2)
浮腫	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
歩行障害	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
冷感	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
インフルエンザ様疾患	1 (1.0)	1 (1.0)	-	-	-	-
悪寒	1 (1.0)	1 (1.0)	-	-	-	-
胸痛	1 (1.0)	1 (1.0)	-	-	-	-
胸部不快感	1 (1.0)	-	1 (1.1)	-	-	-
重力性浮腫	1 (1.0)	1 (1.0)	-	-	-	-
注射部位血腫	1 (1.0)	-	1 (1.1)	-	-	-
注射部位出血	1 (1.0)	1 (1.0)	-	-	-	-
熱感	1 (1.0)	-	-	-	1 (1.2)	-
発熱	1 (1.0)	-	-	1 (1.1)	-	-
非心臓性胸痛	1 (1.0)	1 (1.0)	-	-	-	-
歩行不能	1 (1.0)	-	1 (1.1)	-	-	-
薬物不耐性	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	58	28	11	13	3	3

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
胃腸障害						
Total Pts With at Least one AE	36 (36.0)	24 (24.0)	7 (7.5)	7 (8.0)	6 (7.1)	0
下痢	12 (12.0)	8 (8.0)	-	4 (4.6)	-	-
悪心	8 (8.0)	4 (4.0)	2 (2.2)	2 (2.3)	-	-
口腔内潰瘍形成	3 (3.0)	-	-	1 (1.1)	2 (2.4)	-
歯痛	3 (3.0)	1 (1.0)	1 (1.1)	-	1 (1.2)	-
上腹部痛	3 (3.0)	2 (2.0)	-	-	1 (1.2)	-
腹痛	3 (3.0)	2 (2.0)	-	-	1 (1.2)	-
胃炎	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
胃食道逆流性疾患	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
口内乾燥	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
嘔吐	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
齦歯	2 (2.0)	2 (2.0)	-	-	-	-
アフタ性潰瘍	1 (1.0)	1 (1.0)	-	-	-	-
亜イレウス	1 (1.0)	1 (1.0)	-	-	-	-
鼓腸	1 (1.0)	-	-	1 (1.1)	-	-
歯の脱落	1 (1.0)	1 (1.0)	-	-	-	-
歯肉退縮	1 (1.0)	-	-	-	1 (1.2)	-
歯肉潰瘍	1 (1.0)	1 (1.0)	-	-	-	-
舌苔	1 (1.0)	1 (1.0)	-	-	-	-
舌痛	1 (1.0)	1 (1.0)	-	-	-	-
大腸炎	1 (1.0)	-	1 (1.1)	-	-	-
腸憩室	1 (1.0)	-	1 (1.1)	-	-	-
腹部不快感	1 (1.0)	-	1 (1.1)	-	-	-
腹部膨満	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	54	30	9	9	6	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	33 (33.0)	14 (14.0)	15 (16.1)	8 (9.2)	4 (4.8)	1 (1.2)
発疹	7 (7.0)	3 (3.0)	-	2 (2.3)	1 (1.2)	1 (1.2)
脱毛症	5 (5.0)	2 (2.0)	1 (1.1)	2 (2.3)	-	-
紅斑	3 (3.0)	-	2 (2.2)	1 (1.1)	-	-
多汗症	3 (3.0)	2 (2.0)	-	1 (1.1)	-	-
そう痒症	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
アレルギー性皮膚炎	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
乾癬	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
湿疹	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
皮膚炎	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
皮膚乾燥	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
ざ瘡	1 (1.0)	-	1 (1.1)	-	-	-
ざ瘡様皮膚炎	1 (1.0)	-	1 (1.1)	-	-	-
びまん性脱毛症	1 (1.0)	-	1 (1.1)	-	-	-
結節性紅斑	1 (1.0)	1 (1.0)	-	-	-	-
光線過敏性反応	1 (1.0)	-	-	1 (1.1)	-	-
光線角化症	1 (1.0)	-	1 (1.1)	-	-	-
紅斑性皮疹	1 (1.0)	-	1 (1.1)	-	-	-
寝汗	1 (1.0)	1 (1.0)	-	-	-	-
接触性皮膚炎	1 (1.0)	-	-	-	1 (1.2)	-
全身性そう痒症	1 (1.0)	-	1 (1.1)	-	-	-
全身性皮疹	1 (1.0)	-	1 (1.1)	-	-	-
爪線状隆起	1 (1.0)	-	1 (1.1)	-	-	-
点状出血	1 (1.0)	1 (1.0)	-	-	-	-
皮膚亀裂	1 (1.0)	-	-	-	1 (1.2)	-
皮膚疼痛	1 (1.0)	-	1 (1.1)	-	-	-
嵌入爪	1 (1.0)	1 (1.0)	-	-	-	-
蕁麻疹	1 (1.0)	-	-	1 (1.1)	-	-
Total Number of AEs	47	15	16	10	5	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 04OCT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
傷害、中毒および処置合併症						
Total Pts With at Least one AE	26 (26.0)	12 (12.0)	6 (6.5)	5 (5.7)	6 (7.1)	1 (1.2)
転倒	7 (7.0)	3 (3.0)	-	1 (1.1)	2 (2.4)	1 (1.2)
挫傷	4 (4.0)	1 (1.0)	-	1 (1.1)	1 (1.2)	1 (1.2)
歯牙破折	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
節足動物咬傷	2 (2.0)	-	1 (1.1)	1 (1.1)	-	-
裂傷	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
アルコール中毒	1 (1.0)	-	-	-	1 (1.2)	-
ストレス骨折	1 (1.0)	-	1 (1.1)	-	-	-
眼窩周囲血腫	1 (1.0)	-	-	1 (1.1)	-	-
顔面損傷	1 (1.0)	-	-	-	1 (1.2)	-
筋断裂	1 (1.0)	-	-	1 (1.1)	-	-
腰椎骨折	1 (1.0)	1 (1.0)	-	-	-	-
骨挫傷	1 (1.0)	-	1 (1.1)	-	-	-
手骨折	1 (1.0)	1 (1.0)	-	-	-	-
上顎炎	1 (1.0)	-	1 (1.1)	-	-	-
脊椎圧迫骨折	1 (1.0)	-	-	1 (1.1)	-	-
創傷	1 (1.0)	1 (1.0)	-	-	-	-
足骨折	1 (1.0)	1 (1.0)	-	-	-	-
注射に伴う反応	1 (1.0)	-	1 (1.1)	-	-	-
半月板損傷	1 (1.0)	-	1 (1.1)	-	-	-
皮下血腫	1 (1.0)	1 (1.0)	-	-	-	-
皮膚化学熱傷	1 (1.0)	1 (1.0)	-	-	-	-
肋骨骨折	1 (1.0)	1 (1.0)	-	-	-	-
腱断裂	1 (1.0)	1 (1.0)	-	-	-	-
靭帯捻挫	1 (1.0)	-	-	-	1 (1.2)	-
Total Number of AEs	36	14	6	6	8	2
血管障害						
Total Pts With at Least one AE	23 (23.0)	14 (14.0)	2 (2.2)	4 (4.6)	3 (3.6)	2 (2.4)
高血圧	12 (12.0)	8 (8.0)	1 (1.1)	-	2 (2.4)	1 (1.2)
血腫	5 (5.0)	3 (3.0)	-	1 (1.1)	1 (1.2)	-
深部静脈血栓症	3 (3.0)	1 (1.0)	1 (1.1)	1 (1.1)	-	-
高血圧クリーゼ	2 (2.0)	1 (1.0)	-	-	-	1 (1.2)
レイノー現象	1 (1.0)	-	-	1 (1.1)	-	-
側頭動脈炎	1 (1.0)	-	-	1 (1.1)	-	-
低血圧	1 (1.0)	-	1 (1.1)	-	-	-
表在性血栓性静脈炎	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	26	14	3	4	3	2

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
臨床検査						
Total Pts With at Least one AE	23 (23.0)	10 (10.0)	2 (2.2)	13 (14.9)	1 (1.2)	0
アラニンアミノトランスフェラーゼ増加	5 (5.0)	2 (2.0)	-	3 (3.4)	-	-
アスパラギン酸アミノトランスフェラーゼ増加	4 (4.0)	1 (1.0)	-	3 (3.4)	-	-
肝酵素上昇	4 (4.0)	3 (3.0)	-	1 (1.1)	-	-
体重増加	3 (3.0)	-	1 (1.1)	1 (1.1)	1 (1.2)	-
補体成分C3減少	3 (3.0)	3 (3.0)	-	-	-	-
眼圧上昇	2 (2.0)	2 (2.0)	-	-	-	-
血圧上昇	2 (2.0)	-	-	2 (2.3)	-	-
血中クレアチンホスホキナーゼ増加	2 (2.0)	-	-	2 (2.3)	-	-
補体成分C4減少	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
トランスアミナーゼ上昇	1 (1.0)	-	-	1 (1.1)	-	-
ヘモグロビン減少	1 (1.0)	-	-	1 (1.1)	-	-
血中クレアチニン増加	1 (1.0)	-	-	1 (1.1)	-	-
血中ビリルビン増加	1 (1.0)	-	-	1 (1.1)	-	-
血中甲状腺刺激ホルモン減少	1 (1.0)	1 (1.0)	-	-	-	-
体重減少	1 (1.0)	-	1 (1.1)	-	-	-
Total Number of AEs	33	13	2	17	1	0
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	22 (22.0)	7 (7.0)	5 (5.4)	6 (6.9)	7 (8.3)	1 (1.2)
口腔咽頭痛	7 (7.0)	4 (4.0)	-	2 (2.3)	1 (1.2)	-
咳嗽	6 (6.0)	-	2 (2.2)	1 (1.1)	3 (3.6)	-
呼吸困難	3 (3.0)	1 (1.0)	-	1 (1.1)	1 (1.2)	-
鼻出血	3 (3.0)	1 (1.0)	1 (1.1)	-	-	1 (1.2)
肺塞栓症	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
アレルギー性鼻炎	1 (1.0)	-	-	-	1 (1.2)	-
間質性肺疾患	1 (1.0)	-	-	1 (1.1)	-	-
胸水	1 (1.0)	-	-	-	1 (1.2)	-
鼻茸	1 (1.0)	-	1 (1.1)	-	-	-
鼻潰瘍	1 (1.0)	-	-	-	1 (1.2)	-
労作性呼吸困難	1 (1.0)	-	-	1 (1.1)	-	-
Total Number of AEs	27	7	5	6	8	1
眼障害						
Total Pts With at Least one AE	18 (18.0)	8 (8.0)	6 (6.5)	0	5 (6.0)	0
白内障	5 (5.0)	2 (2.0)	2 (2.2)	-	1 (1.2)	-
眼瞼炎	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
霧視	2 (2.0)	2 (2.0)	-	-	-	-
眼乾燥	1 (1.0)	1 (1.0)	-	-	-	-
眼充血	1 (1.0)	-	1 (1.1)	-	-	-
眼出血	1 (1.0)	-	-	-	1 (1.2)	-
眼痛	1 (1.0)	1 (1.0)	-	-	-	-
強膜炎	1 (1.0)	-	-	-	1 (1.2)	-
結膜出血	1 (1.0)	-	1 (1.1)	-	-	-
視力障害	1 (1.0)	-	-	-	1 (1.2)	-
虹彩炎	1 (1.0)	-	1 (1.1)	-	-	-
虹彩毛様体炎	1 (1.0)	1 (1.0)	-	-	-	-
網膜剥離	1 (1.0)	-	-	-	1 (1.2)	-
Total Number of AEs	19	8	6	0	5	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
精神障害						
Total Pts With at Least one AE	12 (12.0)	8 (8.0)	4 (4.3)	5 (5.7)	0	0
不眠症	4 (4.0)	3 (3.0)	1 (1.1)	-	-	-
うつ病	3 (3.0)	-	1 (1.1)	2 (2.3)	-	-
不安	3 (3.0)	-	1 (1.1)	2 (2.3)	-	-
ストレス	1 (1.0)	1 (1.0)	-	-	-	-
激越	1 (1.0)	1 (1.0)	-	-	-	-
錯乱状態	1 (1.0)	1 (1.0)	-	-	-	-
初期不眠症	1 (1.0)	1 (1.0)	-	-	-	-
身体症状症	1 (1.0)	-	-	1 (1.1)	-	-
睡眠障害	1 (1.0)	-	1 (1.1)	-	-	-
抑うつ気分	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	17	8	4	5	0	0
代謝および栄養障害						
Total Pts With at Least one AE	10 (10.0)	6 (6.0)	2 (2.2)	1 (1.1)	1 (1.2)	0
高コレステロール血症	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
食欲減退	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
糖尿病	2 (2.0)	2 (2.0)	-	-	-	-
高脂血症	1 (1.0)	1 (1.0)	-	-	-	-
食欲亢進	1 (1.0)	-	-	-	1 (1.2)	-
痛風	1 (1.0)	1 (1.0)	-	-	-	-
低ナトリウム血症	1 (1.0)	-	-	1 (1.1)	-	-
Total Number of AEs	10	6	2	1	1	0
血液およびリンパ系障害						
Total Pts With at Least one AE	8 (8.0)	3 (3.0)	3 (3.2)	3 (3.4)	0	1 (1.2)
好中球減少症	4 (4.0)	2 (2.0)	-	2 (2.3)	-	-
白血球減少症	4 (4.0)	-	3 (3.2)	1 (1.1)	-	-
貧血	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
リンパ球減少症	1 (1.0)	1 (1.0)	-	-	-	-
白血球増加症	1 (1.0)	-	-	1 (1.1)	-	-
貪食細胞性組織球症	1 (1.0)	-	-	-	-	1 (1.2)
Total Number of AEs	13	4	3	5	0	1
心臓障害						
Total Pts With at Least one AE	8 (8.0)	4 (4.0)	3 (3.2)	2 (2.3)	0	0
心房細動	2 (2.0)	1 (1.0)	1 (1.1)	-	-	-
動悸	2 (2.0)	2 (2.0)	-	-	-	-
徐脈	1 (1.0)	-	1 (1.1)	-	-	-
上室性頻脈	1 (1.0)	-	1 (1.1)	-	-	-
大動脈弁狭窄	1 (1.0)	-	-	1 (1.1)	-	-
頻脈	1 (1.0)	-	-	1 (1.1)	-	-
頻脈性不整脈	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	9	4	3	2	0	0
耳および迷路障害						
Total Pts With at Least one AE	7 (7.0)	2 (2.0)	3 (3.2)	1 (1.1)	0	2 (2.4)
回転性めまい	2 (2.0)	-	2 (2.2)	-	-	-
耳痛	2 (2.0)	1 (1.0)	-	-	-	1 (1.2)
頭位性回転性めまい	2 (2.0)	1 (1.0)	-	1 (1.1)	-	-
聴力低下	1 (1.0)	-	-	-	-	1 (1.2)
両耳難聴	1 (1.0)	-	1 (1.1)	-	-	-
Total Number of AEs	8	2	3	1	0	2

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ QW + 26 Week Prednisone Taper (N=100)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
腎および尿路障害						
Total Pts With at Least one AE	7 (7.0)	3 (3.0)	3 (3.2)	1 (1.1)	0	0
排尿困難	3 (3.0)	2 (2.0)	1 (1.1)	-	-	-
多尿	1 (1.0)	1 (1.0)	-	-	-	-
尿意切迫	1 (1.0)	-	1 (1.1)	-	-	-
頻尿	1 (1.0)	-	1 (1.1)	-	-	-
慢性腎臓病	1 (1.0)	-	-	1 (1.1)	-	-
Total Number of AEs	7	3	3	1	0	0
内分泌障害						
Total Pts With at Least one AE	6 (6.0)	3 (3.0)	0	0	3 (3.6)	0
甲状腺機能低下症	2 (2.0)	1 (1.0)	-	-	1 (1.2)	-
クッシング症候群	1 (1.0)	1 (1.0)	-	-	-	-
クッシング様症状	1 (1.0)	1 (1.0)	-	-	-	-
甲状腺腫	1 (1.0)	-	-	-	1 (1.2)	-
副腎機能不全	1 (1.0)	-	-	-	1 (1.2)	-
Total Number of AEs	6	3	0	0	3	0
生殖系および乳房障害						
Total Pts With at Least one AE	5 (5.0)	2 (2.0)	1 (1.1)	0	2 (2.4)	0
前立腺炎	1 (1.0)	-	1 (1.1)	-	-	-
乳房圧痛	1 (1.0)	-	-	-	1 (1.2)	-
勃起不全	1 (1.0)	1 (1.0)	-	-	-	-
膣出血	1 (1.0)	1 (1.0)	-	-	-	-
膣分泌物	1 (1.0)	-	-	-	1 (1.2)	-
Total Number of AEs	5	2	1	0	2	0
免疫系障害						
Total Pts With at Least one AE	2 (2.0)	0	0	1 (1.1)	1 (1.2)	0
季節性アレルギー	1 (1.0)	-	-	-	1 (1.2)	-
薬物過敏症	1 (1.0)	-	-	1 (1.1)	-	-
Total Number of AEs	2	0	0	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）						
Total Pts With at Least one AE	2 (2.0)	0	0	0	2 (2.4)	0
神経腫	1 (1.0)	-	-	-	1 (1.2)	-
辺縁帯リンパ腫	1 (1.0)	-	-	-	1 (1.2)	-
Total Number of AEs	2	0	0	0	2	0
外科および内科処置						
Total Pts With at Least one AE	1 (1.0)	0	0	0	0	1 (1.2)
抜歯	1 (1.0)	-	-	-	-	1 (1.2)
Total Number of AEs	1	0	0	0	0	1
製品の問題						
Total Pts With at Least one AE	1 (1.0)	1 (1.0)	0	0	0	0
医療機器破損	1 (1.0)	1 (1.0)	-	-	-	-
Total Number of AEs	1	1	0	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 04OCT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
No. of Pts treated in each period	49	49	48	44	41	40
ALL BODY SYSTEMS						
Total Pts with at Least one AE	47 (95.9)	39 (79.6)	33 (68.8)	33 (75.0)	25 (61.0)	12 (30.0)
Total Number of AEs	384	159	77	76	57	15
感染症および寄生虫症						
Total Pts With at Least one AE	36 (73.5)	19 (38.8)	10 (20.8)	15 (34.1)	9 (22.0)	3 (7.5)
鼻咽頭炎	12 (24.5)	6 (12.2)	2 (4.2)	3 (6.8)	1 (2.4)	-
上気道感染	6 (12.2)	2 (4.1)	3 (6.3)	1 (2.3)	-	-
口腔ヘルペス	5 (10.2)	3 (6.1)	1 (2.1)	1 (2.3)	-	-
胃腸炎	4 (8.2)	-	1 (2.1)	1 (2.3)	1 (2.4)	1 (2.5)
気管支炎	4 (8.2)	1 (2.0)	1 (2.1)	2 (4.5)	-	-
尿路感染	4 (8.2)	3 (6.1)	-	-	1 (2.4)	-
鼻炎	4 (8.2)	1 (2.0)	-	-	1 (2.4)	2 (5.0)
副鼻腔炎	4 (8.2)	1 (2.0)	-	1 (2.3)	2 (4.9)	-
ウイルス感染	2 (4.1)	-	1 (2.1)	1 (2.3)	-	-
口腔真菌感染	2 (4.1)	1 (2.0)	-	1 (2.3)	-	-
带状疱疹	2 (4.1)	-	-	1 (2.3)	1 (2.4)	-
ウイルス性上気道感染	1 (2.0)	-	1 (2.1)	-	-	-
外陰部腔カンジダ症	1 (2.0)	1 (2.0)	-	-	-	-
感染性胆管炎	1 (2.0)	-	-	1 (2.3)	-	-
気道感染	1 (2.0)	-	1 (2.1)	-	-	-
結膜炎	1 (2.0)	1 (2.0)	-	-	-	-
口腔膿瘍	1 (2.0)	-	-	1 (2.3)	-	-
喉頭炎	1 (2.0)	-	-	-	1 (2.4)	-
歯髄炎	1 (2.0)	-	-	1 (2.3)	-	-
真菌性喉頭炎	1 (2.0)	-	-	1 (2.3)	-	-
丹毒	1 (2.0)	1 (2.0)	-	-	-	-
中咽頭カンジダ症	1 (2.0)	1 (2.0)	-	-	-	-
爪囲炎	1 (2.0)	1 (2.0)	-	-	-	-
肺炎	1 (2.0)	-	-	-	1 (2.4)	-
白癬感染	1 (2.0)	-	1 (2.1)	-	-	-
麦粒腫	1 (2.0)	1 (2.0)	-	-	-	-
皮膚感染	1 (2.0)	1 (2.0)	-	-	-	-
蜂巣炎	1 (2.0)	-	-	1 (2.3)	-	-
毛包炎	1 (2.0)	-	-	-	1 (2.4)	-
腔感染	1 (2.0)	-	-	1 (2.3)	-	-
Total Number of AEs	68	25	12	18	10	3

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	28 (57.1)	9 (18.4)	10 (20.8)	16 (36.4)	4 (9.8)	4 (10.0)
関節痛	8 (16.3)	3 (6.1)	2 (4.2)	2 (4.5)	1 (2.4)	-
背部痛	7 (14.3)	4 (8.2)	1 (2.1)	2 (4.5)	-	-
筋骨格痛	6 (12.2)	1 (2.0)	1 (2.1)	3 (6.8)	1 (2.4)	-
筋痙縮	6 (12.2)	5 (10.2)	-	1 (2.3)	-	-
四肢痛	5 (10.2)	1 (2.0)	1 (2.1)	2 (4.5)	1 (2.4)	-
滑液包炎	4 (8.2)	-	2 (4.2)	1 (2.3)	1 (2.4)	-
筋肉痛	4 (8.2)	1 (2.0)	2 (4.2)	-	-	1 (2.5)
骨粗鬆症	2 (4.1)	-	-	2 (4.5)	-	-
脊椎痛	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
変形性関節症	2 (4.1)	-	-	2 (4.5)	-	-
顎痛	1 (2.0)	-	-	1 (2.3)	-	-
関節炎	1 (2.0)	-	1 (2.1)	-	-	-
関節腫脹	1 (2.0)	-	1 (2.1)	-	-	-
筋緊張	1 (2.0)	1 (2.0)	-	-	-	-
筋硬化症	1 (2.0)	-	1 (2.1)	-	-	-
筋骨格系胸痛	1 (2.0)	-	-	1 (2.3)	-	-
筋骨格硬直	1 (2.0)	-	-	-	-	1 (2.5)
頸部痛	1 (2.0)	-	1 (2.1)	-	-	-
骨減少症	1 (2.0)	-	-	-	-	1 (2.5)
斜頸	1 (2.0)	-	-	1 (2.3)	-	-
単径部痛	1 (2.0)	-	-	-	-	1 (2.5)
Total Number of AEs	57	17	14	18	4	4
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	25 (51.0)	15 (30.6)	6 (12.5)	4 (9.1)	3 (7.3)	2 (5.0)
末梢性浮腫	12 (24.5)	5 (10.2)	3 (6.3)	2 (4.5)	1 (2.4)	1 (2.5)
疲労	5 (10.2)	2 (4.1)	1 (2.1)	1 (2.3)	-	1 (2.5)
無力症	3 (6.1)	3 (6.1)	-	-	-	-
胸痛	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
注射部位そう痒感	2 (4.1)	1 (2.0)	-	1 (2.3)	-	-
注射部位反応	2 (4.1)	1 (2.0)	-	-	1 (2.4)	-
発熱	2 (4.1)	1 (2.0)	-	-	1 (2.4)	-
非心臓性胸痛	2 (4.1)	2 (4.1)	-	-	-	-
異常感	1 (2.0)	1 (2.0)	-	-	-	-
空腹	1 (2.0)	1 (2.0)	-	-	-	-
注射部位紅斑	1 (2.0)	-	-	1 (2.3)	-	-
注射部位内出血	1 (2.0)	1 (2.0)	-	-	-	-
注射部位疼痛	1 (2.0)	1 (2.0)	-	-	-	-
注射部位蕁麻疹	1 (2.0)	1 (2.0)	-	-	-	-
不快感	1 (2.0)	1 (2.0)	-	-	-	-
浮腫	1 (2.0)	1 (2.0)	-	-	-	-
末梢腫脹	1 (2.0)	1 (2.0)	-	-	-	-
疼痛	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	40	24	6	5	3	2

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	25 (51.0)	10 (20.4)	13 (27.1)	7 (15.9)	5 (12.2)	0
脱毛症	7 (14.3)	1 (2.0)	4 (8.3)	2 (4.5)	-	-
発疹	5 (10.2)	2 (4.1)	2 (4.2)	-	1 (2.4)	-
そう痒症	4 (8.2)	1 (2.0)	-	1 (2.3)	2 (4.9)	-
寝汗	3 (6.1)	1 (2.0)	1 (2.1)	-	1 (2.4)	-
皮膚乾燥	3 (6.1)	3 (6.1)	-	-	-	-
紅斑性皮疹	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
斑状出血	2 (4.1)	-	2 (4.2)	-	-	-
乾癬	1 (2.0)	-	1 (2.1)	-	-	-
顔面腫脹	1 (2.0)	1 (2.0)	-	-	-	-
光線過敏性反応	1 (2.0)	-	1 (2.1)	-	-	-
紅斑	1 (2.0)	-	-	-	1 (2.4)	-
脂腺障害	1 (2.0)	1 (2.0)	-	-	-	-
水疱	1 (2.0)	-	-	1 (2.3)	-	-
全身性皮疹	1 (2.0)	-	-	1 (2.3)	-	-
皮膚炎	1 (2.0)	-	-	-	1 (2.4)	-
皮膚出血	1 (2.0)	-	-	1 (2.3)	-	-
皮膚病変	1 (2.0)	-	1 (2.1)	-	-	-
皮膚疼痛	1 (2.0)	-	-	1 (2.3)	-	-
Total Number of AEs	37	11	13	7	6	0
神経系障害						
Total Pts With at Least one AE	22 (44.9)	15 (30.6)	7 (14.6)	5 (11.4)	5 (12.2)	0
頭痛	10 (20.4)	4 (8.2)	3 (6.3)	1 (2.3)	2 (4.9)	-
浮動性めまい	10 (20.4)	7 (14.3)	2 (4.2)	1 (2.3)	-	-
坐骨神経痛	2 (4.1)	1 (2.0)	-	1 (2.3)	-	-
錯感覚	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
意識消失	1 (2.0)	-	-	-	1 (2.4)	-
感覚障害	1 (2.0)	1 (2.0)	-	-	-	-
感覚鈍麻	1 (2.0)	1 (2.0)	-	-	-	-
傾眠	1 (2.0)	1 (2.0)	-	-	-	-
血栓性脳卒中	1 (2.0)	-	-	-	1 (2.4)	-
健忘	1 (2.0)	1 (2.0)	-	-	-	-
構語障害	1 (2.0)	1 (2.0)	-	-	-	-
三叉神経痛	1 (2.0)	-	1 (2.1)	-	-	-
手根管症候群	1 (2.0)	-	-	1 (2.3)	-	-
脊髄性跛行症	1 (2.0)	-	-	-	1 (2.4)	-
足根管症候群	1 (2.0)	1 (2.0)	-	-	-	-
注意力障害	1 (2.0)	1 (2.0)	-	-	-	-
味覚消失	1 (2.0)	-	-	1 (2.3)	-	-
Total Number of AEs	37	20	7	5	5	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
胃腸障害						
Total Pts With at Least one AE	18 (36.7)	12 (24.5)	7 (14.6)	3 (6.8)	3 (7.3)	1 (2.5)
下痢	3 (6.1)	1 (2.0)	2 (4.2)	-	-	-
上腹部痛	3 (6.1)	2 (4.1)	-	1 (2.3)	-	-
アフタ性潰瘍	2 (4.1)	1 (2.0)	-	-	-	1 (2.5)
悪心	2 (4.1)	1 (2.0)	-	-	1 (2.4)	-
胃炎	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
胃食道逆流性疾患	2 (4.1)	-	-	1 (2.3)	1 (2.4)	-
嘔吐	2 (4.1)	1 (2.0)	-	-	1 (2.4)	-
胃酸過多	1 (2.0)	-	-	1 (2.3)	-	-
胃腸出血	1 (2.0)	1 (2.0)	-	-	-	-
胃腸障害	1 (2.0)	1 (2.0)	-	-	-	-
過敏性腸症候群	1 (2.0)	-	1 (2.1)	-	-	-
口腔粘膜水泡形成	1 (2.0)	1 (2.0)	-	-	-	-
口内乾燥	1 (2.0)	1 (2.0)	-	-	-	-
歯の知覚過敏	1 (2.0)	-	1 (2.1)	-	-	-
歯肉痛	1 (2.0)	-	1 (2.1)	-	-	-
痔核	1 (2.0)	1 (2.0)	-	-	-	-
食道痙攣	1 (2.0)	-	-	-	1 (2.4)	-
大腸炎	1 (2.0)	1 (2.0)	-	-	-	-
腹部不快感	1 (2.0)	-	1 (2.1)	-	-	-
腹部膨満	1 (2.0)	-	1 (2.1)	-	-	-
便意切迫	1 (2.0)	1 (2.0)	-	-	-	-
便秘	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	31	14	9	3	4	1
眼障害						
Total Pts With at Least one AE	13 (26.5)	6 (12.2)	2 (4.2)	4 (9.1)	1 (2.4)	1 (2.5)
眼乾燥	3 (6.1)	1 (2.0)	1 (2.1)	-	1 (2.4)	-
眼そう痒症	2 (4.1)	2 (4.1)	-	-	-	-
核性白内障	1 (2.0)	-	-	-	-	1 (2.5)
眼の炎症	1 (2.0)	-	-	1 (2.3)	-	-
眼球乾燥症	1 (2.0)	-	-	1 (2.3)	-	-
虚血性視神経症	1 (2.0)	-	-	1 (2.3)	-	-
結膜出血	1 (2.0)	-	-	1 (2.3)	-	-
視力障害	1 (2.0)	1 (2.0)	-	-	-	-
視力低下	1 (2.0)	1 (2.0)	-	-	-	-
硝子体剥離	1 (2.0)	-	-	1 (2.3)	-	-
白内障	1 (2.0)	-	1 (2.1)	-	-	-
霧視	1 (2.0)	1 (2.0)	-	-	-	-
流涙増加	1 (2.0)	1 (2.0)	-	-	-	-
緑内障	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	17	8	2	5	1	1
血管障害						
Total Pts With at Least one AE	13 (26.5)	6 (12.2)	2 (4.2)	3 (6.8)	1 (2.4)	1 (2.5)
高血圧	6 (12.2)	2 (4.1)	-	2 (4.5)	1 (2.4)	1 (2.5)
血腫	3 (6.1)	2 (4.1)	1 (2.1)	-	-	-
ほてり	1 (2.0)	1 (2.0)	-	-	-	-
リンパうっ滞	1 (2.0)	1 (2.0)	-	-	-	-
乾性壊疽	1 (2.0)	-	-	1 (2.3)	-	-
側頭動脈炎	1 (2.0)	-	1 (2.1)	-	-	-
潮紅	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	14	7	2	3	1	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	11 (22.4)	5 (10.2)	3 (6.3)	1 (2.3)	5 (12.2)	1 (2.5)
呼吸困難	4 (8.2)	3 (6.1)	-	-	-	1 (2.5)
口腔咽頭痛	4 (8.2)	2 (4.1)	1 (2.1)	-	1 (2.4)	-
咳嗽	3 (6.1)	1 (2.0)	-	1 (2.3)	1 (2.4)	-
鼻漏	2 (4.1)	1 (2.0)	1 (2.1)	-	-	-
カタル	1 (2.0)	1 (2.0)	-	-	-	-
胸膜痛	1 (2.0)	-	-	-	1 (2.4)	-
好酸球性気管支炎	1 (2.0)	-	-	-	1 (2.4)	-
睡眠時無呼吸症候群	1 (2.0)	-	-	-	1 (2.4)	-
発声障害	1 (2.0)	1 (2.0)	-	-	-	-
鼻出血	1 (2.0)	-	-	-	1 (2.4)	-
鼻茸	1 (2.0)	-	1 (2.1)	-	-	-
慢性閉塞性肺疾患	1 (2.0)	-	-	-	1 (2.4)	-
喘鳴	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	22	10	3	1	7	1
傷害、中毒および処置合併症						
Total Pts With at Least one AE	10 (20.4)	5 (10.2)	1 (2.1)	2 (4.5)	3 (7.3)	0
挫傷	2 (4.1)	2 (4.1)	-	-	-	-
転倒	2 (4.1)	-	1 (2.1)	1 (2.3)	-	-
外傷性血腫	1 (2.0)	-	-	-	1 (2.4)	-
骨挫傷	1 (2.0)	1 (2.0)	-	-	-	-
処置によるめまい	1 (2.0)	-	-	1 (2.3)	-	-
頭部損傷	1 (2.0)	-	-	-	1 (2.4)	-
軟部組織損傷	1 (2.0)	1 (2.0)	-	-	-	-
肉離れ	1 (2.0)	-	-	-	1 (2.4)	-
半月板損傷	1 (2.0)	-	-	-	1 (2.4)	-
裂傷	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	12	5	1	2	4	0
精神障害						
Total Pts With at Least one AE	8 (16.3)	4 (8.2)	1 (2.1)	1 (2.3)	3 (7.3)	0
睡眠障害	3 (6.1)	3 (6.1)	-	-	-	-
うつ病	2 (4.1)	-	-	1 (2.3)	1 (2.4)	-
緊張	1 (2.0)	-	1 (2.1)	-	-	-
失見当識	1 (2.0)	-	-	-	1 (2.4)	-
不安	1 (2.0)	1 (2.0)	-	-	-	-
不眠症	1 (2.0)	-	-	-	1 (2.4)	-
Total Number of AEs	9	4	1	1	3	0
代謝および栄養障害						
Total Pts With at Least one AE	7 (14.3)	2 (4.1)	1 (2.1)	1 (2.3)	2 (4.9)	1 (2.5)
高コレステロール血症	3 (6.1)	-	-	1 (2.3)	1 (2.4)	1 (2.5)
高血糖	1 (2.0)	1 (2.0)	-	-	-	-
低カリウム血症	1 (2.0)	-	1 (2.1)	-	-	-
低ナトリウム血症	1 (2.0)	-	-	-	1 (2.4)	-
低血糖	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	7	2	1	1	2	1

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
臨床検査						
Total Pts With at Least one AE	7 (14.3)	3 (6.1)	1 (2.1)	1 (2.3)	3 (7.3)	0
アラニンアミノトランスフェラーゼ増加	2 (4.1)	1 (2.0)	-	-	1 (2.4)	-
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.0)	1 (2.0)	-	-	-	-
眼圧上昇	1 (2.0)	-	1 (2.1)	-	-	-
血圧上昇	1 (2.0)	-	-	-	1 (2.4)	-
血小板数減少	1 (2.0)	-	-	-	1 (2.4)	-
好中球数減少	1 (2.0)	-	-	1 (2.3)	-	-
体温上昇	1 (2.0)	-	-	-	1 (2.4)	-
体重増加	1 (2.0)	1 (2.0)	-	-	-	-
低比重リポ蛋白増加	1 (2.0)	1 (2.0)	-	-	-	-
白血球数減少	1 (2.0)	-	-	1 (2.3)	-	-
補体成分C3減少	1 (2.0)	1 (2.0)	-	-	-	-
補体成分C4減少	1 (2.0)	-	-	1 (2.3)	-	-
Total Number of AEs	13	5	1	3	4	0
耳および迷路障害						
Total Pts With at Least one AE	4 (8.2)	2 (4.1)	0	1 (2.3)	1 (2.4)	0
耳痛	2 (4.1)	-	-	1 (2.3)	1 (2.4)	-
回転性めまい	1 (2.0)	1 (2.0)	-	-	-	-
耳鳴	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	4	2	0	1	1	0
心臓障害						
Total Pts With at Least one AE	3 (6.1)	2 (4.1)	0	0	0	1 (2.5)
動悸	2 (4.1)	2 (4.1)	-	-	-	-
心房頻脈	1 (2.0)	-	-	-	-	1 (2.5)
Total Number of AEs	3	2	0	0	0	1
生殖系および乳房障害						
Total Pts With at Least one AE	3 (6.1)	1 (2.0)	1 (2.1)	2 (4.5)	0	0
陰部そう痒症	1 (2.0)	1 (2.0)	-	-	-	-
女性化乳房	1 (2.0)	-	-	1 (2.3)	-	-
乳房痛	1 (2.0)	-	1 (2.1)	-	-	-
不正子宮出血	1 (2.0)	-	-	1 (2.3)	-	-
Total Number of AEs	4	1	1	2	0	0
免疫系障害						
Total Pts With at Least one AE	3 (6.1)	0	2 (4.2)	0	1 (2.4)	0
過敏症	1 (2.0)	-	1 (2.1)	-	-	-
節足動物咬傷アレルギー	1 (2.0)	-	1 (2.1)	-	-	-
薬物過敏症	1 (2.0)	-	-	-	1 (2.4)	-
Total Number of AEs	3	0	2	0	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）						
Total Pts With at Least one AE	3 (6.1)	2 (4.1)	0	1 (2.3)	0	0
脂漏性角化症	1 (2.0)	1 (2.0)	-	-	-	-
大腸腺腫	1 (2.0)	-	-	1 (2.3)	-	-
卵巣腺腫	1 (2.0)	1 (2.0)	-	-	-	-
Total Number of AEs	3	2	0	1	0	0
外科および内科処置						
Total Pts With at Least one AE	1 (2.0)	0	0	0	1 (2.4)	0
皮膚新生物切除	1 (2.0)	-	-	-	1 (2.4)	-
Total Number of AEs	1	0	0	0	1	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

t_ae_period_sp Adverse Events by Time Period (New Onset) (WA28119)
 Protocol: WA28119
 Analysis: SAFETY

Treatment: TCZ Q2W + 26 Week Prednisone Taper (N=49)

Body System/ Adverse Event	Total No. (%)	Week0-<12 No. (%)	Week12-<24 No. (%)	Week24-<36 No. (%)	Week36-<48 No. (%)	Week48- No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	1 (2.0)	0	1 (2.1)	0	0	0
血小板減少症	1 (2.0)	-	1 (2.1)	-	-	-
好中球減少症	1 (2.0)	-	1 (2.1)	-	-	-
Total Number of AEs	2	0	2	0	0	0

Investigator text for AEs is coded using MedDRA version 19.0.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632d/t_ae_period.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632d/reports/t_ae_period_sp.out
 040CT2016 17:53

表 2.7.4.8-11 重篤な有害事象一覧 (MRA632JP 試験-二重盲検期間)

aeI02_saeI_ap Listing of Serious Adverse Events
 Protocol: MRA632JP
 Analysis: All Population

Treatment: PLACEBO (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Adverse Event (Investigators text)	Serious?	Day of Onset	Duration in Days	During 24hr from Injection	Injection Site Reaction	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1274/60904	68	M	56.8	出血性ショック	Yes	160	1	No	No	SEVERE	No	RECOVERED/RESOLVED	No	DOSE NOT CHANGED
				出血性胃潰瘍	Yes	160	33	No	No	SEVERE	No	RECOVERED/RESOLVED	Yes	DRUG INTERRUPTED
1280/61202	29	F	43.3	白内障	Yes	15	>64	No	No	MODERATE	No	NOT RECOVERED/NOT RESOLVED	Yes	DOSE NOT CHANGED

CRTN = Clinical Research Task Number (center no.)

'?' = At least one date is missing or invalid.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aeI02.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aeI02_saeI_ap.out
 28DEC2015 18:14

aeI02_saeI_ap Listing of Serious Adverse Events
 Protocol: MRA632JP
 Analysis: All Population

Treatment: MRA-SC 162mg/w (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Adverse Event (Investigators text)	Serious?	Day of Onset	Duration in Days	During 24hr from Injection	Injection Site Reaction	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1273/60801 白内障	66	F	64.4	ステロイド性白内障の悪 化	Yes	73	>124	No	No	MODERATE	No	NOT RECOVERED/NOT RESOLVED	No	DOSE NOT CHANGED

CRTN = Clinical Research Task Number (center no.)

'?' = At least one date is missing or invalid.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/aeI02.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/aeI02_saeI_ap.out
 28DEC2015 18:14

Page 2 of 2

[5.3.5.1-1 表 15.3.2-4を再掲]

表 2.7.4.8-12 重篤な有害事象一覧 (MRA632JP 試験-全期間)

ae103_mt_ap Listing of Serious Adverse Events
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: PLACEBO (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Adverse Event (Investigators text)	Day of onset from MRA-SC 1st injection	Duration in Days	Period	During 24hr from Injection	Injection Site Reaction	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1267/60301	17	F	53.1	複合性局所疼痛候群	372	>9	OPEN	No	No	SEVERE	Yes	2	Yes	1
1268/60401	23	F	45.7	急性腎盂腎炎	494	>20	OPEN	No	No	SEVERE	Yes	2	Yes	2
1268/60402	26	F	72.9	肺炎	373	>15	OPEN	No	No	MODERATE	Yes	2	Yes	2
1269/60501	36	F	44.1	齲歯	236	>326	OPEN	No	No	MODERATE	No	2	Yes	1
1269/60502	21	F	55.5	多発肺梗塞	338	>127	OPEN	No	No	MODERATE	No	2	Yes	2
1274/60904	68	M	56.8	出血性ショック	-66	1	DB	No	No	SEVERE	No	5	No	1
				出血性胃潰瘍	-66	33	DB	No	No	SEVERE	No	5	Yes	2

CRTN = Clinical Research Task Number (center no.)

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Outcome: 1 = FATAL; 2 = NOT RECOVERED/NOT RESOLVED; 3 = RECOVERED/RESOLVED WITH SEQUELAE; 4 = RECOVERING/RESOLVING; 5 = RECOVERED/RESOLVED; 6 =UNKNOWN;

Discontinued or Dose Adjusted: 1 = DOSE NOT CHANGED; 2 = DRUG INTERRUPTED; 3 = DRUG WITHDRAWN; 4 = NOT APPLICABLE; 5 =UNKNOWN;

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/ae103.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/ae103_mt_ap.out
 23JAN2017 10:22

ae103_mt_ap Listing of Serious Adverse Events
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: PLACEBO (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Adverse Event (Investigators text)	Day of onset from MRA-SC 1st injection	Duration in Days	Period	During 24hr from Injection	Injection Site Reaction	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1280/61202 白内障	29	F	43.3	ステロイド性白内障の悪化	-77	162	DB	No	No	MODERATE	No	5	Yes	1

CRTN = Clinical Research Task Number (center no.)
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Outcome: 1 = FATAL; 2 = NOT RECOVERED/NOT RESOLVED; 3 = RECOVERED/RESOLVED WITH SEQUELAE; 4 = RECOVERING/RESOLVING; 5 = RECOVERED/RESOLVED; 6 = UNKNOWN;
 Discontinued or Dose Adjusted: 1 = DOSE NOT CHANGED; 2 = DRUG INTERRUPTED; 3 = DRUG WITHDRAWN; 4 = NOT APPLICABLE; 5 = UNKNOWN;

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/ae103.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/ae103_mt_ap.out
 23JAN2017 10:22

aeI03_mt_ap Listing of Serious Adverse Events
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: All Population

Treatment: MRA-SC 162mg/w (N=18)

CRTN/Pt. No.	Age yr	Sex	Weight kg	Adverse Event (Investigators text)	Day of onset from MRA-SC 1st injection	Duration in Days	Period	During 24hr from Injection	Injection Site Reaction	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1273/60801 白内障	66	F	64.4	ステロイド性白内障の悪化	73	183	DB	No	No	MODERATE	No	5	Yes	1

CRTN = Clinical Research Task Number (center no.)

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Outcome: 1 = FATAL; 2 = NOT RECOVERED/NOT RESOLVED; 3 = RECOVERED/RESOLVED WITH SEQUELAE; 4 = RECOVERING/RESOLVING; 5 = RECOVERED/RESOLVED; 6 = UNKNOWN;

Discontinued or Dose Adjusted: 1 = DOSE NOT CHANGED; 2 = DRUG INTERRUPTED; 3 = DRUG WITHDRAWN; 4 = NOT APPLICABLE; 5 = UNKNOWN;

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632g/aeI03.sas / Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aeI03_mt_ap.out
 23JAN2017 10:22

Page 3 of 3

[5.3.5.1-7 表 11.4-22を再掲]

表 2.7.4.8-13 重篤な有害事象一覧 (WA28119試験-二重盲検期間)

有害事象名の日本語との読み替え一覧は5.3.5.3-1 表 2.4-13参照。

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : PBO QW + 26 Week Prednisone Taper (N=50)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
253740/10242 - 79/F/White								
GASTRITIS EROSION	195	31	2	No	3	Yes	2, 2, 6	3
GASTRITIS EROSION	233	18	2	No	3	Yes	2, 2, 6	3
POSTOPERATIVE WOUND COMPLICATION	311	6	2	No	3		4, 2, 2	3
253740/10245 - 70/M/White								
ERYSIPELAS	254	12	3	Yes:1	3	Yes	4, 2, 6	3
253740/10247 - 80/M/White								
TEMPORAL ARTERITIS	155	24	3	No	3	Yes	4, 4, 6	3
253749/10382 - 80/F/White								
PNEUMONIA	15	7	3	Yes:2	3	Yes	4, 5, 6	3
GLAUCOMA	46	4	1	Yes:2	3		2, 6, 2	3
253753/10103 - 79/M/White								
BREAST CANCER	246	37	2	No	3		5, 2, 6	6

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : PBO QW + 26 Week Prednisone Taper (N=50)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
255226/10864 - 81/F/White NASAL INFLAMMATION STOMATITIS	46 46	61 61	3 3	Yes:1, 2 Yes:1, 2	3 3	Yes Yes	5, 6, 5 5, 6, 5	3 3
255228/10488 - 52/F/White PARAESTHESIA	24	342	3	Yes:2	3		2, 2, 6	3
262959/11001 - 68/F/White ARTHRALGIA	50	18	4	Yes:2	3	Yes	2, 2, 6	3
262959/11003 - 63/F/White OROPHARYNGEAL PAIN	80	10	2	Yes:1, 2	3	Yes	2, 2, 6	3
263034/10624 - 74/M/White HYPERTENSION	167	4	1	No	3	Yes	2, 2, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 2 of 12

Listing of Serious Adverse Events, Safety Population
 Protocol: WA28119

Treatment Group : PBO QW + 26 Week Prednisone Taper (N=50)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
264749/10501 - 66/F/White SYNCOPE	29	1	3	Yes:1	3		2, 2, 6	6

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
 11JUL2016 21:54

Page 3 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : PBO QW + 52 Week Prednisone Taper (N=51)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
253746/10144 - 58/F/White OSTEOARTHRITIS	150	264	3	No	3	Yes	2, 2, 6	3
253747/10343 - 74/F/White TRANSIENT ISCHAEMIC ATTACK HERPES ZOSTER	135 185	1 56	3 3	No Yes:1, 2	3 3	Yes	2, 2, 6 4, 4, 6	3 3
253752/10563 - 65/F/White RESPIRATORY TRACT INFECTION	334	64	3	Yes:1, 2	3	Yes	4, 6, 2	3
253752/10567 - 66/F/White CATARACT	99	107	3	No	3		2, 2, 6	3
TEMPORAL ARTERITIS	99 239	310 14	3 3	No No	3 3	Yes Yes	2, 2, 6 2, 4, 6	3 3
253752/10569 - 78/F/White GENITAL HERPES ZOSTER	15	27	3	Yes:1, 2	3	Yes	4, 2, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 4 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : PBO QW + 52 Week Prednisone Taper (N=51)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
253753/10104 - 55/F/White DYSпноEA EXERTIONAL	123	24	2	Yes:1, 2	3		2, 2, 2	3
255200/11461 - 59/F/White FIBROMYALGIA	36		3	No	2		2, 4, 6	3
255207/10044 - 64/M/White MALIGNANT MELANOMA	315		3	No	5	Yes	2, 2, 2	6
255207/10049 - 68/F/White GASTROENTERITIS	88	4	2	No	3	Yes	4, 2, 6	3
255241/10722 - 61/F/White GASTROENTERITIS	237	12	3	No	3	Yes	2, 6, 2	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 5 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : PBO QW + 52 Week Prednisone Taper (N=51)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
255251/10223 - 76/F/White ASTHMA	232	57	3	No	3	Yes	2, 6, 2	3
255251/10226 - 65/F/White AORTIC VALVE STENOSIS HERPES ZOSTER	184 222	10	3 3	No Yes:1	2 3	Yes	2, 6, 2 2, 6, 2	3 3
255506/11143 - 71/M/White CARDIAC FAILURE CHRONIC HEPATIC ENZYME INCREASED HYPOKALAEMIA RENAL IMPAIRMENT CARDIAC FAILURE	53 59 97 97 135	15 5 5	4 4 4 4 4	Yes:1 Yes:1 No No No	2 3 3 3 2	Yes Yes Yes Yes Yes	2, 2, 6 4, 2, 6 6, 2, 6 6, 2, 6 6, 4, 6	3 6 3 3 3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 6 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ QW + 26 Week Prednisone Taper (N=100)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
253740/10241 - 67/F/White HYPERTENSIVE CRISIS	48	2	3	No	3	Yes	2, 2, 2	3
253740/10248 - 62/F/White DRUG HYPERSENSITIVITY	171	4	3	No	3	Yes	2, 2, 6	3
253755/10268 - 77/F/White TACHYARRHYTHMIA	5	7	3	Yes:2	3		2, 6, 3	3
253755/10269 - 78/M/White DIARRHOEA	164	9	3	No	3	Yes	4, 6, 4	3
ALCOHOL POISONING	254	4	3	No	3	Yes	2, 6, 2	3
HYPERTENSIVE CRISIS	362	2	3	No	3	Yes	2, 6, 4	3
255201/10002 - 73/F/White PNEUMONIA HAEMOPHILUS	226	9	3	Yes:1	3	Yes	5, 5, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 7 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ QW + 26 Week Prednisone Taper (N=100)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
255202/10062 - 84/F/White CELLULITIS	196	37	3	No	3	Yes	4, 2, 6	3
255213/10025 - 74/M/White PLEURAL EFFUSION	335	8	3	No	3		5, 5, 6	3
255215/11224 - 85/F/White SUPRAVENTRICULAR TACHYCARDIA	135	2	3	No	3	Yes	2, 2, 6	3
255215/11227 - 77/M/White CHRONIC SINUSITIS	53	103	3	No	3	Yes	5, 5, 6	3
255228/10490 - 75/M/White PNEUMONIA	14	38	3	Yes:1, 2	3	Yes	5, 6, 3	3
TENDON RUPTURE	36	49	3	No	3		5, 6, 3	4

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 8 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ QW + 26 Week Prednisone Taper (N=100)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
255232/10544 - 72/F/White								
PYELONEPHRITIS	225	22	3	Yes:2	3	Yes	2, 6, 2	3
TEMPORAL ARTERITIS	247	35	3	No	3	Yes	2, 6, 2	3
URINARY TRACT INFECTION	281	7	3	No	3	Yes	2, 6, 2	3
TEMPORAL ARTERITIS	294	13	3	No	3	Yes	2, 6, 2	3
UROSEPSIS	324	40	3	No	3	Yes	6, 6, 6	3
255241/10721 - 55/M/White								
STRESS	27		2	No	2		2, 2, 6	3
TENDON PAIN	114		3	No	2	Yes	2, 2, 6	3
ANXIETY	119	4	3	No	3		2, 2, 6	3
HEADACHE	129		3	No	2		2, 2, 6	3
HERPES ZOSTER	136	90	3	Yes:1	3	Yes	5, 5, 6	3
255505/11104 - 62/M/White								
PULMONARY EMBOLISM	142	11	4	No	3	Yes	2, 2, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 9 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ QW + 26 Week Prednisone Taper (N=100)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
255518/10181 - 84/F/Other GASTROENTERITIS LACERATION	27	9	3	Yes:1	3		5, 2, 2	3 4
	40	2	1	No	3		6, 2, 6	3
255771/10361 - 80/M/White DEEP VEIN THROMBOSIS	106		2	No	2	Yes	6, 6, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE_out
11JUL2016 21:54

Page 10 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ Q2W + 26 Week Prednisone Taper (N=49)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
253752/10570 - 58/F/White DYSPNOEA	344		2	No	2		2, 6, 2	3
253754/10681 - 71/M/White MENISCUS INJURY		131	2	No	3	Yes	2, 2, 6	3
255211/10402 - 81/M/White CELLULITIS	241	14	3	No	3	Yes	5, 4, 6	2 3 4
DRY GANGRENE	241	14	3	No	3		5, 4, 3	3
THROMBOTIC STROKE	254	14	4	No	3	Yes	6, 7, 7	2 3
255503/10602 - 73/F/White HYPERSENSITIVITY	141	2	3	Yes:1	3		5, 2, 6	3
255527/10281 - 78/F/White TEMPORAL ARTERITIS	134		3	No	2	Yes	5, 5, 6	3
CHOLANGITIS INFECTIVE	169	13	1	Yes:1, 2	3	Yes	6, 6, 6	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 11 of 12

Listing of Serious Adverse Events, Safety Population
Protocol: WA28119

Treatment Group : TGZ Q2W + 26 Week Prednisone Taper (N=49)

Center/Patient ID - Age/Sex/Race SAE MedDRA Preferred Term	Study Day of Onset	AE Duration in Days	Most Extreme Intensity (1)	Caused by Study Drug (2)	Outcome (3)	Concomitant or Additional Treatment Given?	Action Taken (4)*	Reason Classified as Serious (5)
260441/11161 - 70/F/White HYPONATRAEMIA	256	22	3	No	3		4, 2, 6	3
263034/10628 - 80/F/White OVARIAN ADENOMA	18	320	1	No	3		2, 6, 2	3

Investigator text for AEs is coded using MedDRA version 19.0.

(1) Most Extreme Intensity: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death.

(2) Caused by Study Drug: 1 = Tocilizumab; 2 = Prednisone.

(3) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.

(4) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.

* : Action taken with blinded Tocilizumab, Action taken with blinded Prednisone, Action taken with open label/escape Prednisone.

(5) Reason classified as serious: 1 = resulted in death; 2 = life threatening; 3 = required or prolonged in patient hospitalization; 4 = disabling; 5 = a congenital anomaly/birth defect in offspring of study subject; 6 = does not meet any of the above serious criteria, but may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/l_ae_ser.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/l_ae_ser_SE.out
11JUL2016 21:54

Page 12 of 12

[5.3.5.1-6 表 2.3-1を再掲]

表 2.7.4.8-14 死亡例一覧 (MRA229JP 試験—二重盲検期間と非盲検期間を併せた期間)

sldd08_ap Listing of Death

Protocol(s): MRA229

Analysis: AS SELECTED Center: ALL CENTERS

All Population

Randomized Group CRTN/Pt. No.	Age yr	Sex	Weight kg	Day of Death	Treatment Group	Time after Last Dose days	Reason for Death	Relation to Trial Treatment
MRA-IV (8mg/kg/4W) 1079/293711	47	F	41.4	482	MRA-IV	107	胃癌、播種性血管内凝固	POSSIBLE

Investigator text for Cause of Death encoded using MedDRA version 13.0.

CRTN = Clinical Research Task Number (center no.)

Output : \$MARSOUT/cdt3489e/emra229a/sldd08_ap.dat

DD08/DD03 04MAR2013:11:58:25

(1 of 1)

[5.3.5.4-3 表 16.2.7-5を再掲]

表 2.7.4.8-15 重篤な有害事象一覧 (MRA229JP 試験-二重盲検期間と非盲検期間を併せた期間)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No.	Age	Sex	Weight	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1044/290512 大腸ポリープ	62	M	67.7	YES	513	63	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 結腸ポリープ* 治験薬のIL-6を抑える作用によってポリープができるとは考えにくい。加齢による偶発的な事象であり、治験薬との因果関係は否定できる。													
1045/290605 肺炎	22	F	41.9	YES	148	29	NO	NO	MILD	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 肺炎*													
1046/290704 右手4、5指伸展不全	63	F	45.8	YES	254	198	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 関節障害* 試験開始前より右手関節の破壊は高度であり、今回生じた右手4、5指伸展不全はそのためによって生じたものであり、治験薬との因果関係は無い。皮下注射前。													
1046/290705 腹部大動脈瘤	71	M	62.0	YES	460	32	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 大動脈瘤* 以前よりの合併症で本人希望で手術となった。													
1049/291003 深部静脈血栓症 (右下肢)	58	M	71.4	YES	198	37	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 深部静脈血栓症* ステロイドの関連も否定できない。今後はD-Dimerなどのfollowします。SC投与後24時間以内													

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slac08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1051/291102 くも膜下出血 Comment: 皮下注射前	59	F	56.0	くも膜下出血*	YES	708	> 50	NO	NO	MODERATE	REMOTE	UNRESOLVED	NO	DOSAGE MODIFIED
1051/291106 右膝関節破壊の進行 Comment: RAが進行したため	36	F	40.7	関節破壊*	YES	359	63	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1053/291306 尿路結石疝痛発作 Comment: 8年前から尿路結石指摘され、たびたび疝痛発作の既往あり。治験開始前より発現していた事象のため治験薬投与による影響は否定できると考える。	47	F	53.9	尿路結石*	YES	170	229	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	NONE
1054/291406 急性胃腸炎	57	F	55.0	胃腸炎*	YES	500	13	NO	NO	MODERATE	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1059/291902 蜂窩織炎	59	F	49.0	蜂巣炎*	YES	143	55	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	NONE
1062/292102 右胸膜炎 両側性肺炎	55	F	48.0	胸膜炎* 肺炎*	YES YES	75	158	NO NO	NO NO	SEVERE SEVERE	PROBABLE PROBABLE	RESO - NO SEQUEL RESO - NO SEQUEL	YES YES	DISCONTINUED DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event	PT	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1063/292203 右股関節破壊進行	58	F	46.1	関節破壊*		YES	222	73	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 原疾患及び合併症である股関節症の悪化によるものであるため、治験薬との因果関係なしと考える 皮下投与前															
1064/292303 卵巣癌	52	F	49.6	卵巣癌*		YES	449	> 63	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	NO	DISCONTINUED
1068/292703 無顆粒球症	64	M	58.5	無顆粒球症*		YES	546	> 79	NO	NO	SEVERE	PROBABLE	UNRESOLVED	NO	DISCONTINUED
Comment: 2012年3月15日院内検査白血球数2300、好中球数800。再考の結果、顆粒球減少が無顆粒球症に事象名変更となった。															
1071/292907 肺炎	42	M	62.0	肺炎*		YES	232	22	NO	NO	MODERATE	PROBABLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1074/293202 腰椎圧迫骨折 (L1, 3)	74	F	53.0	脊椎圧迫骨折*		YES	83	> 51	NO	NO	SEVERE	UNRELATED	UNRESOLVED	YES	DISCONTINUED
Comment: 腰痛の増強傾向があり、2010年12月2日のMRI (脊椎) で高度の圧迫骨折と脊髄への圧迫を認めた。その後の診察でも歩行障害が続き、12月6日重篤と判定した。手術所見として、感染所見なく、治験薬と腰椎病変の因果関係は否定と判断した。															
帯状疱疹				帯状疱疹*		YES	88	46	NO	NO	SEVERE	PROBABLE	RESOLVING	YES	DISCONTINUED
Comment: 軽快のため、フォローアップの必要がなく、治験中止に伴い終了とする。															
脊柱管狭窄症 (L3/4, L4/5)				脊柱管狭窄症*		YES	121	> 13	NO	NO	SEVERE	UNRELATED	UNRESOLVED	NO	DISCONTINUED
Comment: 手術所見として、感染所見なく、治験薬と腰椎病変の因果関係は否定と判断した。															
1074/293205 肺炎	51	F	59.0	肺炎*		YES	377	16	NO	NO	MILD	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

(3 of 15)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome SEQUEL	Treatment Given for AE	Discontinued or Dose Adjusted
1076/293402 带状疱疹	60	F	44.8	带状疱疹*	YES	19	10	NO	NO	MODERATE	PROBABLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1076/293406 大腸ポリープ	71	F	49.8	結腸ポリープ*	YES	130	268	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
白内障 (左眼)				白内障*	YES	375	38	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 治験前から予定されていた手術であった為														
1076/293408 下行結腸穿孔	61	F	61.5	大腸穿孔*	YES	67	33	NO	NO	MODERATE	PROBABLE	RESOLVING	YES	DISCONTINUED
1078/293606 右手指変形	60	F	46.8	指変形*	YES	440	71	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 治験参加以前からの予定手術及び愁訴に対する (悪化なし) 入院・手術のため治験薬との因果関係は認めない。 皮下注射前														
右足底骨隆起				足変形*	YES	440	71	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 治験参加以前からの愁訴に対する (悪化なし) 入院・手術のため治験薬との因果関係は認めない。皮下注射前														
非定型抗酸菌症				非定型マイコバクテリア感染*	YES	510	> 16	NO	NO	MILD	POSSIBLE	UNRESOLVED	NO	DISCONTINUED
Comment: 症状は落ちついており、今後は薬剤により治療していき定期的に胸部X線等でフォローすることで、治験としてのフォローは不要														
1079/293701 肺炎	62	F	54.0	肺炎*	YES	293	43	NO	NO	MODERATE	PROBABLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
(patient continuing ...)														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
(... patient continuing)														
1079/293701 带状疱疹	62	F	54.0	带状疱疹*	YES	641	31	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1079/293702 右遠位橈尺関節脱臼	63	F	50.0	関節脱臼*	YES	527	48	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: RAの自然経過に伴うもの sc後24h以内														
右小指伸筋腱断裂				腱断裂*	YES	539	36	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: RAの自然経過に伴うもの														
盲腸癌				結腸癌*	YES	680	> 29	NO	NO	SEVERE	POSSIBLE	UNRESOLVED	NO	DISCONTINUED
Comment: 2012/5/9の中止時点では、盲腸癌は確認されず、便潜血陽性が認められていた。治験中止後の精査CFにて盲腸癌が確定された為、盲腸癌をAEとする。皮下注射前														
1079/293703 右肺炎	61	F	52.5	肺炎*	YES	236	60	NO	NO	SEVERE	PROBABLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
貧血症				貧血*	YES	673	> 85	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	NO	NONE
Comment: 皮下注射前														
1079/293707 大腸ポリープ (良性)	75	M	53.5	結腸ポリープ*	YES	631	73	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	NONE
Comment: 皮下注射前														
1079/293708 メニエール病の悪化	67	F	53.4	メニエール病*	YES	2	28	YES	NO	MODERATE	REMOTE	RESOLVING	YES	DISCONTINUED
Comment: SC後24h以内														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slac08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s) : MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1079/293711 胃癌 播種性血管内凝固	47	F	41.4	胃癌* 播種性血管内凝固*	YES YES	430 443	> 53 > 40	NO NO	NO NO	SEVERE SEVERE	POSSIBLE POSSIBLE	DEATH DEATH	YES NO	DISCONTINUED DISCONTINUED
1081/293801 アナフィラキシー	63	M	75.5	アナフィラキシー反応*	YES	29	2	YES	NO	SEVERE	PROBABLE	RESO - NO SEQUEL	YES	DISCONTINUED
Comment: 点滴静脈内投与終了直後に発現したため皮下注射は実施せず														
1083/294008 肺炎	53	F	63.1	肺炎*	YES	474	25	NO	NO	MILD	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1085/294208 左股関節関節裂隙狭小化	62	F	50.0	股関節変形*	YES	514	248	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: R A の経時的変化によるもの														
1086/294303 顔面蜂窩織炎	50	F	55.2	蜂巣炎*	YES	357	18	NO	NO	SEVERE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1086/294305 急性喉頭蓋炎	59	F	78.0	喉頭蓋炎*	YES	708	22	NO	NO	SEVERE	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
1092/294801 虚血性腸炎	66	F	51.3	虚血性大腸炎*	YES	57	9	YES	NO	SEVERE	PROBABLE	RESO - NO SEQUEL	YES	DISCONTINUED
Comment: 投与当日に有害事象が発現しているので。SC後24時間以内。														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-IV (8mg/kg/4W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1092/294810 マイコプラズマ肺炎	44	F	65.6	マイコプラズマ性肺炎*	YES	195	32	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1094/295008 高血圧の増悪	59	F	57.0	高血圧*	YES	282	14	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 治験開始以前より、一過性の血圧上昇とそれに伴う頭痛等の症状を認めており、今回は家族や被験者希望により、大事をとって入院・経過観察とした。入院以降、血圧は安定しており、高血圧症は合併症でもあるため、本患者と治験薬との因果関係は、否定できる。														
1094/295009 労作性狭心症	53	M	74.3	狭心症*	YES	361	> 11	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	YES	DISCONTINUED
1095/295103 肝機能障害	32	F	55.8	肝機能異常*	YES	25	22	NO	NO	SEVERE	POSSIBLE	RESOLVING	NO	DISCONTINUED
1095/295106 浮動性めまい	54	F	47.3	浮動性めまい*	YES	710	4	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	NONE
1102/295206 帯状疱疹	50	F	49.6	帯状疱疹*	YES	298	467	NO	NO	SEVERE	PROBABLE	RESOLVING	YES	DOSAGE MODIFIED
Comment: 症状は落ちついており、治験としてのフォローアップは不要であると判断した。														

Investigator text for Adverse Events encoded using MedDRA version 13.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat

AE08/AE01 06MAR2013:11:46:06

(7 of 15)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s) : MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W) : N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1039/290101 気管支喘息発作	69	M	77.0	喘息*	YES	74	5	NO	NO	MODERATE	REMOTE	RESO - NO SEQUEL	YES	NONE
1039/290103 慢性気管支炎の増悪	65	F	46.6	慢性気管支炎*	YES	11	4	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 慢性気管支炎にて、治験開始以前から時々同様の症状があり数日で回復していた。今回も同様に吸入で症状改善しており、現段階では治験薬との因果関係はないと判断する。														
右膝挫創の感染				創傷感染*	YES	688	58	NO	NO	MODERATE	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1042/290302 非浸潤性乳管癌 (右乳房上外側)	44	F	49.0	乳房の上皮内癌*	YES	471	> 27	NO	NO	SEVERE	POSSIBLE	UNRESOLVED	NO	DISCONTINUED
1042/290312 薬疹 (被疑薬オキナゾール)	27	F	52.4	薬疹*	YES	354	6	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 2010/9/7から治験薬投与を開始し、2011/8/5のオープン12回目までの投与にて計24回の治験薬投与が実施されているが、特に投与後異常反応等の事象の発現はないこと、また直近の治験薬投与日が、今回の事象の発現日の3週間前であること、さらに経過から考えて、事象の発現日の前日にオキナゾール膣剤が治験開始後初めて使用されていること、全身に皮疹がみられたことから、オキナゾール膣剤使用による薬疹の可能性が高いと考える。DLST検査結果では判定が陰性であるが、事象発現の経緯及び治験薬の投与再開後に投与後異常反応はみられていないことからオキナゾールが本事象の被疑薬であると考えられる。														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

(8 of 15)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W): N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1043/290402 右変形性股関節症の悪化	51	F	44.1	変形性関節症*	YES	309	220	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 右変形性股関節症の悪化は自然経過により進行したため、治験薬との因果関係は否定できると考える。右人工股関節置換術後の経過は良好で、治験薬の投与再開に支障はないと判断する。2011年12月16日より、治験薬投与再開とした。皮下注射前														
1043/290402 左変形性股関節症				変形性関節症*	YES	409	280	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 合併症の右変形性股関節症により疼痛強く、歩様が悪化したことで左股関節症の増悪を来した。皮下注射前														
1047/290806 急性硬膜下血腫	62	F	52.3	硬膜下血腫*	YES	153	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 凍結路面での転倒したことが原因である。														
1047/290806 高血圧緊急症				高血圧緊急症*	YES	153	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 凍結路面での転倒したことが原因である。														
1047/290806 左後頭部内出血				頭蓋内出血*	YES	153	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 凍結路面での転倒したことが原因である。														
1047/290806 脳挫傷				脳挫傷*	YES	153	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 凍結路面での転倒したことが原因である。														
1047/290806 中枢性嘔吐				嘔吐*	YES	153	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 凍結路面での転倒したことが原因である。														
1049/291010 サブイレウス	74	F	45.8	亜イレウス*	YES	12	> 4	NO	NO	MILD	REMOTE	UNRESOLVED	YES	DISCONTINUED
1049/291010 低ナトリウム血症				低ナトリウム血症*	YES	14	> 2	NO	NO	SEVERE	REMOTE	UNRESOLVED	YES	DISCONTINUED
Comment: 2010年10月12日 Na110mmol/l (院内検査)														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因ae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s) : MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W) : N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1051/291104 带状疱疹	67	M	69.0	带状疱疹*	YES	627	47	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
1051/291109 感冒	67	F	42.2	鼻咽頭炎*	YES	527	13	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
				Comment: 皮下注射後24時間以内 サルモネラ腸炎	YES	667	21	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
				Comment: 皮下注射後24時間以内 * サルモネラ菌性胃腸炎										
1051/291111 左股関節破壊の進行	66	F	58.4	関節破壊*	YES	351	95	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
				Comment: RAが進行したため 皮下注射前 左人工股関節の脱臼	YES	427	19	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
				Comment: 偶発的に発生したもの										
1053/291301 左L4/5腰椎椎間関節囊腫	55	M	53.4	新生物*	YES	23	90	NO	NO	SEVERE	REMOTE	RESOLVING	YES	DISCONTINUED
1054/291407 急性胃腸炎	66	F	45.0	胃腸炎*	YES	41	5	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

(10 of 15)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W); N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1055/291503 大腸ポリープ	62	M	58.1	結腸ポリープ*	YES	43	65	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 治験薬投与前から存在する大腸ポリープである。														
1056/291602 爪周囲梗塞	51	F	52.7	末梢血管塞栓症*	YES	183	42	NO	NO	MODERATE	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 本事象により28~30w休薬。皮下注射前。														
1058/291806 感染性肺炎	64	F	43.6	肺炎*	YES	331	68	NO	NO	MODERATE	PROBABLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
小腸イレウス				イレウス*	YES	373	51	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
1061/292004 右膝関節破壊の進行	67	F	55.5	関節破壊*	YES	386	85	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
右化膿性膝関節炎				細菌性関節炎*	YES	477	> 24	NO	NO	SEVERE	POSSIBLE	UNRESOLVED	YES	DISCONTINUED
Comment: RAの自然経過により進行したため治験薬との因果関係は否定できる。皮下注射前														
1062/292104 肺炎	57	M	62.0	肺炎*	YES	307	31	NO	NO	SEVERE	PROBABLE	RESO - NO SEQUEL	YES	DISCONTINUED
1062/292106 消化管出血	71	F	50.0	胃腸出血*	YES	49	36	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

(11 of 15)

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W): N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1063/292205 左白内障	69	M	58.6	白内障*	YES	298	168	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 加齢及びステロイド使用に伴うものと考えられるので、治験薬と因果関係ないと考える														
右鼠径ヘルニア				鼠径ヘルニア*	YES	304	144	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 加齢による腹壁筋肉弛緩に伴う偶発的事象と考える														
1063/292209 右肘関節破壊進行	59	F	46.7	関節破壊*	YES	267	97	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 原疾患による事象であり、治験薬との因果関係は否定できる。皮下注射前														
1071/292901 間質性肺炎	61	F	39.3	間質性肺炎*	YES	693	> 14	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	YES	DISCONTINUED
1073/293102 左手関節滑膜炎	46	M	71.0	滑膜炎*	YES	365	47	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 原疾患によるものと考えられるため														
1075/293303 鼻中隔彎曲症	25	M	64.0	鼻中隔彎曲*	YES	550	20	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 今回の事象は約10年前の外傷によるもので治験開始前からのものである。したがって、治験薬との因果関係は否定できる。														
1076/293407 環軸椎関節亜脱臼	62	M	57.9	関節脱臼*	YES	295	466	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 原疾患の増悪によるもの														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W): N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1077/293507 大腸ポリープ	69	M	74.0	結腸ポリープ*	YES	281	76	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	NONE
Comment: 2011/6/20入院後2011/6/21にポリペクトミー施術2011/6/22退院される 皮下注前の発現														
1078/293603 下部消化管出血	44	F	55.2	下部消化管出血*	YES	294	> 12	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	YES	DISCONTINUED
Comment: その後2011年5月30日に回復を確認している。														
1078/293603 大腸憩室炎(疑)				憩室炎*	YES	294	> 12	NO	NO	MODERATE	POSSIBLE	UNRESOLVED	YES	NONE
Comment: その後2011年5月30日に回復を確認している。														
1078/293607 蜂窩織炎	38	F	42.1	蜂巣炎*	YES	39	19	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1078/293607 咽後膿瘍				咽頭膿瘍*	YES	312	20	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 皮下注射後24時間以降														
1078/293607 肺炎				肺炎*	YES	522	20	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
1078/293607 薬剤性肝障害				肝障害*	YES	534	8	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: DLST結果は陰性であったが、ミ/マイソンの投与後に肝機能異常出現し、中止によって速やかに改善した経過からはミ/マイソンの薬剤性肝障害が強く疑われる。また現在までの治験薬投与の経過から肝機能異常を認めた既往がなく、治験薬との因果関係は否定的と考える。														
1079/293704 左母趾変形	54	F	52.6	足変形*	YES	171	66	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: SC前。本事象は、原疾患である関節リウマチの自然経過による左母趾変形と考えられ、治験薬との因果関係はないと考える。														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s) : MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W) : N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1079/293709 L1腰椎圧迫骨折	58	M	59.0	脊椎圧迫骨折*	YES	136	160	NO	NO	SEVERE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 2009年11月26日のDEXAの測定結果から骨粗鬆症があり、又重いものを持ち上げたことにより生じた事象と考えられ、治験薬との因果関係はないと考える。														
上行結腸憩室穿孔				憩室穿孔*	YES	572	33	NO	NO	SEVERE	POSSIBLE	RESOLVING	YES	DISCONTINUED
1083/294001 急性胃腸炎	36	F	48.5	胃腸炎*	YES	205	21	NO	NO	MILD	REMOTE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1083/294005 带状疱疹	71	F	44.2	带状疱疹*	YES	706	52	NO	NO	MODERATE	REMOTE	RESOLVING	YES	DOSAGE MODIFIED
1085/294205 右手関節滑膜炎	68	F	57.0	滑膜炎*	YES	167	41	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: RAの経時的変化に伴うものと考えられる														
右手第5指伸筋腱断裂				腱断裂*	YES	359	133	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: RAによるものと考えられる														
1085/294210 関節痛	53	F	67.0	関節痛*	YES	258	122	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 感染所見など明らかな異常所見がみられないことから本事象は、RA症状の一部であり一時的かつ局所的な悪化が発現したと考えられる。														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/slae08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

slae08ser_ap Listing of Patients with Serious Adverse Events
 Serious Adverse Events
 Protocol(s): MRA229
 Analysis: AS SELECTED Center: ALL CENTERS
 All Population
 Treatment: MRA-SC (162mg/2W): N = 174

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Adverse Event (PT)	Serious?	Day of Onset	Duration in Days	During 24hr from Infusion	SC Injection Site?	Intensity	Relation to Trial Treatment	Outcome	Treatment Given for AE	Discontinued or Dose Adjusted
1089/294605 気管支炎	57	F	55.5	気管支炎*	YES	604	17	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
気管支喘息				喘息*	YES	604	17	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
1091/294701 左第一大臼歯骨膜下膿瘍	52	F	59.0	骨膿瘍*	YES	509	43	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 皮下注射後 2 4 時間以内														
1091/294705 交通外傷	47	M	61.0	損傷*	YES	3	27	NO	NO	MODERATE	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: 偶発的事象のため														
1094/295003 下肢静脈瘤	68	F	61.1	静脈瘤*	YES	225	72	NO	NO	MILD	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
Comment: 皮下注射前。本事象は外観上の変化も治験開始以前から変化なく、患者様希望による手術の為の入院であり、治験薬との因果関係は否定できると判断する。														
1094/295005 肺炎球菌性肺炎	58	M	56.1	肺炎球菌性肺炎*	YES	415	28	NO	NO	MODERATE	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
Comment: 皮下注射後 2 4 時間以降														

Investigator text for Adverse Events encoded using MedDRA version 13.0.
 CRTN = Clinical Research Task Number (center no.)
 * Serious adverse event
 Output : \$MARSOUT/cdt3489e/emra229a/sl原因08ser_ap.dat
 AE08/AE01 06MAR2013:11:46:06

(15 of 15)

[5.3.5.4-3 表 16.2.7-6を再掲]

表 2.7.4.8-16 重篤な有害事象一覧 (WA22762試験)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202055/42010 PNEUMONIA*	74	F	46	WHITE	3	417	138	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
202531/43403 ANAEMIA*	54	M	67	WHITE	3	220	11	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202782/27809 PHARYNGEAL ABSCESS*	73	F	67	WHITE	3	316	66	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
ATYPICAL PNEUMONIA*					3	473	55	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
202782/27814 BONE TUBERCULOSIS*	65	F	70	WHITE	3	491	141	RELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
202783/28007 ENDOMETRIAL ADENOMA*	53	F	77	WHITE	3	527	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202783/28013 VENOUS THROMBOSIS*	51	F	74	WHITE	3	283	17	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CELLULITIS*					3	642	32	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202810/11011 ABORTION SPONTANEOUS*	23	F	83	WHITE	2	723	31	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
202887/10001 ANASTOMOTIC ULCER HAEMORRHAGE*	41	F	58	WHITE	3	113	29	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
202901/38809 PELVIC PAIN*	77	F	62	WHITE	4	173	?	RELATED	UNRESOLVED		DISCONTINUED
SHOCK*					5	173	2	RELATED	DEATH	YES	DISCONTINUED
202902/39003 EMPYEMA*	46	F	61	WHITE	3	87	32	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202902/39007 DACRYOCYSTITIS*	54 F	85	WHITE	2	201	60	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202902/39008 URINARY TRACT INFECTION*	64 F	51	WHITE	3	116	5	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202906/39802 FALL*	66 F	64	WHITE	2	243	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
LOWER LIMB FRACTURE*				2	243	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202910/40601 BASAL CELL CARCINOMA*	68 F	42	WHITE	2	320	81	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202915/31801 SUBCUTANEOUS ABSCESS*	24 F	44	ASIAN	3	108	29	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202963/20203 GASTRIC ULCER HAEMORRHAGE*	64 M	76	WHITE	2	437	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202963/20208 CHOLELITHIASIS*	53 M	93	WHITE	3	503	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202964/20401 ATRIAL TACHYCARDIA*	58 F	97	WHITE	1	8	54	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
CORONARY ARTERY DISEASE*				2	414	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202965/18602 CHILLBLAINS*	56 M	67	WHITE	3	368	99	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
202965/18606 OSTEONECROSIS*	43 M	73	WHITE	3	123	418	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
DEVICE DISLOCATION*				3	428	4	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(2 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202965/18606 DEVICE DISLOCATION*	43	M	73	WHITE	2	544	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202979/41204 OSTEOARTHRITIS*	28	M	66	ASIAN	3	316	122	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202981/41603 CERVIX CARCINOMA STAGE 0*	48	F	49	ASIAN	3	380	112	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203018/15405 PNEUMONIA*	46	F	48	WHITE	3	111	13	RELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
BRONCHOPULMONARY ASPERGILLOSIS*					1	603	?	RELATED	UNRESOLVED	YES	DOSE HELD
203019/15606 GRAND MAL CONVULSION*	65	M	92	WHITE	3	161	23	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
GRAND MAL CONVULSION*					2	434	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203020/15801 HEPATIC HAEMATOMA*	51	F	87	WHITE	3	259	156	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
PLEURAL EFFUSION*					4	259	156	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
SEPTIC SHOCK*					4	532	13	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203021/16001 RETROPERITONEAL ABSCESS*	57	F	104	WHITE	3	560	18	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203059/20807 HYPERSENSITIVITY*	59	F	79	WHITE	4	1	<= 1	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203067/22005 INTERVERTEBRAL DISC PROTRUSION*	32	M	84	WHITE	2	406	81	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(3 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203080/10610 DEEP VEIN THROMBOSIS*	49 F	63	WHITE	3	101	198	RELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
CELLULITIS*				3	209	20	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203091/34401 FALL*	74 F	50	WHITE	3	268	22	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
HIP FRACTURE*				3	268	22	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203091/34405 PNEUMONIA*	61 F	81	WHITE	3	193	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
LOBAR PNEUMONIA*				3	217	11	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203096/35401 TRACHEOBRONCHITIS*	54 F	67	WHITE	2	674	12	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203168/11605 CELLULITIS*	54 F	90	WHITE	3	174	24	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203173/24203 ABDOMINAL PAIN*	61 F	63	ASIAN	2	216	16	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203186/37205 INTERVERTEBRAL DISC PROTRUSION*	47 F	83	BLACK	3	97	21	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203187/37402 URINARY TRACT INFECTION*	33 F	84	BLACK	3	426	172	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203189/37804 ABORTION SPONTANEOUS*	34 F	70	BLACK	3	85	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203197/12607 MYOCARDIAL ISCHAEMIA*	65 F	72	WHITE	3	169	?	UNRELATED	UNRESOLVED	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(4 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203197/12609 RHEUMATOID ARTHRITIS*	31 F	59	WHITE	2	43	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203197/12614 SCIATICA*	54 F	90	WHITE	3	137	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203200/13002 CELLULITIS*	32 F	79	WHITE	3	415	8	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
INGUINAL HERNIA*				2	599	34	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203207/13602 HYPERSENSITIVITY*	37 F	62	WHITE	1	198	12	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
GASTROENTERITIS*				1	203	7	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
203252/14404 PYELONEPHRITIS CHRONIC*	57 F	60	WHITE	3	26	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CEREBRAL INFARCTION*				5	716	5	UNRELATED	DEATH	YES	NONE
203254/26609 GASTROINTESTINAL TRACT ADENOMA*	56 F	78	WHITE	1	677	36	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
UMBILICAL HERNIA*				1	709	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203261/32405 AMYLOIDOSIS*	47 M	104	WHITE	3	369	?	UNRELATED	UNRESOLVED	YES	DISCONTINUED
203261/32414 DIABETES MELLITUS*	61 F	68	WHITE	3	270	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203358/17006 BREAST CANCER*	62 F	61	WHITE	3	24	152	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(5 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203479/44802 DYSARTHRIA*	59 F	69	BLACK	2	597	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
HEMIPARESIS*				2	597	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
MIGRAINE*				2	597	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203479/44810 LOCALISED INFECTION*	60 F	75	WHITE	3	638	33	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203486/45202 DIABETIC KETOACIDOSIS*	60 F	103	WHITE	3	130	11	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203490/45405 OSTEOARTHRITIS*	66 F	68	WHITE	4	3	132	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203490/45406 ACUTE MYOCARDIAL INFARCTION*	49 F	75	WHITE	4	92	42	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203500/46601 CHRONIC OBSTRUCTIVE PULMONARY DISEASE*	63 F	141	WHITE	3	403	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203504/47001 FACIAL BONES FRACTURE*	69 M	111	WHITE	2	247	42	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
FALL*				4	247	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
HAEMATOMA*				2	247	42	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
CELLULITIS*				3	429	14	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
COLITIS*				4	592	22	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
GASTRITIS*				4	593	21	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(6 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203504/47001 MEGACOLON*	69 M	111	WHITE	4	593	21	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
PERITONITIS*				4	593	21	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
RENAL FAILURE ACUTE*				4	593	21	RELATED	RESOLVED - NO SEQUELAE		DISCONTINUED
SEPTIC SHOCK*				4	593	21	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
ACIDOSIS*				4	595	19	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
ILEUS*				4	595	?	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203504/47006 CELLULITIS*	49 F	119	WHITE	3	230	45	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
OESOPHAGEAL ULCER*				2	588	95	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203510/47603 CHOLECYSTITIS CHRONIC*	54 F	99	WHITE	2	247	42	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203513/48001 SCHWANNOMA*	54 F	111	BLACK	2	223	52	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203517/48801 INTRADUCTAL PROLIFERATIVE BREAST LESION*	63 F	42	WHITE	3	526	29	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203521/49602 SYNCOPE*	47 M	111	WHITE	3	435	?	UNRELATED	RECOVERING/RESOLVING	NO	DOSE HELD
203526/50605 FEMUR FRACTURE*	67 F	58	WHITE	3	495	15	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
DIVERTICULAR PERFORATION*				4	509	73	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(7 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203526/50605 PELVIC ABSCESS*	67	F	58	WHITE	4	509	73	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
PSEUDOMONAL SEPSIS*					4	509	?	RELATED	UNKNOWN	YES	NONE
RENAL FAILURE ACUTE*					4	509	?	RELATED	UNRESOLVED	YES	NONE
UROSEPSIS*					4	509	?	RELATED	UNKNOWN	YES	NONE
PERITONITIS*					4	514	68	RELATED	RESOLVED - WITH SEQUELAE	YES	NONE
ATRIAL FIBRILLATION*					4	520	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
ENCEPHALOPATHY*					4	561	?	UNRELATED	UNKNOWN	YES	NONE
SEPTIC SHOCK*					4	561	?	RELATED	UNKNOWN	YES	NONE
ACUTE RESPIRATORY FAILURE*					4	566	?	RELATED	UNKNOWN	YES	NONE
DEATH*					5	606	<= 1	RELATED	DEATH	NO	NONE
203531/51204 CEREBRAL HAEMORRHAGE*	76	F	63	WHITE	4	183	21	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
COMMINUTED FRACTURE*					4	183	97	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
JAW FRACTURE*					3	183	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
ROAD TRAFFIC ACCIDENT*					4	183	<= 1	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
203534/51802 LIPASE INCREASED*	72	F	57	AMERICAN INDIAN / ALASKA NATIVE	3	96	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
BRONCHITIS*					2	97	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203538/52401 CHRONIC OBSTRUCTIVE PULMONARY DISEASE*	56	F	84	WHITE	3	87	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CARDIAC FAILURE CONGESTIVE*					3	133	103	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(8 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203538/52401 CHRONIC OBSTRUCTIVE PULMONARY DISEASE*	56 F		84	WHITE	3	133	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203538/52404 HYPERSENSITIVITY*	66 F		119	BLACK	2	9	5	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203547/53601 COLITIS*	55 F		103	BLACK	2	272	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
BILE DUCT STONE*					3	632	20	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CHOLELITHIASIS*					3	632	20	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
THROMBOSIS*					5	662	<= 1	UNRELATED	DEATH	YES	NONE
203547/53602 GASTROENTERITIS*	46 F		56	WHITE	4	152	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203551/54005 ANGINA UNSTABLE*	59 F		102	BLACK	3	317	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
CORONARY ARTERY DISEASE*					3	374	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203551/54006 CHOLECYSTITIS*	60 M		76	WHITE	3	110	27	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203555/54804 LEIOMYOMA*	55 F		53	WHITE	2	26	91	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203556/55004 OSTEOARTHRITIS*	68 F		56	WHITE	3	367	13	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203556/55006 ENCEPHALOPATHY*	53 F		48	WHITE	3	574	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(9 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203557/55202 GASTROESOPHAGEAL REFLUX DISEASE*	65 F	70	WHITE	3	189	106	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203569/55401 ANGINA UNSTABLE*	61 M	78	WHITE	4	714	38	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
203569/55403 ANKLE FRACTURE*	30 F	98	WHITE	3	342	73	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203569/55404 CHOLELITHIASIS*	53 M	100	WHITE	3	226	98	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CELLULITIS*				2	559	21	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203570/55606 CELLULITIS*	64 F	102	WHITE	3	291	27	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203589/22404 CEREBRAL ISCHAEMIA*	67 M	75	WHITE	3	559	8	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203590/22602 LENTIGO MALIGNA*	60 M	79	WHITE	3	427	153	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203689/17602 BRAIN NEOPLASM MALIGNANT*	62 F	53	WHITE	4	69	?	UNRELATED	UNRESOLVED	YES	DISCONTINUED
203762/14812 BREAST CANCER*	64 F	55	WHITE	2	23	273	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203781/17809 URINARY TRACT INFECTION*	52 F	91	NOT AVAILABLE	2	369	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203819/56205 OSTEONECROSIS*	46 F	57	WHITE	3	330	124	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(10 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 162mg SC qw + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
205360/57002 ARTHRITIS INFECTIVE*	71 F	79	WHITE	3	384	27	RELATED	RESOLVED - NO SEQUELAE	YES	DOSAGE MODIFIED
SPINAL COLUMN STENOSIS*				2	511	17	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
SCIATICA*				3	528	12	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
205360/57004 AMAUROSIS*	70 F	84	WHITE	4	191	3	UNRELATED	RESOLVED - WITH SEQUELAE	NO	DOSE HELD
CAROTID ARTERY THROMBOSIS*				4	191	10	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
MYOCARDIAL INFARCTION*				3	641	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
205360/57005 HUMERUS FRACTURE*	72 M	76	WHITE	3	384	15	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
206187/57207 PNEUMONIA*	48 F	70	WHITE	3	93	5	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
206952/56601 CARDIAC VALVE DISEASE*	51 M	77	WHITE	4	41	7	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
ATRIOVENTRICULAR BLOCK FIRST DEGREE*				3	50	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
WHIPPLE'S DISEASE*				4	55	439	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
206952/56604 BURSITIS*	66 F	94	WHITE	3	379	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(11 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY

Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202055/42009 RECTAL HAEMORRHAGE*	24	F	67	ASIAN	2	91	76	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202055/42015 CELLULITIS*	66	F	62	WHITE	2	121	41	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202775/27205 LACERATION*	31	F	89	NOT AVAILABLE	3	633	?	UNRELATED	UNRESOLVED	YES	DOSE HELD
WOUND INFECTION*					3	652	22	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202781/27607 ANKLE FRACTURE*	39	F	56	NOT AVAILABLE	2	209	422	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202781/27613 IMMINENT ABORTION*	24	F	64	NOT AVAILABLE	3	25	<= 1	RELATED	RESOLVED - NO SEQUELAE	NO	NONE
202783/28003 TRACHEITIS*	48	F	35	WHITE	3	535	22	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202810/11013 ISCHAEMIC ULCER*	86	F	62	WHITE	3	60	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
CEREBELLAR ISCHAEMIA*					3	391	22	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
GASTROENTERITIS*					2	520	10	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202810/11016 GROIN ABSCESS*	46	F	80	WHITE	3	96	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202881/43802 OSTEOARTHRITIS*	58	M	82	WHITE	3	260	115	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202883/31007 TRANSIENT ISCHAEMIC ATTACK*	85	F	69	NOT AVAILABLE	3	433	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(12 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202883/31007 URINARY TRACT INFECTION*	85 F	69	NOT AVAILABLE	2	433	5	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
202887/10004 GASTROENTERITIS*	40 F	97	WHITE	2	709	7	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
202900/38614 HAEMATURIA*	72 M	85	WHITE	3	43	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202901/38811 MUSCULOSKELETAL CHEST PAIN*	75 F	64	WHITE	2	15	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
PNEUMONIA*				3	284	6	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
THORACIC VERTEBRAL FRACTURE*				3	491	13	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
SPONDYLOLISTHESIS*				3	567	14	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
DEVICE RELATED INFECTION*				3	613	45	RELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
DEVICE DISLOCATION*				3	687	20	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
DEVICE DISLOCATION*				3	725	32	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
202963/20207 OSTEOARTHRITIS*	49 F	80	WHITE	3	360	237	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202963/20209 HUMERUS FRACTURE*	73 F	96	WHITE	3	170	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
WOUND INFECTION*				3	186	84	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202965/18605 ANAEMIA*	59 F	49	WHITE	2	8	190	RELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(13 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202965/18605 SCIATICA* TOOTH INFECTION*	59	F	49	WHITE	2 3	35 141	? 24	UNRELATED RELATED	UNRESOLVED RESOLVED - NO SEQUELAE	YES YES	NONE NONE
202968/19203 ISCHAEMIC STROKE*	61	M	83	WHITE	4	512	7	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
202979/41202 VERTIGO*	53	F	58	ASIAN	3	356	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202981/41604 CERVICAL DYSPLASIA*	44	F	45	ASIAN	3	349	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203017/15204 INTERVERTEBRAL DISC DEGENERATION*	64	F	69	WHITE	3	395	114	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203018/15401 ATRIAL FIBRILLATION*	64	M	75	WHITE	2	444	98	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203018/15411 ACUTE RESPIRATORY DISTRESS SYNDROME*	67	F	83	WHITE	5	413	12	RELATED	DEATH	YES	NONE
203019/15602 OVARIAN CYST RUPTURED*	45	F	66	WHITE	3	15	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203021/16005 SMALL CELL LUNG CANCER*	61	F	115	WHITE	3	340	?	UNRELATED	UNRESOLVED	YES	DISCONTINUED
203023/16405 RENAL COLIC*	50	F	95	WHITE	2	56	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203058/20602 SPINAL OSTEOARTHRITIS* HYDROCELE*	61	M	82	WHITE	1 1	3 667	48 3	UNRELATED UNRELATED	RESOLVED - NO SEQUELAE RESOLVED - NO SEQUELAE	YES YES	NONE NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(14 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203058/20603 BRONCHOPNEUMONIA*	69	F	90	WHITE	3	94	10	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203059/20806 ISCHAEMIC STROKE*	48	F	64	WHITE	4	99	11	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203059/20809 MORTON' S NEUROMA*	46	F	80	WHITE	2	85	15	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
MORTON' S NEUROMA*					2	170	6	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203080/10607 HAEMORRHAGIC STROKE*	74	F	70	WHITE	3	725	8	RELATED	RESOLVED - WITH SEQUELAE	YES	NONE
203080/10609 PNEUMONIA*	52	M	58	WHITE	3	44	10	RELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
PLEURAL EFFUSION*					3	71	8	RELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
203090/34202 RETINAL ARTERY OCCLUSION*	62	F	88	WHITE	4	139	13	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
ISCHAEMIC CEREBRAL INFARCTION*					5	462	3	UNRELATED	RESOLVED - WITH SEQUELAE DEATH	NO	NONE
203091/34411 COLITIS ISCHAEMIC*	59	M	81	WHITE	4	248	31	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
ENDOCARDITIS*					3	306	43	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203097/35604 FIBROADENOMA OF BREAST*	34	F	52	WHITE	1	472	50	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203168/11603 OSTEOARTHRITIS*	49	F	130	WHITE	2	110	89	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(15 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203169/11801 TRANSIENT ISCHAEMIC ATTACK*	62	M	88	WHITE	2	112	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203171/23807 SYNOVIAL RUPTURE*	45	F	61	ASIAN	2	18	25	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
203171/23809 NON-CARDIAC CHEST PAIN*	59	F	46	ASIAN	1	651	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203172/24001 PNEUMONIA*	63	F	47	ASIAN	2	521	52	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203185/37005 POSTOPERATIVE WOUND INFECTION* ABSCESS LIMB*	66	F	52	WHITE	3	349	80	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
					3	525	25	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203186/37204 INTERVERTEBRAL DISC PROTRUSION* ANGINA UNSTABLE*	57	F	94	WHITE	3	106	82	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
					2	597	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203187/37404 CEREBRAL INFARCTION*	69	F	80	WHITE	3	687	41	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203208/13801 FEMORAL NECK FRACTURE* WOUND INFECTION*	64	F	82	NOT AVAILABLE	4	715	?	UNRELATED	RECOVERING/RESOLVING	YES	NONE
					2	734	36	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203210/26003 INVASIVE DUCTAL BREAST CARCINOMA*	49	F	53	WHITE	3	466	?	UNRELATED	UNRESOLVED	YES	DISCONTINUED
203252/14403 RHEUMATOID ARTHRITIS*	61	F	66	WHITE	3	338	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(16 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203254/26602 ARTHRITIS BACTERIAL* SEPSIS*	58 F		77	WHITE	4 5	144 148	? 2	RELATED RELATED	UNRESOLVED DEATH	YES YES	DISCONTINUED DISCONTINUED
203254/26611 PUBIS FRACTURE*	69 F		51	WHITE	4	73	83	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203255/26810 SPINAL OSTEOARTHRITIS*	67 F		62	WHITE	1	135	13	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203266/33402 HAEMORRHOIDAL HAEMORRHAGE*	68 F		63	WHITE	1	136	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203355/16607 SPHINCTER OF ODDI DYSFUNCTION*	50 F		88	WHITE	2	193	7	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
203361/17203 ARTHRITIS BACTERIAL* DEEP VEIN THROMBOSIS*	64 F		73	WHITE	3 3	3 13	168 ?	UNRELATED UNRELATED	RESOLVED - NO SEQUELAE RESOLVED - NO SEQUELAE	YES YES	DISCONTINUED NONE
203376/32812 CEREBROVASCULAR INSUFFICIENCY*	73 F		62	WHITE	2	22	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203376/32821 TRANSIENT ISCHAEMIC ATTACK*	74 F		49	WHITE	3	103	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203479/44803 SUBCUTANEOUS ABSCESS*	63 F		65	WHITE	3	227	132	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203490/45403 PLEURAL EFFUSION* PNEUMONIA*	58 F		82	WHITE	3 3	623 623	12 12	UNRELATED UNRELATED	RESOLVED - NO SEQUELAE RESOLVED - NO SEQUELAE	YES YES	DOSE HELD DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(17 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203490/45403 RESPIRATORY FAILURE*	58	F	82	WHITE	3	623	12	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
PNEUMOTHORAX*					3	630	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203490/45413 SQUAMOUS CELL CARCINOMA*	58	M	139	WHITE	2	24	251	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203496/46002 DIVERTICULUM INTESTINAL HAEMORRHAGIC*	64	F	116	BLACK	3	454	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203496/46007 ANGINA PECTORIS*	69	F	93	WHITE	3	55	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203497/46201 COLITIS*	70	F	71	WHITE	3	317	6	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
203514/48203 RENAL CELL CARCINOMA*	55	F	85	WHITE	3	633	49	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
203515/48401 HEADACHE*	36	F	128	WHITE	3	435	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203525/50405 JOINT DISLOCATION*	57	F	79	WHITE	3	475	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203525/50406 MUSCULOSKELETAL CHEST PAIN*	60	F	98	WHITE	3	269	8	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203526/50604 PNEUMONIA*	63	F	92	WHITE	3	459	9	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
DEEP VEIN THROMBOSIS*					4	616	85	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
PULMONARY EMBOLISM*					3	616	85	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(18 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY

Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD; N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203526/50604 COMPARTMENT SYNDROME*	63	F	92	WHITE	4	624	5	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
HAEMATOMA*					3	636	65	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203527/50801 FEMUR FRACTURE*	57	F	128	WHITE	3	193	67	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
203531/49803 ABORTION INDUCED*	26	F	62	WHITE	3	530	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203533/51603 PNEUMONIA*	54	F	102	WHITE	3	37	57	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
COSTOCHONDRITIS*					2	71	?	UNRELATED	RECOVERING/RESOLVING	YES	NONE
203534/51805 BURSITIS*	53	M	69	WHITE	3	485	99	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
ARTHRITIS INFECTIVE*					3	561	23	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
ARTHRITIS INFECTIVE*					3	615	30	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203537/52201 CARDIAC FAILURE CONGESTIVE*	84	F	67	WHITE	3	196	?	UNRELATED	UNRESOLVED	YES	DOSE HELD
IDIOPATHIC PULMONARY FIBROSIS*					5	196	256	UNRELATED	DEATH	NO	NONE
HAEMOLYTIC ANAEMIA*					4	366	?	UNRELATED	UNRESOLVED	NO	NONE
SEPTIC SHOCK*					4	366	10	RELATED	RESOLVED - WITH SEQUELAE	NO	NONE
HEPATIC ENCEPHALOPATHY*					3	434	7	UNRELATED	RESOLVED - WITH SEQUELAE	NO	NONE
HEPATIC ENCEPHALOPATHY*					3	450	2	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(19 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203538/52405 PULMONARY HYPERTENSION*	63	F	100	WHITE	2	227	?	UNRELATED	UNRESOLVED	YES	NONE
203538/52407 IMPAIRED GASTRIC EMPTYING*	63	F	80	WHITE	3	10	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
IMPAIRED GASTRIC EMPTYING*					3	107	?	UNRELATED	UNRESOLVED	YES	NONE
203553/54401 SCIATICA*	61	F	77	WHITE	3	97	18	UNRELATED	RESOLVED - WITH SEQUELAE	YES	NONE
203553/54402 MYALGIA*	54	F	57	WHITE	3	337	15	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203573/30401 ANAPHYLACTIC REACTION*	58	F	85	WHITE	3	431	5	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203593/55802 PERIPHERAL ISCHAEMIA*	55	M	79	BLACK	3	146	18	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
POST PROCEDURAL HAEMORRHAGE*					4	166	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
POST PROCEDURAL INFECTION*					4	166	138	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
ACUTE RESPIRATORY FAILURE*					4	172	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203622/23001 OSTEOARTHRITIS*	63	M	74	WHITE	3	333	40	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
HYDROCELE*					1	459	87	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
BURSITIS INFECTIVE*					3	482	184	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203656/14004 LUMBAR HERNIA*	61	F	81	BLACK	3	214	129	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(20 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY

Center: ALL CENTERS

Tocilizumab 8mg/kg IV q4w + DMARD: N = 631

CRTN/Pt. No. Adverse Event	Age yr	Sex	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203656/14004 BURSITIS INFECTIVE*	61	F	81	BLACK	3	400	80	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
INTERVERTEBRAL DISCITIS*					3	493	201	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203784/18009 HEPATIC STEATOSIS*	65	F	57	NOT AVAILABLE	3	170	?	UNRELATED	UNRESOLVED	NO	DOSE HELD
232344/58001 OSTEOARTHRITIS*	79	F	80	WHITE	2	707	9	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
232912/58401 HYPERSENSITIVITY*	69	F	48	WHITE	1	1	<= 1	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(21 of 26)

s1ae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

TOCILIZUMAB SC->IV; N = 48

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202810/11005 SQUAMOUS CELL CARCINOMA*	64 M	85	WHITE	2	182	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202898/38203 ABORTION INDUCED*	27 F	58	AMERICAN INDIAN / ALASKA NATIVE	3	282	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	NO	NONE
202932/44002 OSTEOARTHRITIS*	55 F	70	WHITE	3	94	12	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203355/16611 UPPER LIMB FRACTURE*	61 F	97	WHITE	3	489	40	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203514/48201 PELVIC FLOOR MUSCLE WEAKNESS*	51 F	76	WHITE	2	482	42	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203532/51403 DIVERTICULITIS*	56 F	76	WHITE	2	178	15	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(22 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

TOCILIZUMAB IV->SC: N = 186

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202776/27409 PELVIC ABSCESS*	48 F	89	AMERICAN INDIAN / ALASKA NATIVE	4	114	86	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
202810/11008 PARATHYROID TUMOUR BENIGN*	71 F	74	NOT AVAILABLE	3	7	551	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
CERVICAL VERTEBRAL FRACTURE*				3	170	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
PLEURAL EFFUSION*				3	170	61	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
PNEUMOTHORAX*				3	170	61	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
PULMONARY CONTUSION*				3	170	61	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
RIB FRACTURE*				3	170	61	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
ROAD TRAFFIC ACCIDENT*				3	170	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
STERNAL FRACTURE*				3	170	61	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
202902/39006 COLITIS ULCERATIVE*	54 M	80	WHITE	3	274	?	UNRELATED	RECOVERING/RESOLVING	YES	DISCONTINUED
202908/40203 PNEUMONIA*	80 M	60	WHITE	4	415	39	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
RESPIRATORY FAILURE*				4	415	10	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202910/40606 MITRAL VALVE INCOMPETENCE*	74 F	83	WHITE	3	42	195	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
CARDIAC ARREST*				4	129	<= 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
PNEUMOTHORAX*				4	129	17	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(23 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

TOCILIZUMAB IV->SC: N = 186

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
202910/40606 OSTEOMYELITIS*	74 F	83	WHITE	3	131	53	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
VENOUS THROMBOSIS LIMB*				3	172	93	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
202937/28807 RENAL ABSCESS*	36 F	58	NOT AVAILABLE	4	234	35	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
ADRENAL GLAND INJURY*				4	264	5	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
202979/41201 BURKHOLDERIA PSEUDOMALLEI INFECTION*	62 F	53	ASIAN	3	453	163	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203022/16203 PNEUMONIA*	62 M	54	WHITE	5	162	<= 1	UNRELATED	DEATH	NO	NONE
203059/20810 ABSCESS*	29 M	100	WHITE	3	322	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
LYMPHADENOPATHY*				3	322	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203066/21801 ARTHROPOD STING*	63 F	59	WHITE	2	265	16	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
BREAST CANCER*				3	525	?	UNRELATED	UNRESOLVED	YES	NONE
203091/34402 UTERINE LEIOMYOMA*	72 F	65	WHITE	2	416	29	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
UTERINE POLYP*				3	416	29	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
CHOLECYSTITIS CHRONIC*				3	434	11	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
SMALL INTESTINAL PERFORATION*				4	451	28	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
PERITONITIS*				4	453	26	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'?' = At least one date is missing or invalid.

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(24 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

TOCILIZUMAB IV->SC: N = 186

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203091/34402 MYOCARDIAL INFARCTION*	72 F	65	WHITE	3	462	17	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203172/24003 CHOLANGITIS ACUTE*	60 F	51	ASIAN	1	549	57	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203206/25601 DIVERTICULAR PERFORATION*	57 F	82	WHITE	3	441	13	RELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
PERICOLIC ABSCESS*				3	441	13	RELATED	RESOLVED - WITH SEQUELAE	YES	DISCONTINUED
203252/14401 UTERINE LEIOMYOMA*	55 F	72	WHITE	3	86	19	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
RHEUMATOID ARTHRITIS*				2	216	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203255/26810 LUMBAR RADICULOPATHY*	67 F	62	WHITE	1	6	9	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
PNEUMONIA*				3	114	20	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
PLEURISY*				2	148	19	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DOSE HELD
INFECTIOUS PLEURAL EFFUSION*				4	167	25	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
203261/32406 DEEP VEIN THROMBOSIS*	55 M	88	WHITE	3	100	49	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
203484/45003 CELLULITIS*	56 F	79	WHITE	3	171	3	RELATED	RESOLVED - WITH SEQUELAE	YES	NONE
SEPSIS*				5	172	2	RELATED	SEQUELAE DEATH	YES	NONE
203525/50408 TRANSIENT GLOBAL AMNESIA*	66 M	72	WHITE	3	192	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(25 of 26)

slae01_s Listing of all Serious Adverse Events by Trial Treatment and CRTN/ Patient Number (Safety Population)

Protocol(s): T22762B

Analysis: SAFETY Center: ALL CENTERS

TOCILIZUMAB IV->SC: N = 186

CRTN/Pt. No. Adverse Event	Age Sex yr	Weight kg	Race	CTC Grade	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
203525/50408 CELLULITIS*	66 M	72	WHITE	1	447	25	RELATED	RESOLVED - NO SEQUELAE	YES	NONE
203554/54603 PNEUMONIA*	70 F	55	ASIAN	3	103	17	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
203560/30601 LARYNGITIS*	48 F	82	WHITE	3	50	4	RELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
NEUTROPENIA*				4	50	4	RELATED	RESOLVED - NO SEQUELAE	NO	DOSE HELD
203762/14810 INTERVERTEBRAL DISC DISORDER*	60 F	68	WHITE	2	69	5	UNRELATED	RESOLVED - NO SEQUELAE	YES	DOSE HELD
MUSCLE ABSCESS*				2	110	130	RELATED	RESOLVED - NO SEQUELAE		DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.0.

CRTN = Clinical Research Task Number (center no.)

* Serious adverse event

'Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only

Patients in the switcher columns are re-baselined to the visit of their first open label dose

AE08/AE01 10DEC2013:15:36:17

(26 of 26)

表 2.7.4.8-17 重篤な有害事象一覧 (NA25220試験)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD); N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont.or Dose Adjusted
204230/57603									
GRAND MAL CONVULSION									
3	131	6	TCZ PFS SC INJECTION	3	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE	
DRUG HYPERSENSITIVITY									
1	135	9	TCZ PFS SC INJECTION	7	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE	
204242/57651									
DEEP VEIN THROMBOSIS									
2	97	113	TCZ PFS SC INJECTION	12	RELATED	UNKNOWN	YES	NONE	
204247/57701									
CERVICAL SPINAL STENOSIS(E)									
3	112	170	TCZ PFS SC INJECTION	1	UNRELATED	RESOLVED - WITH SEQUELAE	YES	DRUG INTERRUPTED	
204247/57703									
CELLULITIS(E)									
3	344	55	TCZ PFS SC INJECTION	3	RELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED	
204261/57952									
SEPSIS									
5	26	?	TCZ PFS SC INJECTION	8	RELATED	DEATH	YES	NOT APPLICABLE	
204321/58501									
CELLULITIS(E)									
3	366	5	TCZ PFS SC INJECTION	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE	

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(1 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment ----- Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont.or Dose Adjusted
204321/58505									
BIPOLAR DISORDER	3	161	4	TCZ PFS SC INJECTION	5	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
DIABETIC KETOACIDOSIS	3	206	5	TCZ PFS SC INJECTION	7	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204446/58802									
NEUTROPENIA	3	504	49	TCZ PFS SC INJECTION	< 1	RELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
204447/58851									
SYNCOPE (E)	3	609	<= 1	TCZ PFS SC INJECTION	6	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204447/58853									
PERICARDITIS (E)	2	660	29	TCZ PFS SC INJECTION	2	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
PLEURISY (E)	2	660	29	TCZ PFS SC INJECTION	2	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
PNEUMONIA STAPHYLOCOCCAL (E)	2	660	29	TCZ PFS SC INJECTION	2	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
STAPHYLOCOCCAL BACTERAEEMIA (E)	2	664	25	TCZ PFS SC INJECTION	6	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204447/58854									
INGUINAL HERNIA (E)	3	156	17	TCZ PFS SC INJECTION	< 1	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(2 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS
 TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
204988/36102									
PULMONARY TUBERCULOSIS	2	471	?	TCZ PFS SC INJECTION	8	RELATED	RECOVERING/ RESOLVING	YES	DISCONTINUED
PLEURAL EFFUSION	2	479	28	TCZ PFS SC INJECTION	2	UNRELATED	RESOLVED – NO SEQUELAE	YES	NOT APPLICABLE
204990/43004									
TRANSIENT ISCHAEMIC ATTACK	3	395	4	TCZ PFS SC INJECTION	3	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
HYPERTENSION	2	465	?	TCZ PFS SC INJECTION	3	UNRELATED	RECOVERING/ RESOLVING	YES	NONE
204990/43005									
LOWER RESPIRATORY TRACT INFECTION	3	16	6	TCZ PFS SC INJECTION	15	UNRELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
204991/43051									
SYNCOPE	4	319	12	TCZ PFS SC INJECTION	10	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
RECTAL CANCER	3	534	?	TCZ PFS SC INJECTION	1	UNRELATED	UNRESOLVED	YES	DISCONTINUED
204996/55103									
ACUTE MYOCARDIAL INFARCTION	5	290	?	TCZ PFS SC INJECTION	9	UNRELATED	DEATH	YES	NOT APPLICABLE

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(3 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
205271/31001 PNEUMONIA (E)	3	296	21	TCZ PFS SC INJECTION	< 1	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
205273/36053 SEPSIS	5	14	?	TCZ PFS SC INJECTION	13	RELATED	DEATH	YES	NOT APPLICABLE
205731/32106 NEUTROPENIA	4	587	29	TCZ PFS SC INJECTION	11	RELATED	RESOLVED – NO SEQUELAE		DISCONTINUED
205762/10002 PULMONARY TUBERCULOSIS	3	163	?	TCZ PFS SC INJECTION	8	RELATED	UNRESOLVED	YES	DISCONTINUED
205763/10056 ABSCCESS SOFT TISSUE (E)	2	203	238	TCZ PFS SC INJECTION	7	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
ABSCCESS SOFT TISSUE (E)	1	575	104	TCZ PFS SC INJECTION	8	RELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
CELLULITIS (E)	1	575	104	TCZ PFS SC INJECTION	8	RELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
205765/10102 GASTROENTERITIS (E)	2	361	11	TCZ PFS SC INJECTION	3	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(4 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS
 TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment ----- Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
205765/10103 CHOLELITHIASIS	2	443	197	TCZ PFS SC INJECTION	8	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
205991/32257 PNEUMONIA	3	75	15	TCZ PFS SC INJECTION	3	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
206024/16102 PYREXIA	3	428	9	TCZ PFS SC INJECTION	7	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
206052/39502 OVARIAN CYST	2	144	5	TCZ PFS SC INJECTION	9	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
206055/39652 ABDOMINAL ADHESIONS	2	240	6	TCZ PFS SC INJECTION	< 1	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
206394/12104 ADENOCARCINOMA PANCREAS	3	83	?	TCZ PFS SC INJECTION	29	UNRELATED	RECOVERING/ RESOLVING	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(5 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)
 Protocol(s): T25220B
 Analysis: SAFETY Center: ALL CENTERS
 TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
206394/12105									
LOWER RESPIRATORY TRACT INFECTION	5	32	?	TCZ PFS SC INJECTION	1	RELATED	DEATH		NOT APPLICABLE
PLEURAL EFFUSION	4	32	?	TCZ PFS SC INJECTION	1	RELATED	UNRESOLVED	YES	DRUG INTERRUPTED
SEPTIC SHOCK	4	132	?	TCZ PFS SC INJECTION	101	RELATED	UNRESOLVED	NO	DRUG INTERRUPTED
206394/12107									
PNEUMONIA (E)	2	673	8	TCZ PFS SC INJECTION	7	RELATED	RESOLVED – NO SEQUELAE	YES	NOT APPLICABLE
206394/12117									
ERYSIPELAS	3	79	25	TCZ PFS SC INJECTION	9	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
ARTHRITIS BACTERIAL	3	169	31	TCZ PFS SC INJECTION	99	RELATED	RESOLVED – NO SEQUELAE	YES	NOT APPLICABLE
OSTEOMYELITIS	3	169	?	TCZ PFS SC INJECTION	99	RELATED	RECOVERING/RESOLVING	YES	NOT APPLICABLE
206395/12155									
RENAL CANCER	3	100	140	TCZ PFS SC INJECTION	1	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
206397/12254									
ANGINA PECTORIS	3	183	7	TCZ PFS SC INJECTION	14	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.
 CRTN = Clinical Research Task Number (center no.)
 For processing, missing TT end date and time are replaced by TT start date and time.
 '?' = At least one date is missing or invalid.
 (E) Escape therapy received at time of assessment
 AE08/AE05 23APR2014:14:22:03

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
206399/12354	LOCALISED INFECTION 3	405	?	TCZ PFS SC INJECTION	< 1	RELATED	UNRESOLVED	YES	DRUG INTERRUPTED
207389/37003	ATRIAL FIBRILLATION 2	225	9	TCZ PFS SC INJECTION	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED
207393/37166	PYODERMA GANGRENOSUM 2	231	20	TCZ PFS SC INJECTION	6	RELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED
209872/32504	CELLULITIS (E) 3	629	85	TCZ PFS SC INJECTION	6	RELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED
	URINARY TRACT INFECTION (E) 3	633	81	TCZ PFS SC INJECTION	3	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
209872/32508	GASTRITIS EROSIIVE (E) 3	281	8	TCZ PFS SC INJECTION	9	RELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED
210439/59202	DIVERTICULUM INTESTINAL HAEMORRHAGIC 3	56	<= 1	TCZ PFS SC INJECTION	13	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(7 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment ----- Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
230722/30251									
CONSTIPATION (E)	2	135	5	TCZ PFS SC INJECTION	1	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
HIP FRACTURE (E)	2	357	41	TCZ PFS SC INJECTION	6	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231361/37314									
OVARIAN CYST	2	134	53	TCZ PFS SC INJECTION	6	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
231361/37325									
ABSCESS	3	146	28	TCZ PFS SC INJECTION	6	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231365/37502									
BRONCHITIS	3	463	20	TCZ PFS SC INJECTION	12	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231371/14005									
MUSCULOSKELETAL CHEST PAIN	3	575	4	TCZ PFS SC INJECTION	14	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231380/14204									
SCHWANNOMA	3	111	?	TCZ PFS SC INJECTION	12	UNRELATED	UNRESOLVED	NO	NONE

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(8 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w (162 mg SC + DMARD): N = 437

CRTN/Pt. No. Adverse Event	CTC Grade	Day of Onset	Duration in days	Trial Treatment	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
				Actually Received					
231384/28007									
SUPRAVENTRICULAR TACHYCARDIA	3	336	6	TCZ PFS SC INJECTION	14	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
PNEUMONIA	2	625	19	TCZ PFS SC INJECTION	9	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231384/28008									
INGUINAL HERNIA	3	407	3	TCZ PFS SC INJECTION	14	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
232416/12605									
PANCREATITIS ACUTE	2	98	12	TCZ PFS SC INJECTION	15	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
233552/12708									
BRONCHOPNEUMONIA	3	120	17	TCZ PFS SC INJECTION	5	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(9 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w -> TCZ AI q2w (162 mg SC + DMARD): N = 168

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
204230/57603 GRAND MAL CONVULSION	2	53	6	TCZ AI SC INJECTION	10	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204242/57651 ANGINA PECTORIS	5	40	?	TCZ AI SC INJECTION	25	UNRELATED	DEATH	YES	NOT APPLICABLE
204258/57804 CALCULUS URETERIC	3	199	84	TCZ AI SC INJECTION	12	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204260/57902 NON-CARDIAC CHEST PAIN(E)	2	377	3	TCZ AI SC INJECTION	6	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204447/58852 BREAST CANCER(E)	3	423	?	TCZ AI SC INJECTION	10	UNRELATED	RECOVERING/RESOLVING	YES	DISCONTINUED
204987/36001 ENDOMETRIAL HYPERTROPHY	3	445	22	TCZ AI SC INJECTION	10	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
205530/12006 OVARIAN EPITHELIAL CANCER	3	163	?	TCZ AI SC INJECTION	8	RELATED	RECOVERING/RESOLVING	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(10 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w -> TCZ AI q2w (162 mg SC + DMARD): N = 168

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
205541/49104									
LUMBAR RADICULOPATHY									
4		10	59	TCZ AI SC INJECTION	9	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
INTERVERTEBRAL DISC PROTRUSION									
1		75	300	TCZ AI SC INJECTION	4	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
JOINT ABSCESS									
4		92	78	TCZ AI SC INJECTION	21	RELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
CONSTIPATION									
3		134	2	TCZ AI SC INJECTION	63	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
205731/32111									
OVARIAN CYST TORSION									
3		368	3	TCZ AI SC INJECTION	3	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
205763/10057									
LUDWIG ANGINA									
3		170	45	TCZ AI SC INJECTION	1	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
205782/19005									
PYREXIA									
5		124	?	TCZ AI SC INJECTION	25	RELATED	DEATH	YES	DRUG INTERRUPTED
206394/12106									
PANCREATITIS ACUTE									
4		37	7	TCZ AI SC INJECTION	6	RELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(11 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w -> TCZ AI q2w (162 mg SC + DMARD): N = 168

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
206397/12263									
MYELOYDYLASTIC SYNDROME	3	241	?	TCZ AI SC INJECTION	2	RELATED	UNRESOLVED	YES	DISCONTINUED
DIARRHOEA	2	243	20	TCZ AI SC INJECTION	4	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
206460/32354									
CATARACT	3	354	41	TCZ AI SC INJECTION	2	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
207393/37167									
MYOCARDIAL INFARCTION	5	332	?	TCZ AI SC INJECTION	9	UNRELATED	DEATH	NO	NOT APPLICABLE
208683/12552									
NEUTROPENIA	4	419	13	TCZ AI SC INJECTION	< 1	RELATED	RESOLVED - NO SEQUELAE		DISCONTINUED
231384/28006									
DEEP VEIN THROMBOSIS	2	176	9	TCZ AI SC INJECTION	19	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
232416/12605									
PANCREATITIS ACUTE	2	85	8	TCZ AI SC INJECTION	13	UNRELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED
PANCREATITIS ACUTE	2	196	4	TCZ AI SC INJECTION	26	UNRELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(12 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

TCZ PFS q2w -> TCZ AI q2w (162 mg SC + DMARD): N = 168

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
232416/12610									
ARTHRTIS BACTERIAL									
2	247	137	TCZ AI SC INJECTION	12	RELATED	RESOLVED - WITH SEQUELAE	YES	DRUG INTERRUPTED	
OSTEOMYELITIS									
2	247	137	TCZ AI SC INJECTION	12	RELATED	RESOLVED - WITH SEQUELAE	YES	DRUG INTERRUPTED	

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(13 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

Placebo PFS q2w -> TCZ PFS q2w (162 mg SC + DMARD); N = 61

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment ----- Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
205785/19053									
URINARY TRACT INFECTION									
3	115	3	TCZ PFS SC INJECTION	15	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED	
233552/12706									
ACUTE MYOCARDIAL INFARCTION									
5	260	?	TCZ PFS SC INJECTION	7	RELATED	DEATH	NO	NOT APPLICABLE	

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(14 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

Placebo PFS q2w -> TCZ AI q2w (162 mg SC + DMARD): N = 59

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment ----- Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
206393/12052									
ANAL SQUAMOUS CELL CARCINOMA (E)									
3		336	177	TCZ AI SC INJECTION	4	RELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(15 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

Placebo PFS q2w (162 mg SC + DMARD): N = 218

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
204211/57002									
CERVICAL VERTEBRAL FRACTURE	3	120	113	Placebo PFS SC INJECTION	7	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
204214/57151									
CELLULITIS (E)	3	414	44	TCZ PFS SC INJECTION	5	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
204223/57401									
LOCALISED INFECTION (E)	2	225	56	TCZ PFS SC INJECTION	14	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
LEIOMYOSARCOMA (E)	3	289	?	TCZ PFS SC INJECTION	78	UNRELATED	UNRESOLVED	YES	NOT APPLICABLE
204229/57555									
PNEUMONIA	3	29	23	Placebo PFS SC INJECTION	3	UNRELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
SEPSIS	2	34	10	Placebo PFS SC INJECTION	8	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
204261/57955									
ACUTE MYOCARDIAL INFARCTION (E)	3	96	4	TCZ PFS SC INJECTION	11	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
PNEUMONIA (E)	3	509	28	TCZ PFS SC INJECTION	1	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(16 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

Placebo PFS q2w (162 mg SC + DMARD): N = 218

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
204444/58751									
COCCIDIOIDOMYCOSIS	2	3	?	Placebo PFS SC INJECTION	2	UNRELATED	RECOVERING/RESOLVING	YES	DISCONTINUED
204993/55003									
OSTEOARTHRITIS	3	2	84	Placebo PFS SC INJECTION	1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
PANCREATIC CARCINOMA (E)	4	554	?	TCZ PFS SC INJECTION	< 1	RELATED	UNRESOLVED	YES	DISCONTINUED
UPPER GASTROINTESTINAL HAEMORRHAGE (E)	5	658	?	TCZ PFS SC INJECTION	76	UNRELATED	DEATH	NO	NOT APPLICABLE
205273/36051									
PULMONARY TUBERCULOSIS (E)	3	247	155	TCZ PFS SC INJECTION	1	UNRELATED	RESOLVED - NO SEQUELAE	YES	DISCONTINUED
205731/32105									
BASAL CELL CARCINOMA (E)	1	336	28	TCZ PFS SC INJECTION	< 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
SQUAMOUS CELL CARCINOMA (E)	1	336	28	TCZ PFS SC INJECTION	< 1	UNRELATED	RESOLVED - NO SEQUELAE	YES	NONE
205785/19054									
GASTRODUODENAL ULCER (E)	3	256	2	TCZ PFS SC INJECTION	14	UNRELATED	RESOLVED - NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

'?' = At least one date is missing or invalid.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(17 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)

Protocol(s): T25220B

Analysis: SAFETY Center: ALL CENTERS

Placebo PFS q2w (162 mg SC + DMARD): N = 218

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
205788/67002									
CHOLECYSTITIS	ACUTE (E)	3	394	6	TCZ PFS SC INJECTION	1	RELATED	RESOLVED – NO SEQUELAE	YES NONE
205817/39151									
ESCHERICHIA INFECTION (E)	2	137	9	TCZ PFS SC INJECTION	1	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
205820/39255									
LYMPHADENITIS (E)	3	401	30	TCZ PFS SC INJECTION	8	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
206054/39602									
ULCERATIVE KERATITIS (E)	2	220	11	TCZ PFS SC INJECTION	7	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
206397/12253									
INTERVERTEBRAL DISC PROTRUSION	3	76	32	Placebo PFS SC INJECTION	5	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
SPINAL COLUMN STENOSIS	3	76	32	Placebo PFS SC INJECTION	5	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
POSTOPERATIVE WOUND INFECTION	3	118	205	Placebo PFS SC INJECTION	47	UNRELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
ADRENOCORTICAL INSUFFICIENCY ACUTE	2	128	7	Placebo PFS SC INJECTION	57	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.

CRTN = Clinical Research Task Number (center no.)

For processing, missing TT end date and time are replaced by TT start date and time.

(E) Escape therapy received at time of assessment

AE08/AE05 23APR2014:14:22:03

(18 of 19)

slae05_s Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)
 Protocol(s): T25220B
 Analysis: SAFETY Center: ALL CENTERS
 Placebo PFS q2w (162 mg SC + DMARD): N = 218

CRTN/Pt. No.	CTC Grade	Day of Onset	Duration in days	Trial Treatment Actually Received	Time after Last Dose days	Relation to Trial Treatment	Outcome	Trt given for AE	Discont. or Dose Adjusted
206397/12259 PNEUMONIA	3	80	19	Placebo PFS SC INJECTION	9	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
207252/16203 MALIGNANT MELANOMA (E)	3	368	54	TCZ PFS SC INJECTION	10	UNRELATED	RESOLVED – NO SEQUELAE	YES	DISCONTINUED
CELLULITIS (E)	3	426	20	TCZ PFS SC INJECTION	68	UNRELATED	RESOLVED – NO SEQUELAE	YES	NOT APPLICABLE
231361/37312 SUBCUTANEOUS ABSCESS (E)	3	585	15	TCZ PFS SC INJECTION	3	RELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231361/37319 CHOLELITHIASIS	3	135	4	Placebo PFS SC INJECTION	8	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED
231382/14251 SYNOVIAL CYST	3	28	2	Placebo PFS SC INJECTION	< 1	UNRELATED	RESOLVED – NO SEQUELAE	YES	NONE
231384/28003 ACUTE MYOCARDIAL INFARCTION (E)	2	483	65	TCZ PFS SC INJECTION	5	UNRELATED	RESOLVED – NO SEQUELAE	YES	DRUG INTERRUPTED

Investigator text for Adverse Events encoded using MedDRA version 16.1.
 CRTN = Clinical Research Task Number (center no.)
 For processing, missing TT end date and time are replaced by TT start date and time.
 (E) Escape therapy received at time of assessment
 AE08/AE05 23APR2014:14:22:03

(19 of 19)

[5.3.5.4-7 Listing of all Serious Adverse Events with Actual Received Treatment (Safety Population)を再掲]

表 2.7.4.8-18 臨床検査値のCTCAEによるシフトテーブル (MRA632JP 試験-二重盲検期間)

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Hemoglobin (g/L) (HYPER)

WORST	Baseline						Missing	Total
	0	1	2	3	4	5		
PLACEBO (N=18)								
0	16 (88.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (88.9%)
1	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)								
0	15 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Hemoglobin (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	12 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (66.7%)
1	4 (22.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)
2	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	8 (44.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (50.0%)
1	3 (16.7%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (38.9%)
2	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	12 (66.7%)	5 (27.8%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Leukocytes (WBC) (10⁹/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Leukocytes (WBC) (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	15 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Neutrophils (10⁹/L) (HYPO)

WORST	Baseline							Total
	0	1	2	3	4	5	Missing	
PLACEBO (N=18)								
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)								
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Lymphocytes (10⁹/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	12 (66.7%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (72.2%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	4 (22.2%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	15 (83.3%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (88.9%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Lymphocytes (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	10 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (55.6%)
1	1 (5.6%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
2	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	14 (77.8%)	2 (11.1%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	7 (38.9%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (44.4%)
1	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	4 (22.2%)	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (33.3%)
3	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	14 (77.8%)	2 (11.1%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Platelets (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Total Bilirubin (umol/L) (HYPER)

WORST	Baseline							Total
	0	1	2	3	4	5	Missing	
PLACEBO (N=18)								
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)								
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Alkaline Phosphate (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	16 (88.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (88.9%)
1	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:ASAT (SGOT) (U/L) (HYPER)

		Baseline								
WORST		0	1	2	3	4	5	Missing	Total	
PLACEBO (N=18)										
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)	
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)	
MRA-SC 162mg/w (N=18)										
0	14 (77.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)	
1	3 (16.7%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)	

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:ALAT (SGPT) (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	15 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	9 (50.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (55.6%)
1	7 (38.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (38.9%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Gamma-GTP (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	12 (66.7%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (72.2%)
1	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	13 (72.2%)	3 (16.7%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	11 (61.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (61.1%)
1	5 (27.8%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (33.3%)
2	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Cholesterol (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	8 (44. 4%)	1 (5. 6%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	9 (50. 0%)
1	4 (22. 2%)	5 (27. 8%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	9 (50. 0%)
2	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
3	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
4	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
5	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Missing	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Total	12 (66. 7%)	6 (33. 3%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	18 (100. 0%)
MRA-SC 162mg/w (N=18)									
0	6 (33. 3%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	6 (33. 3%)
1	2 (11. 1%)	7 (38. 9%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	9 (50. 0%)
2	0 (0. 0%)	1 (5. 6%)	2 (11. 1%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	3 (16. 7%)
3	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
4	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
5	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Missing	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Total	8 (44. 4%)	8 (44. 4%)	2 (11. 1%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	18 (100. 0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc. sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp. out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Creatinine (umol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
1	13 (72.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
1	12 (66.7%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (88.9%)
2	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	13 (72.2%)	5 (27.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Albumin (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	6 (33.3%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (38.9%)
1	7 (38.9%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (61.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	13 (72.2%)	5 (27.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	13 (72.2%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	1 (5.6%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	14 (77.8%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Triglycerides (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	7 (38.9%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (61.1%)
1	3 (16.7%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)
2	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	11 (61.1%)	7 (38.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	5 (27.8%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (33.3%)
1	6 (33.3%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (55.6%)
2	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	11 (61.1%)	7 (38.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Creatine phosphokinase (CPK) total (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Sodium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Sodium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Potassium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Potassium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	10 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (55.6%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	6 (33.3%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (44.4%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	7 (38.9%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (50.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	7 (38.9%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (50.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	14 (77.8%)	0 (0.0%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Corr. Calcium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Corr. Calcium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	12 (66.7%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (88.9%)
1	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	14 (77.8%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	13 (72.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
1	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Phosphorous inorganic (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	15 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
2	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	13 (72.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
1	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
2	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	15 (83.3%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Uric Acid (umol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	15 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	0 (0.0%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	14 (77.8%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (83.3%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	2 (11.1%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	0 (0.0%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Fibrinogen (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	0 (0.0%)	11 (61.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (61.1%)
1	0 (0.0%)	6 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (33.3%)
2	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	0 (0.0%)	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	10 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (55.6%)
3	0 (0.0%)	8 (44.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (44.4%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	0 (0.0%)	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Troponin T (ug/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	17 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	17 (94.4%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	14 (77.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
1	2 (11.1%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (88.9%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

shft01ctc_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Proteinuria (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
PLACEBO (N=18)									
0	14 (77.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
1	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
2	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
MRA-SC 162mg/w (N=18)									
0	14 (77.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (77.8%)
1	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632a/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632a/reports/shft01ctc_sp.out
 04FEB2016 10:39

[5.3.5.1-1 表 15.3.4-3を再掲]

表 2.7.4.8-19 臨床検査値の CTCAE によるシフトテーブル (MRA632JP 試験-全期間の本剤全投与例)

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Hemoglobin (g/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	32 (88.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (88.9%)
1	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Hemoglobin (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	14 (38.9%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (41.7%)
1	9 (25.0%)	5 (13.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (38.9%)
2	3 (8.3%)	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (16.7%)
3	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	26 (72.2%)	8 (22.2%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Leukocytes (WBC) (10⁹/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Leukocytes (WBC) (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	29 (80.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (80.6%)
1	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
2	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
3	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Neutrophils (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	27 (75.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (75.0%)
1	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
2	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
3	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Lymphocytes (10⁹/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	29 (80.6%)	0 (0.0%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (88.9%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	33 (91.7%)	0 (0.0%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Lymphocytes (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	12 (33.3%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (36.1%)
1	7 (19.4%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.2%)
2	8 (22.2%)	2 (5.6%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (30.6%)
3	1 (2.8%)	0 (0.0%)	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	28 (77.8%)	3 (8.3%)	3 (8.3%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Platelets (10⁹/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Total Bilirubin (umol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	31 (86.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (86.1%)
1	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
2	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Alkaline Phosphate (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	33 (91.7%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (97.2%)
1	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	34 (94.4%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:ASAT (SGOT) (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	23 (63.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (63.9%)
1	11 (30.6%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (36.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	34 (94.4%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:ALAT (SGPT) (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	21 (58.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (58.3%)
1	10 (27.8%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (36.1%)
2	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	31 (86.1%)	4 (11.1%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Gamma-GTP (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	22 (61.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (61.1%)
1	8 (22.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.0%)
2	0 (0.0%)	1 (2.8%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	30 (83.3%)	2 (5.6%)	2 (5.6%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Cholesterol (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	10 (27.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (27.8%)
1	13 (36.1%)	8 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (58.3%)
2	2 (5.6%)	1 (2.8%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (13.9%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	25 (69.4%)	9 (25.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Creatinine (umol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
1	22 (61.1%)	9 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (86.1%)
2	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	26 (72.2%)	10 (27.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Albumin (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	22 (61.1%)	6 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (77.8%)
1	2 (5.6%)	6 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.2%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	24 (66.7%)	12 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Triglycerides (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	11 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (30.6%)
1	12 (33.3%)	6 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (50.0%)
2	1 (2.8%)	5 (13.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (16.7%)
3	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	24 (66.7%)	12 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Creatine phosphokinase (CPK) total (U/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Sodium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	35 (97.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (97.2%)
1	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Sodium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	35 (97.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (97.2%)
1	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Potassium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Potassium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	16 (44. 4%)	0 (0. 0%)	2 (5. 6%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	18 (50. 0%)
1	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
2	14 (38. 9%)	0 (0. 0%)	4 (11. 1%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	18 (50. 0%)
3	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
4	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
5	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Missing	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)
Total	30 (83. 3%)	0 (0. 0%)	6 (16. 7%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	36 (100. 0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc. sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp. out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Corr. Calcium (mmol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	34 (94.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	34 (94.4%)
1	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Corr. Calcium (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	22 (61.1%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (63.9%)
1	11 (30.6%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (36.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	33 (91.7%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Phosphorous inorganic (mmol/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	23 (63.9%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (66.7%)
1	2 (5.6%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (13.9%)
2	6 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (16.7%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	31 (86.1%)	4 (11.1%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Uric Acid (umol/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	25 (69.4%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (72.2%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	7 (19.4%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.2%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	32 (88.9%)	0 (0.0%)	0 (0.0%)	4 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Fibrinogen (g/L) (HYPO)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
1	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
2	6 (16.7%)	7 (19.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (36.1%)
3	8 (22.2%)	13 (36.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (58.3%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	16 (44.4%)	20 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter: Troponin T (ug/L) (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	30 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (83.3%)
1	3 (8.3%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (13.9%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	33 (91.7%)	2 (5.6%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

shft01ctc_mt_sp Shift table of CTC grade for Laboratory Data : baseline x worst
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Parameter:Proteinuria (HYPER)

WORST	Baseline							Missing	Total
	0	1	2	3	4	5			
MRA-SC 162mg/W Total (N=36)									
0	23 (63.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (63.9%)
1	10 (27.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (27.8%)
2	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (100.0%)

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/shft01ctc.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/shft01ctc_mt_sp.out
 12JAN2017 17:15

[5.3.5.1-7 表 11.3-26を再掲]

表 2.7.4.8-20 臨床検査値の CTCAE によるシフトテーブル (WA28119試験-二重盲検期間)

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline, Hematology, Safety Population
Protocol: WA28119

Baseline NCI-CTCAE Grade	Post-Baseline NCI-CTCAE Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Hemoglobin (High)					
0	Total	49 (98.0%)	51 (100.0%)	100 (100.0%)	48 (98.0%)
	0	49 (98.0%)	48 (94.1%)	90 (90.0%)	46 (93.9%)
1	Total	1 (2.0%)	0	0	1 (2.0%)
	0	1 (2.0%)	0	0	0
Total	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	50 (100.0%)	48 (94.1%)	90 (90.0%)	46 (93.9%)
1	Total	0	0	0	1 (2.0%)
	0	0	0	0	1 (2.0%)
Hemoglobin (Low)					
0	Total	43 (86.0%)	45 (88.2%)	93 (93.0%)	46 (93.9%)
	0	33 (66.0%)	38 (74.5%)	88 (88.0%)	45 (91.8%)
1	Total	10 (20.0%)	7 (13.7%)	5 (5.0%)	1 (2.0%)
	0	10 (20.0%)	7 (13.7%)	5 (5.0%)	1 (2.0%)
1	Total	7 (14.0%)	5 (9.8%)	7 (7.0%)	3 (6.1%)
	0	2 (4.0%)	2 (3.9%)	3 (3.0%)	2 (4.1%)
2	Total	5 (10.0%)	3 (5.9%)	4 (4.0%)	1 (2.0%)
	0	5 (10.0%)	3 (5.9%)	4 (4.0%)	1 (2.0%)
Total	Total	0	1 (2.0%)	0	0
	0	0	1 (2.0%)	0	0
1	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	35 (70.0%)	40 (78.4%)	91 (91.0%)	47 (95.9%)
2	Total	15 (30.0%)	11 (21.6%)	9 (9.0%)	2 (4.1%)
	0	15 (30.0%)	11 (21.6%)	9 (9.0%)	2 (4.1%)

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade. Baseline is the patient's last observation prior to initiation of study drug.

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline, Hematology, Safety Population
 Protocol: WA28119

Baseline NCI-CTCAE Grade	Post-Baseline NCI-CTCAE Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Lymphocytes Abs (High)	Total	48 (96.0%)	47 (92.2%)	92 (92.0%)	44 (89.8%)
	0	44 (88.0%)	45 (88.2%)	87 (87.0%)	40 (81.6%)
	2	4 (8.0%)	2 (3.9%)	5 (5.0%)	4 (8.2%)
2	Total	2 (4.0%)	4 (7.8%)	8 (8.0%)	5 (10.2%)
	0	0	0	2 (2.0%)	2 (4.1%)
	2	2 (4.0%)	4 (7.8%)	6 (6.0%)	3 (6.1%)
Total	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	44 (88.0%)	45 (88.2%)	89 (89.0%)	42 (85.7%)
	2	6 (12.0%)	6 (11.8%)	11 (11.0%)	7 (14.3%)

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade. Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_shift.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_shift_SE_HEM.out
 11JUL2016 22:39 Page 2 of 5

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline, Hematology, Safety Population
 Protocol: WA28119

Baseline NCI-CTCAE Grade	Post-Baseline NCI-CTCAE Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Lymphocytes Abs (Low)	Total	44 (88.0%)	47 (92.2%)	85 (85.0%)	43 (87.8%)
	0	38 (76.0%)	41 (80.4%)	77 (77.0%)	38 (77.6%)
	1	0	0	0	1 (2.0%)
	2	4 (8.0%)	6 (11.8%)	7 (7.0%)	3 (6.1%)
	3	2 (4.0%)	0	1 (1.0%)	1 (2.0%)
1	Total	0	0	1 (1.0%)	0
	2	0	0	1 (1.0%)	0
2	Total	4 (8.0%)	3 (5.9%)	11 (11.0%)	5 (10.2%)
	0	1 (2.0%)	2 (3.9%)	6 (6.0%)	2 (4.1%)
	1	0	0	1 (1.0%)	0
	2	3 (6.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
3	Total	1 (2.0%)	1 (2.0%)	3 (3.0%)	1 (2.0%)
	0	1 (2.0%)	0	0	1 (2.0%)
	2	0	0	2 (2.0%)	0
	3	0	1 (2.0%)	1 (1.0%)	0
4	Total	1 (2.0%)	0	0	0
	4	1 (2.0%)	0	0	0
Total	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	40 (80.0%)	43 (84.3%)	83 (83.0%)	41 (83.7%)
	1	0	0	1 (1.0%)	1 (2.0%)
	2	7 (14.0%)	7 (13.7%)	13 (13.0%)	5 (10.2%)
	3	2 (4.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
	4	1 (2.0%)	0	0	0

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade. Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_shift.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_shift_SE_HEM.out
 11JUL2016 22:39 Page 3 of 5

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline, Hematology, Safety Population
 Protocol: WA28119

Baseline NCI-CTCAE Grade	Post-Baseline NCI-CTCAE Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Neutrophils, Total, Abs	0	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	1	49 (98.0%)	48 (94.1%)	51 (51.0%)	32 (65.3%)
	2	0	2 (3.9%)	28 (28.0%)	9 (18.4%)
	3	1 (2.0%)	1 (2.0%)	17 (17.0%)	6 (12.2%)
	Total	0	0	0	4 (4.0%)
Total	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	49 (98.0%)	48 (94.1%)	51 (51.0%)	32 (65.3%)
	1	0	2 (3.9%)	28 (28.0%)	9 (18.4%)
	2	1 (2.0%)	1 (2.0%)	17 (17.0%)	6 (12.2%)
	3	0	0	4 (4.0%)	2 (4.1%)
Platelet	0	50 (100.0%)	51 (100.0%)	99 (99.0%)	47 (95.9%)
	1	50 (100.0%)	50 (98.0%)	92 (92.0%)	42 (85.7%)
	Total	0	1 (2.0%)	7 (7.0%)	5 (10.2%)
1	Total	0	0	1 (1.0%)	0
	0	0	0	1 (1.0%)	0
Missing	Total	0	0	0	2 (4.1%)
	0	0	0	0	2 (4.1%)
Total	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	50 (100.0%)	50 (98.0%)	93 (93.0%)	44 (89.8%)
	1	0	1 (2.0%)	7 (7.0%)	5 (10.2%)

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade. Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_shift.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_shift_SE_HEM.out
 11JUL2016 22:39 Page 4 of 5

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline, Hematology, Safety Population
 Protocol: WA28119

Baseline NCI-CTCAE Grade	Post-Baseline NCI-CTCAE Grade	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
White Blood Cell Count (High)	0	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
Total	0	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	Total	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
White Blood Cell Count (Low)	0	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	49 (98.0%)	49 (96.1%)	69 (69.0%)	36 (73.5%)
	1	0	1 (2.0%)	21 (21.0%)	8 (16.3%)
	2	1 (2.0%)	1 (2.0%)	9 (9.0%)	5 (10.2%)
	3	0	0	1 (1.0%)	0
Total	0	50 (100.0%)	51 (100.0%)	100 (100.0%)	49 (100.0%)
	0	49 (98.0%)	49 (96.1%)	69 (69.0%)	36 (73.5%)
	1	0	1 (2.0%)	21 (21.0%)	8 (16.3%)
	2	1 (2.0%)	1 (2.0%)	9 (9.0%)	5 (10.2%)
	3	0	0	1 (1.0%)	0

Table entries provide the number of patients with the highest post-baseline NCI-CTCAE grade. Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_lb_shift.sas / Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_lb_shift_SE_HEM.out
 11JUL2016 22:39 Page 5 of 5

[5.3.5.1-3 P 1888を再掲]

表 2.7.4.8-21 年齢別有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)

aet01age_mt_sp Safety Summary by Age
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

	< 18 years (N=6)	18 -< 65 years (N=27)	65 - years (N=3)
Total number of patients with at least one adverse event	6 (100.0%)	26 (96.3%)	2 (66.7%)
Total number of events	43	144	14
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one			
AE with fatal outcome	0	0	0
Serious AE	1 (16.7%)	4 (14.8%)	1 (33.3%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to dose modification/interruption	0	3 (11.1%)	0
Related Serious AE	1 (16.7%)	2 (7.4%)	0
AE leading to withdrawal from treatment	0	0	0
AE leading to dose modification/interruption	3 (50.0%)	13 (48.1%)	0
Related AE	4 (66.7%)	12 (44.4%)	2 (66.7%)
Related AE leading to withdrawal from treatment	0	0	0
Severe AE	1 (16.7%)	1 (3.7%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.
 Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet01age.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet01age_mt_sp.out
 12JAN2017 17:19
 Page 1 of 1

[5.3.5.1-7 表 11.3-16を再掲]

表 2.7.4.8-22 年齢別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)

aet03age_mt_sp Adverse Events by Age
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 18 years (N=6)	18 -< 65 years (N=27)	65 - years (N=3)
- Any adverse events -	34 (94.4%)	6 (100.0%)	26 (96.3%)	2 (66.7%)
感染症および寄生虫症				
- Overall -	31 (86.1%)	6 (100.0%)	23 (85.2%)	2 (66.7%)
鼻咽喉炎	18 (50.0%)	2 (33.3%)	14 (51.9%)	2 (66.7%)
咽喉炎	7 (19.4%)	1 (16.7%)	6 (22.2%)	0
上気道感染	7 (19.4%)	1 (16.7%)	5 (18.5%)	1 (33.3%)
胃腸炎	5 (13.9%)	1 (16.7%)	4 (14.8%)	0
感染性腸炎	4 (11.1%)	1 (16.7%)	3 (11.1%)	0
口腔ヘルペス	3 (8.3%)	0	3 (11.1%)	0
膀胱炎	3 (8.3%)	0	3 (11.1%)	0
インフルエンザ	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
外陰部腫カンジダ症	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
副鼻腔炎	2 (5.6%)	0	2 (7.4%)	0
せつ	1 (2.8%)	1 (16.7%)	0	0
ウイルス性腸炎	1 (2.8%)	0	1 (3.7%)	0
カンピロバクター胃腸炎	1 (2.8%)	1 (16.7%)	0	0
ヘモフィルス性肺炎	1 (2.8%)	0	1 (3.7%)	0
β溶血性レンサ球菌感染	1 (2.8%)	0	1 (3.7%)	0
急性腎盂腎炎	1 (2.8%)	0	1 (3.7%)	0
歯冠周囲炎	1 (2.8%)	0	1 (3.7%)	0
歯周炎	1 (2.8%)	0	0	1 (33.3%)
食道カンジダ症	1 (2.8%)	0	1 (3.7%)	0
爪囲炎	1 (2.8%)	0	1 (3.7%)	0
尿路感染	1 (2.8%)	0	1 (3.7%)	0
肺炎	1 (2.8%)	0	1 (3.7%)	0
麦粒腫	1 (2.8%)	0	1 (3.7%)	0
皮膚真菌感染	1 (2.8%)	0	1 (3.7%)	0
鼻炎	1 (2.8%)	0	1 (3.7%)	0
毛包炎	1 (2.8%)	0	1 (3.7%)	0
癬風	1 (2.8%)	0	1 (3.7%)	0
胃腸障害				
- Overall -	16 (44.4%)	4 (66.7%)	11 (40.7%)	1 (33.3%)
下痢	4 (11.1%)	1 (16.7%)	2 (7.4%)	1 (33.3%)
悪心	3 (8.3%)	3 (50.0%)	0	0
腹痛	3 (8.3%)	0	3 (11.1%)	0
齦歯	3 (8.3%)	0	3 (11.1%)	0
口唇炎	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
口内炎	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
腹部不快感	2 (5.6%)	0	2 (7.4%)	0
胃腸の炎症	1 (2.8%)	0	1 (3.7%)	0
過敏性腸症候群	1 (2.8%)	1 (16.7%)	0	0
歯肉痛	1 (2.8%)	1 (16.7%)	0	0
腸炎	1 (2.8%)	0	1 (3.7%)	0
便秘	1 (2.8%)	0	1 (3.7%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03age.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03age_mt_sp.out
 12JAN2017 17:05

aet03age_mt_sp Adverse Events by Age
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 18 years (N=6)	18 -< 65 years (N=27)	65 - years (N=3)
皮膚および皮下組織障害				
- Overall -	16 (44.4%)	2 (33.3%)	13 (48.1%)	1 (33.3%)
ざ瘡	3 (8.3%)	1 (16.7%)	2 (7.4%)	0
皮下出血	3 (8.3%)	0	3 (11.1%)	0
湿疹	2 (5.6%)	0	2 (7.4%)	0
発疹	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
皮膚乾燥	2 (5.6%)	0	2 (7.4%)	0
蕁麻疹	2 (5.6%)	0	2 (7.4%)	0
そう痒症	1 (2.8%)	1 (16.7%)	0	0
寒冷蕁麻疹	1 (2.8%)	0	1 (3.7%)	0
結節性紅斑	1 (2.8%)	0	1 (3.7%)	0
多形紅斑	1 (2.8%)	0	1 (3.7%)	0
脱毛症	1 (2.8%)	0	1 (3.7%)	0
点状出血	1 (2.8%)	1 (16.7%)	0	0
皮膚剥脱	1 (2.8%)	1 (16.7%)	0	0
嵌入爪	1 (2.8%)	0	0	1 (33.3%)
筋骨格系および結合組織障害				
- Overall -	11 (30.6%)	1 (16.7%)	9 (33.3%)	1 (33.3%)
筋肉痛	4 (11.1%)	0	3 (11.1%)	1 (33.3%)
背部痛	4 (11.1%)	0	4 (14.8%)	0
四肢痛	2 (5.6%)	0	2 (7.4%)	0
顎関節症候群	1 (2.8%)	0	1 (3.7%)	0
関節痛	1 (2.8%)	0	1 (3.7%)	0
筋骨格痛	1 (2.8%)	0	1 (3.7%)	0
頸部痛	1 (2.8%)	0	1 (3.7%)	0
足底筋膜炎	1 (2.8%)	1 (16.7%)	0	0
椎間板突出	1 (2.8%)	0	1 (3.7%)	0
変形性関節症	1 (2.8%)	0	0	1 (33.3%)
神経系障害				
- Overall -	9 (25.0%)	3 (50.0%)	4 (14.8%)	2 (66.7%)
失神寸前の状態	3 (8.3%)	1 (16.7%)	2 (7.4%)	0
頭痛	3 (8.3%)	2 (33.3%)	1 (3.7%)	0
感覚鈍麻	2 (5.6%)	0	1 (3.7%)	1 (33.3%)
緊張性頭痛	1 (2.8%)	0	1 (3.7%)	0
傾眠	1 (2.8%)	1 (16.7%)	0	0
坐骨神経痛	1 (2.8%)	0	0	1 (33.3%)
複合性局所疼痛症候群	1 (2.8%)	1 (16.7%)	0	0
傷害、中毒および処置合併症				
- Overall -	7 (19.4%)	0	6 (22.2%)	1 (33.3%)
挫傷	3 (8.3%)	0	2 (7.4%)	1 (33.3%)
肋骨骨折	2 (5.6%)	0	2 (7.4%)	0
処置による疼痛	1 (2.8%)	0	1 (3.7%)	0
節足動物刺傷	1 (2.8%)	0	1 (3.7%)	0
足骨折	1 (2.8%)	0	1 (3.7%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03age.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03age_mt_sp.out
 12JAN2017 17:05

aet03age_mt_sp Adverse Events by Age
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 18 years (N=6)	18 -< 65 years (N=27)	65 - years (N=3)
眼障害				
- Overall -	6 (16.7%)	1 (16.7%)	4 (14.8%)	1 (33.3%)
アレルギー性結膜炎	1 (2.8%)	0	1 (3.7%)	0
眼乾燥	1 (2.8%)	0	1 (3.7%)	0
眼瞼炎	1 (2.8%)	0	1 (3.7%)	0
眼瞼発疹	1 (2.8%)	0	1 (3.7%)	0
視力障害	1 (2.8%)	1 (16.7%)	0	0
嚢下白内障	1 (2.8%)	0	1 (3.7%)	0
白内障	1 (2.8%)	0	0	1 (33.3%)
呼吸器、胸郭および縦隔障害				
- Overall -	6 (16.7%)	1 (16.7%)	4 (14.8%)	1 (33.3%)
肺梗塞	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
咳嗽	1 (2.8%)	0	1 (3.7%)	0
気縦隔症	1 (2.8%)	1 (16.7%)	0	0
声帯肥厚	1 (2.8%)	0	1 (3.7%)	0
鼻出血	1 (2.8%)	0	0	1 (33.3%)
咯血	1 (2.8%)	0	1 (3.7%)	0
血液およびリンパ系障害				
- Overall -	5 (13.9%)	1 (16.7%)	4 (14.8%)	0
鉄欠乏性貧血	4 (11.1%)	1 (16.7%)	3 (11.1%)	0
貧血	1 (2.8%)	0	1 (3.7%)	0
精神障害				
- Overall -	5 (13.9%)	3 (50.0%)	2 (7.4%)	0
不眠症	3 (8.3%)	3 (50.0%)	0	0
うつ病	1 (2.8%)	1 (16.7%)	0	0
パニック障害	1 (2.8%)	0	1 (3.7%)	0
不安	1 (2.8%)	0	1 (3.7%)	0
臨床検査				
- Overall -	5 (13.9%)	1 (16.7%)	4 (14.8%)	0
アラニンアミノトランスフェラーゼ増加	3 (8.3%)	1 (16.7%)	2 (7.4%)	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	1 (16.7%)	1 (3.7%)	0
γ-グルタミルトランスフェラーゼ増加	1 (2.8%)	0	1 (3.7%)	0
胸部X線異常	1 (2.8%)	0	1 (3.7%)	0
胸部コンピュータ断層撮影異常	1 (2.8%)	0	1 (3.7%)	0
白血球数減少	1 (2.8%)	0	1 (3.7%)	0
一般・全身障害および投与部位の状態				
- Overall -	3 (8.3%)	2 (33.3%)	0	1 (33.3%)
胸痛	1 (2.8%)	0	0	1 (33.3%)
注射部位出血	1 (2.8%)	1 (16.7%)	0	0
疼痛	1 (2.8%)	1 (16.7%)	0	0
肝胆道系障害				
- Overall -	2 (5.6%)	0	2 (7.4%)	0
肝機能異常	2 (5.6%)	0	2 (7.4%)	0
腎および尿路障害				
- Overall -	2 (5.6%)	2 (33.3%)	0	0
緊張性膀胱	1 (2.8%)	1 (16.7%)	0	0
血尿	1 (2.8%)	1 (16.7%)	0	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03age.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03age_mt_sp.out
 12JAN2017 17:05

aet03age_mt_sp Adverse Events by Age
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 18 years (N=6)	18 -< 65 years (N=27)	65 - years (N=3)
生殖系および乳房障害				
- Overall -	2 (5.6%)	0	2 (7.4%)	0
月経困難症	1 (2.8%)	0	1 (3.7%)	0
産褥期乳汁分泌増加	1 (2.8%)	0	1 (3.7%)	0
卵巣嚢胞	1 (2.8%)	0	1 (3.7%)	0
代謝および栄養障害				
- Overall -	2 (5.6%)	0	2 (7.4%)	0
脂質異常症	1 (2.8%)	0	1 (3.7%)	0
食欲減退	1 (2.8%)	0	1 (3.7%)	0
内分泌障害				
- Overall -	1 (2.8%)	0	1 (3.7%)	0
ステロイド離脱症候群	1 (2.8%)	0	1 (3.7%)	0
免疫系障害				
- Overall -	1 (2.8%)	0	1 (3.7%)	0
造影剤アレルギー	1 (2.8%)	0	1 (3.7%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03age.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03age_mt_sp.out
 12JAN2017 17:05

表 2.7.4.8-23 性別有害事象の発現状況の要約 (MRA632JP 試験-全期間の本剤全投与例)

aet01sex_mt_sp Safety Summary by Sex
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

Treatment:MRA-SC 162mg/W Total (N=36)

	Male (N=5)	Female (N=31)
Total number of patients with at least one adverse event	4 (80.0%)	30 (96.8%)
Total number of events	18	183
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	0	6 (19.4%)
Serious AE leading to withdrawal from treatment	0	0
Serious AE leading to dose modification/interruption	0	3 (9.7%)
Related Serious AE	0	3 (9.7%)
AE leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	2 (40.0%)	14 (45.2%)
Related AE	2 (40.0%)	16 (51.6%)
Related AE leading to withdrawal from treatment	0	0
Severe AE	0	2 (6.5%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.
 Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet01sex.sas /
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet01sex_mt_sp.out
 12JAN201717:18
 Page 1 of 1

[5.3.5.1-7 表 11.3-18を再掲]

表 2.7.4.8-24 性別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)

aet03sex_mt_sp Adverse Events by Sex
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	Male (N=5)	Female (N=31)
- Any adverse events -	34 (94.4%)	4 (80.0%)	30 (96.8%)
感染症および寄生虫症			
- Overall -	31 (86.1%)	3 (60.0%)	28 (90.3%)
鼻咽頭炎	18 (50.0%)	1 (20.0%)	17 (54.8%)
咽頭炎	7 (19.4%)	0	7 (22.6%)
上気道感染	7 (19.4%)	0	7 (22.6%)
胃腸炎	5 (13.9%)	0	5 (16.1%)
感染性腸炎	4 (11.1%)	1 (20.0%)	3 (9.7%)
口腔ヘルペス	3 (8.3%)	0	3 (9.7%)
膀胱炎	3 (8.3%)	0	3 (9.7%)
インフルエンザ	2 (5.6%)	1 (20.0%)	1 (3.2%)
外陰部腔カンジダ症	2 (5.6%)	0	2 (6.5%)
副鼻腔炎	2 (5.6%)	1 (20.0%)	1 (3.2%)
せつ	1 (2.8%)	1 (20.0%)	0
ウイルス性腸炎	1 (2.8%)	0	1 (3.2%)
カンピロバクター胃腸炎	1 (2.8%)	0	1 (3.2%)
ヘモフィルス性肺炎	1 (2.8%)	1 (20.0%)	0
β溶血性レンサ球菌感染	1 (2.8%)	0	1 (3.2%)
急性腎盂腎炎	1 (2.8%)	0	1 (3.2%)
歯冠周囲炎	1 (2.8%)	0	1 (3.2%)
歯周炎	1 (2.8%)	0	1 (3.2%)
食道カンジダ症	1 (2.8%)	0	1 (3.2%)
爪囲炎	1 (2.8%)	0	1 (3.2%)
尿路感染	1 (2.8%)	0	1 (3.2%)
肺炎	1 (2.8%)	0	1 (3.2%)
麦粒腫	1 (2.8%)	0	1 (3.2%)
皮膚真菌感染	1 (2.8%)	0	1 (3.2%)
鼻炎	1 (2.8%)	0	1 (3.2%)
毛包炎	1 (2.8%)	0	1 (3.2%)
癬風	1 (2.8%)	0	1 (3.2%)
胃腸障害			
- Overall -	16 (44.4%)	2 (40.0%)	14 (45.2%)
下痢	4 (11.1%)	0	4 (12.9%)
悪心	3 (8.3%)	1 (20.0%)	2 (6.5%)
腹痛	3 (8.3%)	0	3 (9.7%)
歯菌	3 (8.3%)	0	3 (9.7%)
口唇炎	2 (5.6%)	0	2 (6.5%)
口内炎	2 (5.6%)	0	2 (6.5%)
腹部不快感	2 (5.6%)	0	2 (6.5%)
胃腸の炎症	1 (2.8%)	0	1 (3.2%)
過敏性腸症候群	1 (2.8%)	1 (20.0%)	0
歯肉痛	1 (2.8%)	1 (20.0%)	0
腸炎	1 (2.8%)	0	1 (3.2%)
便秘	1 (2.8%)	0	1 (3.2%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03sex.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03sex_mt_sp.out
 12JAN2017 17:06

aet03sex_mt_sp Adverse Events by Sex
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	Male (N=5)	Female (N=31)
皮膚および皮下組織障害			
- Overall -	16 (44.4%)	1 (20.0%)	15 (48.4%)
ざ瘡	3 (8.3%)	1 (20.0%)	2 (6.5%)
皮下出血	3 (8.3%)	0	3 (9.7%)
湿疹	2 (5.6%)	0	2 (6.5%)
発疹	2 (5.6%)	0	2 (6.5%)
皮膚乾燥	2 (5.6%)	0	2 (6.5%)
蕁麻疹	2 (5.6%)	0	2 (6.5%)
そう痒症	1 (2.8%)	0	1 (3.2%)
寒冷蕁麻疹	1 (2.8%)	0	1 (3.2%)
結節性紅斑	1 (2.8%)	0	1 (3.2%)
多形紅斑	1 (2.8%)	0	1 (3.2%)
脱毛症	1 (2.8%)	0	1 (3.2%)
点状出血	1 (2.8%)	0	1 (3.2%)
皮膚剥脱	1 (2.8%)	0	1 (3.2%)
嵌入爪	1 (2.8%)	0	1 (3.2%)
筋骨格系および結合組織障害			
- Overall -	11 (30.6%)	1 (20.0%)	10 (32.3%)
筋肉痛	4 (11.1%)	0	4 (12.9%)
背部痛	4 (11.1%)	1 (20.0%)	3 (9.7%)
四肢痛	2 (5.6%)	0	2 (6.5%)
顎関節症候群	1 (2.8%)	0	1 (3.2%)
関節痛	1 (2.8%)	0	1 (3.2%)
筋骨格痛	1 (2.8%)	0	1 (3.2%)
頸部痛	1 (2.8%)	0	1 (3.2%)
足底筋膜炎	1 (2.8%)	0	1 (3.2%)
椎間板突出	1 (2.8%)	0	1 (3.2%)
変形性関節症	1 (2.8%)	0	1 (3.2%)
神経系障害			
- Overall -	9 (25.0%)	1 (20.0%)	8 (25.8%)
失神寸前の状態	3 (8.3%)	0	3 (9.7%)
頭痛	3 (8.3%)	1 (20.0%)	2 (6.5%)
感覚鈍麻	2 (5.6%)	0	2 (6.5%)
緊張性頭痛	1 (2.8%)	0	1 (3.2%)
傾眠	1 (2.8%)	0	1 (3.2%)
坐骨神経痛	1 (2.8%)	0	1 (3.2%)
複合性局所疼痛症候群	1 (2.8%)	0	1 (3.2%)
傷害、中毒および処置合併症			
- Overall -	7 (19.4%)	0	7 (22.6%)
挫傷	3 (8.3%)	0	3 (9.7%)
肋骨骨折	2 (5.6%)	0	2 (6.5%)
処置による疼痛	1 (2.8%)	0	1 (3.2%)
節足動物刺傷	1 (2.8%)	0	1 (3.2%)
足骨折	1 (2.8%)	0	1 (3.2%)
眼障害			
- Overall -	6 (16.7%)	1 (20.0%)	5 (16.1%)
アレルギー性結膜炎	1 (2.8%)	0	1 (3.2%)
眼乾燥	1 (2.8%)	0	1 (3.2%)
眼瞼炎	1 (2.8%)	0	1 (3.2%)
眼瞼発疹	1 (2.8%)	0	1 (3.2%)
視力障害	1 (2.8%)	1 (20.0%)	0
嚢下白内障	1 (2.8%)	0	1 (3.2%)
白内障	1 (2.8%)	0	1 (3.2%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03sex.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03sex_mt_sp.out
 12JAN2017 17:06

aet03sex_mt_sp Adverse Events by Sex
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	Male (N=5)	Female (N=31)
呼吸器、胸郭および縦隔障害			
- Overall -	6 (16.7%)	1 (20.0%)	5 (16.1%)
肺梗塞	2 (5.6%)	1 (20.0%)	1 (3.2%)
咳嗽	1 (2.8%)	0	1 (3.2%)
気縦隔症	1 (2.8%)	1 (20.0%)	0
声帯肥厚	1 (2.8%)	0	1 (3.2%)
鼻出血	1 (2.8%)	0	1 (3.2%)
喀血	1 (2.8%)	0	1 (3.2%)
血液およびリンパ系障害			
- Overall -	5 (13.9%)	1 (20.0%)	4 (12.9%)
鉄欠乏性貧血	4 (11.1%)	1 (20.0%)	3 (9.7%)
貧血	1 (2.8%)	0	1 (3.2%)
精神障害			
- Overall -	5 (13.9%)	1 (20.0%)	4 (12.9%)
不眠症	3 (8.3%)	1 (20.0%)	2 (6.5%)
うつ病	1 (2.8%)	0	1 (3.2%)
パニック障害	1 (2.8%)	0	1 (3.2%)
不安	1 (2.8%)	0	1 (3.2%)
臨床検査			
- Overall -	5 (13.9%)	0	5 (16.1%)
アラニンアミノトランスフェラーゼ増加	3 (8.3%)	0	3 (9.7%)
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	0	2 (6.5%)
γ-グルタミルトランスフェラーゼ増加	1 (2.8%)	0	1 (3.2%)
胸部X線異常	1 (2.8%)	0	1 (3.2%)
胸部コンピュータ断層撮影異常	1 (2.8%)	0	1 (3.2%)
白血球数減少	1 (2.8%)	0	1 (3.2%)
一般・全身障害および投与部位の状態			
- Overall -	3 (8.3%)	1 (20.0%)	2 (6.5%)
胸痛	1 (2.8%)	0	1 (3.2%)
注射部位出血	1 (2.8%)	1 (20.0%)	0
疼痛	1 (2.8%)	0	1 (3.2%)
肝胆道系障害			
- Overall -	2 (5.6%)	0	2 (6.5%)
肝機能異常	2 (5.6%)	0	2 (6.5%)
腎および尿路障害			
- Overall -	2 (5.6%)	0	2 (6.5%)
緊張性膀胱	1 (2.8%)	0	1 (3.2%)
血尿	1 (2.8%)	0	1 (3.2%)
生殖系および乳房障害			
- Overall -	2 (5.6%)	0	2 (6.5%)
月経困難症	1 (2.8%)	0	1 (3.2%)
産褥期乳汁分泌増加	1 (2.8%)	0	1 (3.2%)
卵巣嚢胞	1 (2.8%)	0	1 (3.2%)
代謝および栄養障害			
- Overall -	2 (5.6%)	0	2 (6.5%)
脂質異常症	1 (2.8%)	0	1 (3.2%)
食欲減退	1 (2.8%)	0	1 (3.2%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03sex.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03sex_mt_sp.out
 12JAN2017 17:06

aet03sex_mt_sp Adverse Events by Sex
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	Male (N=5)	Female (N=31)
内分泌障害			
- Overall -	1 (2.8%)	0	1 (3.2%)
ステロイド離脱症候群	1 (2.8%)	0	1 (3.2%)
免疫系障害			
- Overall -	1 (2.8%)	0	1 (3.2%)
造影剤アレルギー	1 (2.8%)	0	1 (3.2%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03sex.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03sex_mt_sp.out
 12JAN2017 17:06

表 2.7.4.8-25 初回投与前の体重別有害事象の発現状況の要約
(MRA632JP 試験-全期間の本剤全投与例)

aet01wgt_mt_sp Safety Summary by Weight
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

Treatment:MRA-SC 162mg/W Total (N=36)

	< 54.9 kg (N=17)	54.9 - kg (N=19)
Total number of patients with at least one adverse event	16 (94.1%)	18 (94.7%)
Total number of events	100	101
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	3 (17.6%)	3 (15.8%)
Serious AE leading to withdrawal from treatment	0	0
Serious AE leading to dose modification/interruption	1 (5.9%)	2 (10.5%)
Related Serious AE	2 (11.8%)	1 (5.3%)
AE leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	5 (29.4%)	11 (57.9%)
Related AE	9 (52.9%)	9 (47.4%)
Related AE leading to withdrawal from treatment	0	0
Severe AE	2 (11.8%)	0

Percentages are based on N in the column headings.
Investigator text for Adverse Events encoded using MedDRA version 17.1.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet01wgt.sas
/ Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet01wgt_mt_sp.out
12JAN201717:17
Page 1 of 1

[5.3.5.1-7 表 11.3-20を再掲]

表 2.7.4.8-26 初回投与前の体重別有害事象の集計 (MRA632JP 試験-全期間の本剤全投与例)

aet03wgt_mt_sp Adverse Events by Weight
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 54.9 kg (N=17)	54.9 - kg (N=19)
- Any adverse events -	34 (94.4%)	16 (94.1%)	18 (94.7%)
感染症および寄生虫症			
- Overall -	31 (86.1%)	15 (88.2%)	16 (84.2%)
鼻咽頭炎	18 (50.0%)	10 (58.8%)	8 (42.1%)
咽頭炎	7 (19.4%)	3 (17.6%)	4 (21.1%)
上気道感染	7 (19.4%)	3 (17.6%)	4 (21.1%)
胃腸炎	5 (13.9%)	1 (5.9%)	4 (21.1%)
感染性腸炎	4 (11.1%)	0	4 (21.1%)
口腔ヘルペス	3 (8.3%)	1 (5.9%)	2 (10.5%)
膀胱炎	3 (8.3%)	1 (5.9%)	2 (10.5%)
インフルエンザ	2 (5.6%)	1 (5.9%)	1 (5.3%)
外陰部腔カンジダ症	2 (5.6%)	2 (11.8%)	0
副鼻腔炎	2 (5.6%)	0	2 (10.5%)
せつ	1 (2.8%)	0	1 (5.3%)
ウイルス性腸炎	1 (2.8%)	1 (5.9%)	0
カンピロバクター胃腸炎	1 (2.8%)	1 (5.9%)	0
ヘモフィルス性肺炎	1 (2.8%)	0	1 (5.3%)
β溶血性レンサ球菌感染	1 (2.8%)	1 (5.9%)	0
急性腎盂腎炎	1 (2.8%)	1 (5.9%)	0
歯冠周囲炎	1 (2.8%)	1 (5.9%)	0
歯周炎	1 (2.8%)	1 (5.9%)	0
食道カンジダ症	1 (2.8%)	1 (5.9%)	0
爪囲炎	1 (2.8%)	1 (5.9%)	0
尿路感染	1 (2.8%)	0	1 (5.3%)
肺炎	1 (2.8%)	0	1 (5.3%)
麦粒腫	1 (2.8%)	1 (5.9%)	0
皮膚真菌感染	1 (2.8%)	0	1 (5.3%)
鼻炎	1 (2.8%)	1 (5.9%)	0
毛包炎	1 (2.8%)	0	1 (5.3%)
癬風	1 (2.8%)	0	1 (5.3%)
胃腸障害			
- Overall -	16 (44.4%)	9 (52.9%)	7 (36.8%)
下痢	4 (11.1%)	3 (17.6%)	1 (5.3%)
悪心	3 (8.3%)	2 (11.8%)	1 (5.3%)
腹痛	3 (8.3%)	1 (5.9%)	2 (10.5%)
齲歯	3 (8.3%)	2 (11.8%)	1 (5.3%)
口唇炎	2 (5.6%)	1 (5.9%)	1 (5.3%)
口内炎	2 (5.6%)	2 (11.8%)	0
腹部不快感	2 (5.6%)	0	2 (10.5%)
胃腸の炎症	1 (2.8%)	0	1 (5.3%)
過敏性腸症候群	1 (2.8%)	1 (5.9%)	0
歯肉痛	1 (2.8%)	0	1 (5.3%)
腸炎	1 (2.8%)	0	1 (5.3%)
便秘	1 (2.8%)	1 (5.9%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03wgt.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03wgt_mt_sp.out
 12JAN2017 17:07

aet03wgt_mt_sp Adverse Events by Weight
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 54.9 kg (N=17)	54.9 - kg (N=19)
皮膚および皮下組織障害			
- Overall -	16 (44.4%)	8 (47.1%)	8 (42.1%)
ざ瘡	3 (8.3%)	1 (5.9%)	2 (10.5%)
皮下出血	3 (8.3%)	3 (17.6%)	0
湿疹	2 (5.6%)	1 (5.9%)	1 (5.3%)
発疹	2 (5.6%)	1 (5.9%)	1 (5.3%)
皮膚乾燥	2 (5.6%)	2 (11.8%)	0
蕁麻疹	2 (5.6%)	0	2 (10.5%)
そう痒症	1 (2.8%)	1 (5.9%)	0
寒冷蕁麻疹	1 (2.8%)	1 (5.9%)	0
結節性紅斑	1 (2.8%)	0	1 (5.3%)
多形紅斑	1 (2.8%)	1 (5.9%)	0
脱毛症	1 (2.8%)	1 (5.9%)	0
点状出血	1 (2.8%)	1 (5.9%)	0
皮膚剥脱	1 (2.8%)	1 (5.9%)	0
嵌入爪	1 (2.8%)	0	1 (5.3%)
筋骨格系および結合組織障害			
- Overall -	11 (30.6%)	6 (35.3%)	5 (26.3%)
筋肉痛	4 (11.1%)	3 (17.6%)	1 (5.3%)
背部痛	4 (11.1%)	2 (11.8%)	2 (10.5%)
四肢痛	2 (5.6%)	2 (11.8%)	0
顎関節症候群	1 (2.8%)	0	1 (5.3%)
関節痛	1 (2.8%)	0	1 (5.3%)
筋骨格痛	1 (2.8%)	0	1 (5.3%)
頸部痛	1 (2.8%)	1 (5.9%)	0
足底筋膜炎	1 (2.8%)	1 (5.9%)	0
椎間板突出	1 (2.8%)	0	1 (5.3%)
変形性関節症	1 (2.8%)	0	1 (5.3%)
神経系障害			
- Overall -	9 (25.0%)	6 (35.3%)	3 (15.8%)
失神寸前の状態	3 (8.3%)	2 (11.8%)	1 (5.3%)
頭痛	3 (8.3%)	2 (11.8%)	1 (5.3%)
感覚鈍麻	2 (5.6%)	0	2 (10.5%)
緊張性頭痛	1 (2.8%)	1 (5.9%)	0
傾眠	1 (2.8%)	1 (5.9%)	0
坐骨神経痛	1 (2.8%)	1 (5.9%)	0
複合性局所疼痛症候群	1 (2.8%)	1 (5.9%)	0
傷害、中毒および処置合併症			
- Overall -	7 (19.4%)	4 (23.5%)	3 (15.8%)
挫傷	3 (8.3%)	2 (11.8%)	1 (5.3%)
肋骨骨折	2 (5.6%)	1 (5.9%)	1 (5.3%)
処置による疼痛	1 (2.8%)	1 (5.9%)	0
節足動物刺傷	1 (2.8%)	0	1 (5.3%)
足骨折	1 (2.8%)	1 (5.9%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03wgt.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632c/reports/aet03wgt_mt_sp.out
 12JAN2017 17:07

aet03wgt_mt_sp Adverse Events by Weight
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 54.9 kg (N=17)	54.9 - kg (N=19)
眼障害			
- Overall -	6 (16.7%)	3 (17.6%)	3 (15.8%)
アレルギー性結膜炎	1 (2.8%)	1 (5.9%)	0
眼乾燥	1 (2.8%)	1 (5.9%)	0
眼瞼炎	1 (2.8%)	1 (5.9%)	0
眼瞼発疹	1 (2.8%)	0	1 (5.3%)
視力障害	1 (2.8%)	0	1 (5.3%)
嚢下白内障	1 (2.8%)	1 (5.9%)	0
白内障	1 (2.8%)	0	1 (5.3%)
呼吸器、胸郭および縦隔障害			
- Overall -	6 (16.7%)	1 (5.9%)	5 (26.3%)
肺梗塞	2 (5.6%)	0	2 (10.5%)
咳嗽	1 (2.8%)	0	1 (5.3%)
気縦隔症	1 (2.8%)	0	1 (5.3%)
声帯肥厚	1 (2.8%)	0	1 (5.3%)
鼻出血	1 (2.8%)	0	1 (5.3%)
咯血	1 (2.8%)	1 (5.9%)	0
血液およびリンパ系障害			
- Overall -	5 (13.9%)	1 (5.9%)	4 (21.1%)
鉄欠乏性貧血	4 (11.1%)	1 (5.9%)	3 (15.8%)
貧血	1 (2.8%)	0	1 (5.3%)
精神障害			
- Overall -	5 (13.9%)	2 (11.8%)	3 (15.8%)
不眠症	3 (8.3%)	2 (11.8%)	1 (5.3%)
うつ病	1 (2.8%)	1 (5.9%)	0
パニック障害	1 (2.8%)	0	1 (5.3%)
不安	1 (2.8%)	0	1 (5.3%)
臨床検査			
- Overall -	5 (13.9%)	2 (11.8%)	3 (15.8%)
アラニンアミノトランスフェラーゼ増加	3 (8.3%)	1 (5.9%)	2 (10.5%)
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	1 (5.9%)	1 (5.3%)
γ-グルタミルトランスフェラーゼ増加	1 (2.8%)	0	1 (5.3%)
胸部X線異常	1 (2.8%)	1 (5.9%)	0
胸部コンピュータ断層撮影異常	1 (2.8%)	1 (5.9%)	0
白血球数減少	1 (2.8%)	0	1 (5.3%)
一般・全身障害および投与部位の状態			
- Overall -	3 (8.3%)	2 (11.8%)	1 (5.3%)
胸痛	1 (2.8%)	0	1 (5.3%)
注射部位出血	1 (2.8%)	1 (5.9%)	0
疼痛	1 (2.8%)	1 (5.9%)	0
肝胆道系障害			
- Overall -	2 (5.6%)	0	2 (10.5%)
肝機能異常	2 (5.6%)	0	2 (10.5%)
腎および尿路障害			
- Overall -	2 (5.6%)	2 (11.8%)	0
緊張性膀胱	1 (2.8%)	1 (5.9%)	0
血尿	1 (2.8%)	1 (5.9%)	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03wgt.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03wgt_mt_sp.out
 12JAN2017 17:07

aet03wgt_mt_sp Adverse Events by Weight
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 54.9 kg (N=17)	54.9 - kg (N=19)
生殖系および乳房障害			
- Overall -	2 (5.6%)	0	2 (10.5%)
月経困難症	1 (2.8%)	0	1 (5.3%)
産褥期乳汁分泌増加	1 (2.8%)	0	1 (5.3%)
卵巣嚢胞	1 (2.8%)	0	1 (5.3%)
代謝および栄養障害			
- Overall -	2 (5.6%)	1 (5.9%)	1 (5.3%)
脂質異常症	1 (2.8%)	1 (5.9%)	0
食欲減退	1 (2.8%)	0	1 (5.3%)
内分泌障害			
- Overall -	1 (2.8%)	1 (5.9%)	0
ステロイド離脱症候群	1 (2.8%)	1 (5.9%)	0
免疫系障害			
- Overall -	1 (2.8%)	0	1 (5.3%)
造影剤アレルギー	1 (2.8%)	0	1 (5.3%)

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03wgt.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03wgt_mt_sp.out
 12JAN2017 17:07

表 2.7.4.8-27 体重別有害事象の発現状況の要約 (WA28119試験-二重盲検期間)

Overview of Adverse Events, by Weight, Safety Population
Protocol: WA28119

Weight: < 60kg (N=65)

	PBO QW + 26 Week Prednisone Taper (N=14)	PBO QW + 52 Week Prednisone Taper (N=11)	TCZ QW + 26 Week Prednisone Taper (N=27)	TCZ Q2W + 26 Week Prednisone Taper (N=13)
Total number of patients with at least one adverse event	14 (100.0%)	9 (81.8%)	26 (96.3%)	12 (92.3%)
Total number of events	121	58	240	147
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	1 (7.1%)	0	2 (7.4%)	1 (7.7%)
Total number of patients with at least one AE with fatal outcome	0	0	0	0
Serious AE	2 (14.3%)	1 (9.1%)	2 (7.4%)	2 (15.4%)
Serious AE leading to withdrawal from treatment	1 (7.1%)	0	0	0
Serious AE leading to dose modification/interruption	1 (7.1%)	1 (9.1%)	1 (3.7%)	1 (7.7%)
Serious AE related to TCZ	1 (7.1%)	0	0	0
Serious AE related to Prednisone	1 (7.1%)	0	0	0
AE leading to withdrawal from treatment	2 (14.3%)	0	2 (7.4%)	1 (7.7%)
AE leading to dose modification/interruption	4 (28.6%)	4 (36.4%)	11 (40.7%)	2 (15.4%)
AE related to TCZ	5 (35.7%)	2 (18.2%)	15 (55.6%)	8 (61.5%)
AE related to Prednisone	8 (57.1%)	4 (36.4%)	13 (48.1%)	10 (76.9%)
Related AE leading to withdrawal from treatment	1 (7.1%)	0	1 (3.7%)	1 (7.7%)
Related AE leading to dose modification/interruption	2 (14.3%)	1 (9.1%)	4 (14.8%)	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: < 60kg (N=65)

	PBO QW + 26 Week Prednisone Taper (N=14)	PBO QW + 52 Week Prednisone Taper (N=11)	TCZ QW + 26 Week Prednisone Taper (N=27)	TCZ Q2W + 26 Week Prednisone Taper (N=13)
Adverse Events of Special Interest -				
Infections and Infestations Adverse Events	10 (71.4%)	6 (54.5%)	21 (77.8%)	11 (84.6%)
Opportunistic Infections Adverse Events	0	0	0	0
Malignancy Adverse Events	0	0	0	0
Malignancy Adverse Events (excluding NMSC)	0	0	0	0
Serious Hepatic Adverse Events	0	0	0	0
Serious Stroke Adverse Events	0	0	0	0
Serious Myocardial Infarction Adverse Events	0	0	0	0
Anaphylactic Reaction Adverse Events (SMQN)	0	0	0	0
Anaphylactic Reaction Adverse Events (Sampson's criteria)	0	0	0	0
Serious Gastrointestinal Perforation Adverse Events	0	0	0	0
Gastrointestinal Perforation Adverse Events Confirmed by Medical Review	0	0	0	0
Serious Bleeding Adverse Events	0	0	0	0
Serious Demyelinating Adverse Events	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
Protocol: WA28119

Weight: 60kg - 100kg (N=171)

	PBO QW + 26 Week Prednisone Taper (N=33)	PBO QW + 52 Week Prednisone Taper (N=36)	TCZ QW + 26 Week Prednisone Taper (N=70)	TCZ Q2W + 26 Week Prednisone Taper (N=32)
Total number of patients with at least one adverse event	32 (97.0%)	34 (94.4%)	69 (98.6%)	31 (96.9%)
Total number of events	338	378	547	247
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	4 (5.7%)	2 (6.3%)
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	8 (24.2%)	12 (33.3%)	13 (18.6%)	4 (12.5%)
Serious AE leading to withdrawal from treatment	1 (3.0%)	0	6 (8.6%)	2 (6.3%)
Serious AE leading to dose modification/interruption	3 (9.1%)	6 (16.7%)	3 (4.3%)	0
Serious AE related to TCZ	3 (9.1%)	6 (16.7%)	4 (5.7%)	2 (6.3%)
Serious AE related to Prednisone	4 (12.1%)	4 (11.1%)	3 (4.3%)	1 (3.1%)
AE leading to withdrawal from treatment	3 (9.1%)	0	9 (12.9%)	4 (12.5%)
AE leading to dose modification/interruption	8 (24.2%)	13 (36.1%)	21 (30.0%)	7 (21.9%)
AE related to TCZ	14 (42.4%)	14 (38.9%)	36 (51.4%)	16 (50.0%)
AE related to Prednisone	21 (63.6%)	18 (50.0%)	36 (51.4%)	17 (53.1%)
Related AE leading to withdrawal from treatment	1 (3.0%)	0	5 (7.1%)	1 (3.1%)
Related AE leading to dose modification/interruption	5 (15.2%)	8 (22.2%)	9 (12.9%)	5 (15.6%)

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
06SEP2016 12:20

Page 3 of 8

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: 60kg - 100kg (N=171)

	PBO QW + 26 Week Prednisone Taper (N=33)	PBO QW + 52 Week Prednisone Taper (N=36)	TCZ QW + 26 Week Prednisone Taper (N=70)	TCZ Q2W + 26 Week Prednisone Taper (N=32)
Adverse Events of Special Interest -				
Infections and Infestations Adverse Events	26 (78.8%)	25 (69.4%)	51 (72.9%)	22 (68.8%)
Opportunistic Infections Adverse Events	0	2 (5.6%)	0	1 (3.1%)
Malignancy Adverse Events	0	1 (2.8%)	1 (1.4%)	0
Malignancy Adverse Events (excluding NMSC)	0	1 (2.8%)	1 (1.4%)	0
Serious Hepatic Adverse Events	0	0	0	0
Serious Stroke Adverse Events	0	1 (2.8%)	0	0
Serious Myocardial Infarction Adverse Events	0	0	0	0
Anaphylactic Reaction Adverse Events (SMQN)	0	0	0	0
Anaphylactic Reaction Adverse Events (Sampson's criteria)	0	0	0	1 (3.1%)
Serious Gastrointestinal Perforation Adverse Events	0	0	0	0
Gastrointestinal Perforation Adverse Events Confirmed by Medical Review	0	0	0	0
Serious Bleeding Adverse Events	0	0	0	0
Serious Demyelinating Adverse Events	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: > 100kg (N=13)

	PBO QW + 26 Week Prednisone Taper (N=3)	PBO QW + 52 Week Prednisone Taper (N=4)	TCZ QW + 26 Week Prednisone Taper (N=3)	TCZ Q2W + 26 Week Prednisone Taper (N=3)
Total number of patients with at least one adverse event	2 (66.7%)	4 (100.0%)	3 (100.0%)	3 (100.0%)
Total number of events	11	50	23	34
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	1 (33.3%)	0	0	0
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	1 (33.3%)	0	0	1 (33.3%)
Serious AE leading to withdrawal from treatment	1 (33.3%)	0	0	1 (33.3%)
Serious AE leading to dose modification/interruption	0	0	0	1 (33.3%)
Serious AE related to TCZ	0	0	0	0
Serious AE related to Prednisone	0	0	0	0
AE leading to withdrawal from treatment	1 (33.3%)	0	0	1 (33.3%)
AE leading to dose modification/interruption	0	0	1 (33.3%)	1 (33.3%)
AE related to TCZ	2 (66.7%)	2 (50.0%)	1 (33.3%)	1 (33.3%)
AE related to Prednisone	2 (66.7%)	3 (75.0%)	1 (33.3%)	2 (66.7%)
Related AE leading to withdrawal from treatment	0	0	0	0
Related AE leading to dose modification/interruption	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: > 100kg (N=13)

	PBO QW + 26 Week Prednisone Taper (N=3)	PBO QW + 52 Week Prednisone Taper (N=4)	TCZ QW + 26 Week Prednisone Taper (N=3)	TCZ Q2W + 26 Week Prednisone Taper (N=3)
Adverse Events of Special Interest -				
Infections and Infestations Adverse Events	2 (66.7%)	2 (50.0%)	3 (100.0%)	2 (66.7%)
Opportunistic Infections Adverse Events	0	0	0	0
Malignancy Adverse Events	1 (33.3%)	0	0	0
Malignancy Adverse Events (excluding NMSC)	1 (33.3%)	0	0	0
Serious Hepatic Adverse Events	0	0	0	0
Serious Stroke Adverse Events	0	0	0	1 (33.3%)
Serious Myocardial Infarction Adverse Events	0	0	0	0
Anaphylactic Reaction Adverse Events (SMQN)	0	0	0	0
Anaphylactic Reaction Adverse Events (Sampson's criteria)	0	0	0	0
Serious Gastrointestinal Perforation Adverse Events	0	0	0	0
Gastrointestinal Perforation Adverse Events Confirmed by Medical Review	0	0	0	0
Serious Bleeding Adverse Events	0	0	0	0
Serious Demyelinating Adverse Events	0	0	0	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: Missing (N=1)

	TCZ Q2W + 26 Week Prednisone Taper (N=1)
Total number of patients with at least one adverse event	1 (100.0%)
Total number of events	4
Total number of deaths	0
Total number of patients withdrawn from study due to an AE	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	0
Serious AE leading to withdrawal from treatment	0
Serious AE leading to dose modification/interruption	0
Serious AE related to TCZ	0
Serious AE related to Prednisone	0
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	0
AE related to TCZ	1 (100.0%)
AE related to Prednisone	1 (100.0%)
Related AE leading to withdrawal from treatment	0
Related AE leading to dose modification/interruption	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

Overview of Adverse Events, by Weight, Safety Population
 Protocol: WA28119

Weight: Missing (N=1)

	TCZ Q2W + 26 Week Prednisone Taper (N=1)
Adverse Events of Special Interest -	
Infections and Infestations Adverse Events	1 (100.0%)
Opportunistic Infections Adverse Events	0
Malignancy Adverse Events	0
Malignancy Adverse Events (excluding NMSC)	0
Serious Hepatic Adverse Events	0
Serious Stroke Adverse Events	0
Serious Myocardial Infarction Adverse Events	0
Anaphylactic Reaction Adverse Events (SMQN)	0
Anaphylactic Reaction Adverse Events (Sampson's criteria)	0
Serious Gastrointestinal Perforation Adverse Events	0
Gastrointestinal Perforation Adverse Events Confirmed by Medical Review	0
Serious Bleeding Adverse Events	0
Serious Demyelinating Adverse Events	0

Investigator text for AEs encoded using MedDRA version 19.0.

Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Program: /opt/BIOSTAT/prod/cn11935e/i28119a/t_ae_oview_ah134.sas
 Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/t_ae_oview_ah134_SE.out
 06SEP2016 12:20

表 2.7.4.8-28 治験薬投与開始時の副腎皮質ステロイド投与量別、有害事象の発現状況の要約
(MRA632JP 試験-全期間の本剤全投与例)

aet01cs_mt_sp Safety Summary by Corticosteroid
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

Treatment: MRA-SC 162mg/W Total (N=36)

	< 0.6 mg/kg (N=27)	0.6 -< 0.8 mg/kg (N=4)	0.8 - mg/kg (N=5)
Total number of patients with at least one adverse event	26 (96.3%)	3 (75.0%)	5 (100.0%)
Total number of events	143	25	33
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one			
AE with fatal outcome	0	0	0
Serious AE	4 (14.8%)	1 (25.0%)	1 (20.0%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to dose modification/interruption	2 (7.4%)	1 (25.0%)	0
Related Serious AE	2 (7.4%)	1 (25.0%)	0
AE leading to withdrawal from treatment	0	0	0
AE leading to dose modification/interruption	14 (51.9%)	2 (50.0%)	0
Related AE	14 (51.9%)	2 (50.0%)	2 (40.0%)
Related AE leading to withdrawal from treatment	0	0	0
Severe AE	2 (7.4%)	0	0

Percentages are based on N in the column headings.
Investigator text for Adverse Events encoded using MedDRA version 17.1.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet01cs.sas /
Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet01cs_mt_sp.out
12JAN2017 17:22
Page 1 of 1

[5.3.5.1-7 表 11.3-22を再掲]

表 2.7.4.8-29 治験薬投与開始時の副腎皮質ステロイド投与量別, 有害事象発現例数
(MRA632JP 試験-全期間の本剤全投与例)

aet03cstr_mt_sp Adverse Events by Corticosteroid
Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
Protocol: MRA632JP
Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 0.6 mg/kg (N=27)	0.6 -< 0.8 mg/kg (N=4)	0.8 - mg/kg (N=5)
- Any adverse events -	34 (94.4%)	26 (96.3%)	3 (75.0%)	5 (100.0%)
感染症および寄生虫症				
- Overall -	31 (86.1%)	24 (88.9%)	3 (75.0%)	4 (80.0%)
鼻咽喉炎	18 (50.0%)	14 (51.9%)	2 (50.0%)	2 (40.0%)
咽頭炎	7 (19.4%)	5 (18.5%)	2 (50.0%)	0
上気道感染	7 (19.4%)	6 (22.2%)	1 (25.0%)	0
胃腸炎	5 (13.9%)	4 (14.8%)	1 (25.0%)	0
感染性腸炎	4 (11.1%)	4 (14.8%)	0	0
口腔ヘルペス	3 (8.3%)	3 (11.1%)	0	0
膀胱炎	3 (8.3%)	1 (3.7%)	1 (25.0%)	1 (20.0%)
インフルエンザ	2 (5.6%)	2 (7.4%)	0	0
外陰部腔カンジダ症	2 (5.6%)	1 (3.7%)	0	1 (20.0%)
副鼻腔炎	2 (5.6%)	1 (3.7%)	1 (25.0%)	0
せつ	1 (2.8%)	1 (3.7%)	0	0
ウイルス性腸炎	1 (2.8%)	0	1 (25.0%)	0
カンピロバクター胃腸炎	1 (2.8%)	0	1 (25.0%)	0
ヘモフィルス性肺炎	1 (2.8%)	1 (3.7%)	0	0
β溶血性レンサ球菌感染	1 (2.8%)	0	1 (25.0%)	0
急性腎盂腎炎	1 (2.8%)	1 (3.7%)	0	0
歯冠周囲炎	1 (2.8%)	1 (3.7%)	0	0
歯周炎	1 (2.8%)	1 (3.7%)	0	0
食道カンジダ症	1 (2.8%)	1 (3.7%)	0	0
爪囲炎	1 (2.8%)	0	1 (25.0%)	0
尿路感染	1 (2.8%)	0	0	1 (20.0%)
肺炎	1 (2.8%)	0	1 (25.0%)	0
麦粒腫	1 (2.8%)	1 (3.7%)	0	0
皮膚真菌感染	1 (2.8%)	0	0	1 (20.0%)
鼻炎	1 (2.8%)	1 (3.7%)	0	0
毛包炎	1 (2.8%)	0	1 (25.0%)	0
癬風	1 (2.8%)	1 (3.7%)	0	0
胃腸障害				
- Overall -	16 (44.4%)	12 (44.4%)	0	4 (80.0%)
下痢	4 (11.1%)	3 (11.1%)	0	1 (20.0%)
悪心	3 (8.3%)	2 (7.4%)	0	1 (20.0%)
腹痛	3 (8.3%)	2 (7.4%)	0	1 (20.0%)
齦歯	3 (8.3%)	1 (3.7%)	0	2 (40.0%)
口唇炎	2 (5.6%)	2 (7.4%)	0	0
口内炎	2 (5.6%)	2 (7.4%)	0	0
腹部不快感	2 (5.6%)	1 (3.7%)	0	1 (20.0%)
胃腸の炎症	1 (2.8%)	1 (3.7%)	0	0
過敏性腸症候群	1 (2.8%)	1 (3.7%)	0	0
歯肉痛	1 (2.8%)	1 (3.7%)	0	0
腸炎	1 (2.8%)	1 (3.7%)	0	0
便秘	1 (2.8%)	1 (3.7%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03cstr.sas
Output: /opt/BIOSTAT/prod/cdt3489g/gmra632c/reports/aet03cstr_mt_sp.out
12JAN2017 17:06

aet03cstr_mt_sp Adverse Events by Corticosteroid
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 0.6 mg/kg (N=27)	0.6 -< 0.8 mg/kg (N=4)	0.8 - mg/kg (N=5)
皮膚および皮下組織障害				
- Overall -	16 (44.4%)	11 (40.7%)	2 (50.0%)	3 (60.0%)
ざ瘡	3 (8.3%)	1 (3.7%)	1 (25.0%)	1 (20.0%)
皮下出血	3 (8.3%)	2 (7.4%)	0	1 (20.0%)
湿疹	2 (5.6%)	1 (3.7%)	1 (25.0%)	0
発疹	2 (5.6%)	2 (7.4%)	0	0
皮膚乾燥	2 (5.6%)	2 (7.4%)	0	0
蕁麻疹	2 (5.6%)	2 (7.4%)	0	0
そう痒症	1 (2.8%)	0	0	1 (20.0%)
寒冷蕁麻疹	1 (2.8%)	0	1 (25.0%)	0
結節性紅斑	1 (2.8%)	1 (3.7%)	0	0
多形紅斑	1 (2.8%)	0	1 (25.0%)	0
脱毛症	1 (2.8%)	0	0	1 (20.0%)
点状出血	1 (2.8%)	0	0	1 (20.0%)
皮膚剥脱	1 (2.8%)	1 (3.7%)	0	0
嵌入爪	1 (2.8%)	1 (3.7%)	0	0
筋骨格系および結合組織障害				
- Overall -	11 (30.6%)	7 (25.9%)	1 (25.0%)	3 (60.0%)
筋肉痛	4 (11.1%)	3 (11.1%)	1 (25.0%)	0
背部痛	4 (11.1%)	2 (7.4%)	0	2 (40.0%)
四肢痛	2 (5.6%)	1 (3.7%)	1 (25.0%)	0
顎関節症候群	1 (2.8%)	0	0	1 (20.0%)
関節痛	1 (2.8%)	1 (3.7%)	0	0
筋骨格痛	1 (2.8%)	1 (3.7%)	0	0
頸部痛	1 (2.8%)	0	1 (25.0%)	0
足底筋膜炎	1 (2.8%)	1 (3.7%)	0	0
椎間板突出	1 (2.8%)	1 (3.7%)	0	0
変形性関節症	1 (2.8%)	1 (3.7%)	0	0
神経系障害				
- Overall -	9 (25.0%)	8 (29.6%)	0	1 (20.0%)
失神寸前の状態	3 (8.3%)	3 (11.1%)	0	0
頭痛	3 (8.3%)	3 (11.1%)	0	0
感覚鈍麻	2 (5.6%)	2 (7.4%)	0	0
緊張性頭痛	1 (2.8%)	1 (3.7%)	0	0
傾眠	1 (2.8%)	0	0	1 (20.0%)
坐骨神経痛	1 (2.8%)	1 (3.7%)	0	0
複合性局所疼痛症候群	1 (2.8%)	1 (3.7%)	0	0
傷害、中毒および処置合併症				
- Overall -	7 (19.4%)	7 (25.9%)	0	0
挫傷	3 (8.3%)	3 (11.1%)	0	0
肋骨骨折	2 (5.6%)	2 (7.4%)	0	0
処置による疼痛	1 (2.8%)	1 (3.7%)	0	0
節足動物刺傷	1 (2.8%)	1 (3.7%)	0	0
足骨折	1 (2.8%)	1 (3.7%)	0	0

Percentages are based on N in the column headings.

Investigator text for Adverse Events encoded using MedDRA version 17.1.

Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03cstr.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632c/reports/aet03cstr_mt_sp.out
 12JAN2017 17:06

aet03cstr_mt_sp Adverse Events by Corticosteroid
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 0.6 mg/kg (N=27)	0.6 -< 0.8 mg/kg (N=4)	0.8 - mg/kg (N=5)
眼障害				
- Overall -	6 (16.7%)	4 (14.8%)	0	2 (40.0%)
アレルギー性結膜炎	1 (2.8%)	0	0	1 (20.0%)
眼乾燥	1 (2.8%)	1 (3.7%)	0	0
眼瞼炎	1 (2.8%)	0	0	1 (20.0%)
眼瞼発疹	1 (2.8%)	1 (3.7%)	0	0
視力障害	1 (2.8%)	1 (3.7%)	0	0
嚢下白内障	1 (2.8%)	0	0	1 (20.0%)
白内障	1 (2.8%)	1 (3.7%)	0	0
呼吸器、胸郭および縦隔障害				
- Overall -	6 (16.7%)	6 (22.2%)	0	0
肺梗塞	2 (5.6%)	2 (7.4%)	0	0
咳嗽	1 (2.8%)	1 (3.7%)	0	0
気縦隔症	1 (2.8%)	1 (3.7%)	0	0
声帯肥厚	1 (2.8%)	1 (3.7%)	0	0
鼻出血	1 (2.8%)	1 (3.7%)	0	0
咯血	1 (2.8%)	1 (3.7%)	0	0
血液およびリンパ系障害				
- Overall -	5 (13.9%)	5 (18.5%)	0	0
鉄欠乏性貧血	4 (11.1%)	4 (14.8%)	0	0
貧血	1 (2.8%)	1 (3.7%)	0	0
精神障害				
- Overall -	5 (13.9%)	1 (3.7%)	2 (50.0%)	2 (40.0%)
不眠症	3 (8.3%)	1 (3.7%)	1 (25.0%)	1 (20.0%)
うつ病	1 (2.8%)	0	0	1 (20.0%)
パニック障害	1 (2.8%)	0	1 (25.0%)	0
不安	1 (2.8%)	0	0	1 (20.0%)
臨床検査				
- Overall -	5 (13.9%)	4 (14.8%)	0	1 (20.0%)
アラニンアミノトランスフェラーゼ増加	3 (8.3%)	3 (11.1%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (5.6%)	2 (7.4%)	0	0
γ-グルタミルトランスフェラーゼ増加	1 (2.8%)	1 (3.7%)	0	0
胸部X線異常	1 (2.8%)	0	0	1 (20.0%)
胸部コンピュータ断層撮影異常	1 (2.8%)	0	0	1 (20.0%)
白血球数減少	1 (2.8%)	1 (3.7%)	0	0
一般・全身障害および投与部位の状態				
- Overall -	3 (8.3%)	2 (7.4%)	0	1 (20.0%)
胸痛	1 (2.8%)	1 (3.7%)	0	0
注射部位出血	1 (2.8%)	1 (3.7%)	0	0
疼痛	1 (2.8%)	0	0	1 (20.0%)
肝胆道系障害				
- Overall -	2 (5.6%)	2 (7.4%)	0	0
肝機能異常	2 (5.6%)	2 (7.4%)	0	0
腎および尿路障害				
- Overall -	2 (5.6%)	1 (3.7%)	0	1 (20.0%)
緊張性膀胱	1 (2.8%)	0	0	1 (20.0%)
血尿	1 (2.8%)	1 (3.7%)	0	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03cstr.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03cstr_mt_sp.out
 12JAN2017 17:06

aet03cstr_mt_sp Adverse Events by Corticosteroid
 Snapshot Date: 10JAN2017 Cutoff Date: 10NOV2016
 Protocol: MRA632JP
 Analysis: SAFETY

MRA-SC 162mg/W Total (N=36)

MedDRA System Organ Class MedDRA Preferred Term	Total (N=36)	< 0.6 mg/kg (N=27)	0.6 -< 0.8 mg/kg (N=4)	0.8 - mg/kg (N=5)
生殖系および乳房障害				
- Overall -	2 (5.6%)	1 (3.7%)	1 (25.0%)	0
月経困難症	1 (2.8%)	0	1 (25.0%)	0
産褥期乳汁分泌増加	1 (2.8%)	0	1 (25.0%)	0
卵巣嚢胞	1 (2.8%)	1 (3.7%)	0	0
代謝および栄養障害				
- Overall -	2 (5.6%)	1 (3.7%)	0	1 (20.0%)
脂質異常症	1 (2.8%)	1 (3.7%)	0	0
食欲減退	1 (2.8%)	0	0	1 (20.0%)
内分泌障害				
- Overall -	1 (2.8%)	0	0	1 (20.0%)
ステロイド離脱症候群	1 (2.8%)	0	0	1 (20.0%)
免疫系障害				
- Overall -	1 (2.8%)	1 (3.7%)	0	0
造影剤アレルギー	1 (2.8%)	1 (3.7%)	0	0

Percentages are based on N in the column headings.
 Investigator text for Adverse Events encoded using MedDRA version 17.1.
 Multiple occurrences of the same adverse event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt3489g/gmra632c/aet03cstr.sas
 Output: /opt/BIOSTAT/prod/cdt3489g/gmra632g/reports/aet03cstr_mt_sp.out
 12JAN2017 17:06

表 2.7.4.8-30 副腎皮質ステロイドによると考えられる有害事象発現例数 (WA28119試験-二重盲検期間)

MedDRA System Organ Class MedDRA Preferred Term	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Total number of patients with at least one adverse event	14 (28.0%)	15 (29.4%)	21 (21.0%)	9 (18.4%)
Overall total number of events	17	19	28	9
精神障害				
Total number of patients with at least one adverse event	6 (12.0%)	5 (9.8%)	6 (6.0%)	3 (6.1%)
Total number of events	7	5	7	3
不眠症	4 (8.0%)	4 (7.8%)	4 (4.0%)	1 (2.0%)
うつ病	3 (6.0%)	1 (2.0%)	3 (3.0%)	2 (4.1%)
眼障害				
Total number of patients with at least one adverse event	3 (6.0%)	5 (9.8%)	5 (5.0%)	1 (2.0%)
Total number of events	3	7	5	1
白内障	3 (6.0%)	5 (9.8%)	5 (5.0%)	1 (2.0%)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	2 (4.0%)	2 (3.9%)	4 (4.0%)	3 (6.1%)
Total number of events	2	2	4	3
骨粗鬆症	1 (2.0%)	1 (2.0%)	1 (1.0%)	2 (4.1%)
骨減少症	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
ミオパチー	1 (2.0%)	0	1 (1.0%)	0
臨床検査				
Total number of patients with at least one adverse event	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
Total number of events	2	2	2	1
眼圧上昇	2 (4.0%)	2 (3.9%)	2 (2.0%)	1 (2.0%)
代謝および栄養障害				
Total number of patients with at least one adverse event	2 (4.0%)	0	2 (2.0%)	1 (2.0%)
Total number of events	2	0	2	1
糖尿病	2 (4.0%)	0	2 (2.0%)	0
高血糖	0	0	0	1 (2.0%)

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

A list of preferred terms related to Corticosteroids was produced by Medical Review.

MedDRA System Organ Class MedDRA Preferred Term	疼痛BO QW + 26 Week Prednisone Taper (N=50)	疼痛BO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	0	1 (2.0%)	3 (3.0%)	0
Total number of events	0	1	3	0
腱断裂	0	1 (2.0%)	1 (1.0%)	0
腰椎骨折	0	0	1 (1.0%)	0
ストレス骨折	0	0	1 (1.0%)	0
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	1 (2.0%)	1 (2.0%)	2 (2.0%)	0
Total number of events	1	1	2	0
ざ瘡	1 (2.0%)	1 (2.0%)	1 (1.0%)	0
ざ瘡様皮膚炎	0	0	1 (1.0%)	0
血管障害				
Total number of patients with at least one adverse event	0	1 (2.0%)	2 (2.0%)	0
Total number of events	0	1	2	0
高血圧クリーゼ	0	1 (2.0%)	2 (2.0%)	0
内分泌障害				
Total number of patients with at least one adverse event	0	0	1 (1.0%)	0
Total number of events	0	0	1	0
副腎機能不全	0	0	1 (1.0%)	0

Investigator text for AEs is coded using MedDRA version 19.0.

Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

A list of preferred terms related to Corticosteroids was produced by Medical Review.

Page 2 of 2

[5.3.5.1-6 表 2.2-2を改変]

アクテムラ皮下注162 mg シリンジ・AI (トシリズマブ (遺伝子組換え))

[大型血管炎]

第2部 (モジュール2) : CTD の概要 (サマリー)

2.7.5 参考文献

中外製薬株式会社

目次

	<u>頁</u>
2.7.5 参考文献.....	3

2.7.5 参考文献

- (1) 2.7.2で引用した文献
該当なし
- (2) 2.7.3で引用した文献
「[2.7.3.6 参考文献](#)」参照
- (3) 2.7.4で引用した文献
「[2.7.4.7 参考文献](#)」参照
- (4) 2.7.6で引用した文献
「[2.7.6.10 参考文献](#)」参照