## 2.7.5 参考文献

参考文献は，各セクションの末尾に記載した。

## M20-017 試験

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| 治験の標題：高脂肪/高カロリー食摂取後及び絶食下において，ウパダシチニブの第 III 相試験で使用した湿式造粒製剤に対する市販予定製剤のバイオアベイラビリティを評価する第 I 相試験 | |
| 施設数 / 実施国名：<br>2 施設 / 米国 | |
| 治験責任医師：<br>[redacted]MD | |
| 公表文献 (参考資料) ：<br>なし | |
| 治験期間：<br>最初の被験者の初回来院日：20[redacted] 年 [redacted] 月 [redacted] 日<br>最後の被験者の最終来院日：20[redacted] 年 [redacted] 月 [redacted] 日 | 開発のフェーズ：I |
| 目的：<br>パート 1：高脂肪/高カロリー食摂取後及び絶食下において，ウパダシチニブの市販予定製剤（15 mg）のバイオアベイラビリティを臨床試験用製剤（15 mg）と比較して評価する。<br>パート 2：高脂肪/高カロリー食摂取後及び絶食下において，ウパダシチニブの市販予定製剤（30 mg）のバイオアベイラビリティを臨床試験用製剤（30 mg）と比較して評価する。 | |
| 被験者数 (計画時と解析時) ：<br>計画時：80 名，解析時 80 名 | |
| 診断と主要な組入れ基準：<br>スクリーニングの時点で 18 歳から 55 歳の健康な男女 | |
| 治験方法：<br>単回投与，非盲検，無作為化，4 期，4 順序，2 パートのクロスオーバー試験を実施した。各期の投与後 72 時間まで，ウパダシチニブの濃度測定用の血液試料を採取した。 | |
| 被験薬，用量，投与方法及びバッチ番号：<br>ウパダシチニブの臨床試験用 15 mg 錠（ER17Y）：バルクロット番号 [redacted]<br>ウパダシチニブの市販予定 15 mg 錠（ER17）：バルクロット番号 [redacted]<br>ウパダシチニブの臨床試験用 30 mg 錠（ER18Y）：バルクロット番号 [redacted]<br>ウパダシチニブの市販予定 30 mg 錠（ER18）：バルクロット番号 [redacted]<br>パート 1 では 15 mg，パート 2 では 30 mg の用量で経口投与した。<br>治療期間：<br>パート 1：4 日間の間隔をあけてウパダシチニブ 15 mg を 4 回単回投与<br>パート 2：4 日間の間隔をあけてウパダシチニブ 30 mg を 4 回単回投与 | |
| 対照薬，用量，投与方法及びバッチ番号：<br>該当なし | |
| 評価基準：<br>薬物動態：<br>$C_{max}$，$T_{max}$，$t_{1/2}$，$AUC_t$，$AUC_{inf}$，$AUC_{0-12}$，$AUC_{12-t}$ | |
| 統計手法： | |

薬物動態：

各パートにおいて，$C_{max}$，$AUC_t$，$AUC_{inf}$，$AUC_{0-12}$，$AUC_{12-t}$の自然対数変換値について線形混合効果解析を実施した。混合モデリングでは，それぞれの試験レジメンを対応する標準レジメンと比較した。

各パートにおいて，$C_{max}$，$AUC_t$，$AUC_{inf}$，$AUC_{0-12}$，$AUC_{12-t}$の自然対数変換値を解析することにより，標準レジメンに対する試験レジメンのバイオアベイラビリティ，すなわち市販予定製剤に対する高脂肪/高カロリー食後又は絶食下での臨床試験製剤のバイオアベイラビリティの点推定値及びその90%信頼区間を評価した。

要約/結論

薬物動態の結果：

絶食下及び高脂肪/高カロリー食摂取後におけるウパダシチニブ15 mg製剤のバイオアベイラビリティの点推定値及び90%信頼区間

| レジメン | 薬物動態パラメータ | 中心値 | | 相対バイオアベイラビリティ | |
|---|---|---|---|---|---|
| 試験 vs.標準 | （単位） | 試験 | 標準 | 点推定値 | 90%信頼区間 |
| B vs. A | $C_{max}$（ng/mL） | 29.1 | 28.1 | 1.038 | 0.936 - 1.150 |
| | $AUC_t$（ng•h/mL） | 250 | 256 | 0.973 | 0.919 - 1.031 |
| | $AUC_{inf}$（ng•h/mL） | 254 | 265 | 0.960 | 0.907 - 1.015 |
| | $AUC_{0-12}$（ng•h/mL） | 184 | 184 | 1.003 | 0.938 - 1.072 |
| | $AUC_{12-t}$（ng•h/mL） | 62.7 | 70.3 | 0.892 | 0.823 - 0.968 |
| D vs. C | $C_{max}$（ng/mL） | 47.4 | 48.4 | 0.980 | 0.915 - 1.049 |
| | $AUC_t$（ng•h/mL） | 318 | 335 | 0.949 | 0.906 - 0.994 |
| | $AUC_{inf}$（ng•h/mL） | 323 | 339 | 0.952 | 0.910 - 0.997 |
| | $AUC_{0-12}$（ng•h/mL） | 267 | 281 | 0.949 | 0.897 - 1.004 |
| | $AUC_{12-t}$（ng•h/mL） | 49.1 | 51.4 | 0.956 | 0.882 - 1.036 |

レジメンA：絶食下で臨床試験製剤（ER17Y）15 mgを単回投与（レジメンBに対する標準レジメン）

レジメンB：絶食下で市販予定製剤（ER17）15 mgを単回投与（レジメンAに対する試験レジメン）

レジメンC：高脂肪/高カロリー食後に臨床試験製剤（ER17Y）15 mgを単回投与（レジメンDに対する標準レジメン）

レジメンD：高脂肪/高カロリー食後に市販予定製剤（ER17）15 mgを単回投与（レジメンCに対する試験レジメン）

絶食下及び高脂肪/高カロリー食摂取後におけるウパダシチニブ30 mg製剤のバイオアベイラビリティの点推定値及び90%信頼区間

| レジメン | 薬物動態パラメータ | 中心値 | | 相対バイオアベイラビリティ | |
|---|---|---|---|---|---|
| 試験 vs.標準 | （単位） | 試験 | 標準 | 点推定値 | 90%信頼区間 |
| F vs. E | $C_{max}$（ng/mL） | 69.4 | 62.1 | 1.117 | 1.042 - 1.197 |
| | $AUC_t$（ng•h/mL） | 513 | 499 | 1.029 | 0.971 - 1.091 |
| | $AUC_{inf}$（ng•h/mL） | 524 | 509 | 1.029 | 0.971 - 1.091 |
| | $AUC_{0-12}$（ng•h/mL） | 394 | 369 | 1.069 | 0.995 - 1.149 |
| | $AUC_{12-t}$（ng•h/mL） | 113 | 121 | 0.931 | 0.837 - 1.036 |
| H vs. G | $C_{max}$（ng/mL） | 94.7 | 94.9 | 0.998 | 0.930 - 1.070 |

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|---|---|---|---|---|
| $AUC_t$（ng•h/mL） | 622 | 627 | 0.992 | 0.952 - 1.032 |
| $AUC_{inf}$（ng•h/mL） | 630 | 634 | 0.994 | 0.954 - 1.035 |
| $AUC_{0-12}$（ng•h/mL） | 511 | 514 | 0.993 | 0.946 - 1.043 |
| $AUC_{12-t}$（ng•h/mL） | 106 | 107 | 0.986 | 0.915 - 1.063 |

レジメン E：絶食下で臨床試験製剤（ER18Y）30 mg を単回投与（レジメン F に対する標準レジメン）

レジメン F：絶食下で市販予定製剤（ER18）30 mg を単回投与（レジメン E に対する試験レジメン）

レジメン G：高脂肪/高カロリー食後に臨床試験製剤（ER18Y）30 mg を単回投与（レジメン H に対する標準レジメン）

レジメン H：高脂肪/高カロリー食後に市販予定製剤（ER18）30 mg を単回投与（レジメン G に対する試験レジメン）

安全性の結果：

検討したレジメンの忍容性はおおむね良好であった。1 名が高度の胆石症のため試験を中止したが，本事象は治験責任医師によって治験薬と関連なしと評価された。試験期間中に臨床的に重要なバイタルサイン及び臨床検査値異常は認められなかった。報告された有害事象に特定のパターンはなく，本試験において新たな安全性の問題は認められなかった。

結論:

15 mg 含量の市販予定製剤（ER17）は，絶食下及び高脂肪/高カロリー食摂取後において 15 mg 含量の臨床試験用製剤（ER17Y）と生物学的に同等である。30 mg 含量の市販予定製剤（ER18）は，絶食条件下及び高脂肪/高カロリー食摂取後において 30 mg 含量の臨床試験用製剤（ER18Y）と生物学的に同等である。

## M15-572 試験（投与 24 週時）

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| 治験の標題：<br>1 種類以上の非生物学的疾患修飾性抗リウマチ薬（DMARD）による治療で効果不十分な活動性乾癬性関節炎患者におけるウパダシチニブ（ABT-494）とプラセボ及びアダリムマブとの第 III 相ランダム化二重盲検比較試験-*SELECT-PsA1* |
| 治験実施施設：<br>44 ヵ国（アルゼンチン，オーストラリア，ベラルーシ，ベルギー，ボスニア・ヘルツェゴビナ，ブラジル，ブルガリア，カナダ，チリ，中国，香港，コロンビア，クロアチア，チェコ共和国，エストニア，ドイツ，ギリシャ，ハンガリー，アイルランド，イスラエル，イタリア，日本，韓国，ラトビア，リトアニア，マレーシア，メキシコ，オランダ，ニュージーランド，ポーランド，ポルトガル，ロシア連邦，セルビア，シンガポール，スロバキア，スロベニア，南アフリカ，スペイン，スイス，台湾，トルコ，イギリス，ウクライナ，米国［プエルトリコを含む］），281 施設 |
| 治験責任医師：<br>[redacted], FRCP, PhD，他 |
| 公表文献（参考資料）：<br>なし |

| | |
|---|---|
| 治験期間（年数）：<br>最初の被験者の初回来院日：2017 年 4 月 27 日<br>最後の被験者の最終来院日：20[redacted] 年 [redacted] 月 [redacted] 日（投与 24 週時） | 開発のフェーズ：III |

目的：

第 1 ピリオド

主要目的：

1 種類以上の非生物学的疾患修飾性抗リウマチ薬（以下「non-bDMARD」）投与で効果不十分又は忍容性のない（以下「non-bDMARD-IR」）中等症から重症の活動性乾癬性関節炎患者を対象に，ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）を投与したときの有効性（乾癬性関節炎の症状・徴候）をプラセボ又はアダリムマブと比較する。

副次目的：

（1）non-bDMARD-IR（1 種類以上）の中等症から重症の活動性乾癬性関節炎患者を対象に，ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）を投与したときの有効性（構造的損傷の防止）をプラセボと比較する，
（2）non-bDMARD-IR（1 種類以上）の中等症から重症の活動性乾癬性関節炎患者を対象に，ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）を投与したときの安全性及び忍容性をプラセボ又はアダリムマブと比較する。

第 2 ピリオド

第 1 ピリオドを完了した乾癬性関節炎患者を対象に，ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）を投与したときの長期的な安全性，忍容性及び有効性を評価する。

24 週間治験総括報告書（以下「CSR W24」）のデータカットオフ日（20[redacted] 年 [redacted] 月 [redacted] 日）時点において，第 1 ピリオドの投与 24 週時まで完了していた（すなわち，全被験者が完了又は中止していた）。第 2 ピリオドは実施中である。本項には，第 1 ピリオドの投与 24 週時までの有効性データ，投与 24 週時までの短期的な安全性データ，及び CSR W24 の 20[redacted] 年 [redacted] 月 [redacted] 日のデータカットオフ日時点までの長期的な安全性データを含めた。

被験者数 (計画時と解析時)：

計画時：1640 名，解析時：1705 名（ウパダシチニブ 15 mg 群：430 名，ウパダシチニブ 30 mg 群：423 名，アダ

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|---|
| リムマブ群：429 名，プラセボ群：423 名） |
| 診断と主要な組入れ基準：<br>スクリーニング来院時の 6 ヵ月以上前に発症し，乾癬性関節炎の分類基準に基づき乾癬性関節炎と診断された 18 歳以上の成人男性及び女性を本試験に組み入れた。<br>以下の全てに該当する患者を適格な被験者とした：<br>● ベースライン時の疾患活動性を有する（スクリーニング及びベースライン来院時の圧痛関節数［以下「TJC」］が 3 ヵ所以上［68 関節に基づく］及び腫脹関節数［以下「SJC」］が 3 ヵ所以上［66 関節に基づく］と定義）<br>● スクリーニング時に中央画像判定機関による X 線画像の判定で 1 ヵ所以上の骨のびらんを有する，又は高感度 C-反応性蛋白（以下「hs-CRP」）が施設基準値上限を上回る場合のいずれかに該当する<br>● 活動性尋常性乾癬と診断された又は尋常性乾癬の既往歴が確認できる<br>● 1 種類以上の non-bDMARD によるこれまでの治療で効果不十分（最低 12 週間の治療で効果が認められない）である，又は疾患修飾性抗リウマチ薬（以下「DMARD」）に忍容性がない若しくは DMARD が禁忌であると治験責任医師に判定されている<br>以下の患者を除外した：<br>● 生物学的免疫調整剤，ヤヌスキナーゼ阻害薬による治療歴がある<br>● 治験薬投与開始前の 30 日間又は薬剤の 5 半減期（どちらか長い方の期間）以内に，他の治験薬を使用した，又は登録時に他の介入臨床試験に組み入れられている<br>● ベースライン時に 3 種類以上の non-bDMARD を投与している，メトトレキサート，スルファサラジン，レフルノミド，アプレミラスト，ヒドロキシクロロキン，ブシラミン若しくはイグラチモド以外の non-bDMARD を使用している，又はメトトレキサートとレフルノミドを併用している<br>● 線維筋痛症の既往歴がある，17 歳以前に発現した関節炎の既往歴がある，又は乾癬性関節炎以外の炎症性関節疾患（関節リウマチ，痛風，結合組織疾患の合併，強皮症，多発性筋炎，皮膚筋炎，全身性エリテマトーデスを含むがこれらに限定しない）と診断されている（診断名が乾癬性関節炎に変更された，又は乾癬性関節炎の診断が追加された場合は，反応性関節炎又は軸性脊椎関節炎［強直性脊椎炎及び X 線検査で異常が認められない軸性脊椎関節炎を含む］の既往歴がある患者は組み入れ可能とした）<br>● スクリーニング期間中の臨床検査値が以下の基準に該当する：血清アスパラギン酸アミノトランスフェラーゼ（以下「AST」）が基準値上限（以下「ULN」）の 2 倍超，血清アラニンアミノトランスフェラーゼ（以下「ALT」）が ULN の 2 倍超，推定糸球体濾過率（4 変数を用いた Modification of Diet in Renal Disease 簡易式に基づく）が 40 mL/min/1.73m$^2$ 未満，総白血球数が 2500/μL 未満，好中球数（絶対値）が 1500/μL 未満，血小板数が 100000/μL 未満，リンパ球数（絶対値）が 800/μL 未満，及びヘモグロビンが 10 g/dL 未満 |
| 治験方法：<br>本試験は国際共同第 III 相試験であり，倫理的配慮から過度な人数の被験者を組み入れることなく，科学的及び規則上の目的を達成するために，全世界の約 350 施設で約 1640 名の被験者を組み入れる計画とした。<br>本試験は，2 つの投与期間で構成された。試験期間は以下のとおり構成することとした：1）35 日間のスクリーニング期間，2）24 週間のランダム化，二重盲検，プラセボ及び実薬対照投与期間，並びにその後の追加 32 週間のウパダシチニブ実薬対照投与期間からなる計 56 週間の盲検期間（第 1 ピリオド），3）投与期間の合計を約 3 年までとする長期継続投与期間（［最後の被験者が第 1 ピリオドの最終来院を完了するまで盲検とする］第 2 ピリオド），4）30 日間の電話連絡又は来院による追跡調査期間，及び 5）70 日間の電話連絡による追跡調査期間。<br>適格基準を満たす被験者を，乾癬の程度（体表面積［以下「BSA」］3%以上，3%未満），1 種類以上の DMARD の現在の使用の有無，指趾炎の有無，腱付着部炎の有無によって層別化（但し，中国人及び日本人の被験者は乾癬の程度［BSA 3%以上，3%未満］のみにより層別化）し，2:2:2:1:1 の割合で以下の 5 つの投与群のうち 1 つにランダム化した。<br>グループ 1：ウパダシチニブ 15 mg 1 日 1 回（N = 410）<br>グループ 2：ウパダシチニブ 30 mg 1 日 1 回（N = 410） |

グループ 3：アダリムマブ 40 mg 隔週（N = 410）
グループ 4：プラセボ→ウパダシチニブ 15 mg 1 日 1 回（N = 205）
グループ 5：プラセボ→ウパダシチニブ 30 mg 1 日 1 回（N = 205）
ヒドロキシクロロキン，スルファサラジン，ブシラミン又はイグラチモドを併用投与していた被験者は約 15%を超えないように組入れを行うこととした。

被験薬，用量 / 含量 / 濃度，投与法，ロット番号：
ウパダシチニブ 15 mg 徐放錠（経口），バルクロット番号：[redacted]
ウパダシチニブ 30 mg 徐放錠（経口），バルクロット番号：[redacted]
治療期間：
第 1 ピリオド：56 週間，第 2 ピリオド：最長 3 年間

対照薬，用量 / 含量 / 濃度，投与法，ロット番号：
ウパダシチニブに対応するプラセボの錠剤（経口），バルクロット番号：[redacted]
アダリムマブ 40 mg，1 mL プレフィルドシリンジ剤（皮下），バルクロット番号：[redacted]
アダリムマブに対応するプラセボの 1 mL プレフィルドシリンジ剤（皮下），バルクロット番号：[redacted]

評価基準：
有効性：
主要評価項目は，投与 12 週時の米国リウマチ学会（以下「ACR」）20%改善基準を達成した被験者の割合（以下「ACR20 反応率」）とした。
主な多重性を調整した副次評価項目（特に記載がない限り，ウパダシチニブ各用量とプラセボの比較）：

- 投与 12 週時の健康評価質問票－障害指数（以下「HAQ-DI」）ベースラインからの変化量
- 投与 16 週時において，乾癬の医師による静的全般的評価（以下「sIGA」）スコアが 0 又は 1 であり，ベースラインと比較して 2 ポイント以上の改善が認められた被験者の割合
- 投与 16 週時の乾癬の面積と重症度の指数（以下「PASI」）75%改善基準を達成した被験者の割合（以下「PASI75 反応率」）（ベースラインで BSA の 3%以上の乾癬を有していた被験者が対象）
- 投与 24 週時の乾癬性関節炎用改変 Sharp/van der Heijde スコア（以下「SHS」）のベースラインからの変化量
- 投与 24 週時の最低疾患活動性（以下「MDA」）を達成した被験者の割合
- 投与 24 週時の腱付着部炎が消失した被験者（リーズ腱付着部炎指標［以下「LEI」］= 0）の割合
- 投与 12 週時の ACR20 反応率（アダリムマブに対するウパダシチニブの非劣性）
- 投与 12 週時における Short Form 36 項目健康調査票（以下「SF-36」）の身体的健康度（以下「PCS」）のベースラインからの変化量
- 投与 12 週の慢性疾患療法の機能的評価－倦怠感（以下「FACIT-F」）におけるベースラインからの変化量
- 投与 12 週時の ACR20 反応率（アダリムマブに対するウパダシチニブの優越性）
- 投与 24 週時の指趾炎が消失した被験者（リーズ指趾炎指標［以下「LDI」］= 0）の割合
- 投与 12 週時の患者による疼痛度評価（数値化格付けスケール［以下「NRS」］）のベースラインからの変化量（アダリムマブに対するウパダシチニブの優越性）
- 投与 12 週時の HAQ-DI のベースラインからの変化量（アダリムマブに対するウパダシチニブの優越性）
- 投与 16 週時の乾癬症状自己評価（以下「SAPS」）質問票におけるベースラインからの変化量

追加の主な副次評価項目（ウパダシチニブの各用量とプラセボの比較）として，投与 12 週時の ACR50%改善基

準を達成した被験者の割合（以下「ACR50 反応率」）及び ACR70%改善基準を達成した被験者の割合（以下「ACR70 反応率」），並びに投与 2 週時の ACR20 反応率を評価した。

追加の有効性評価項目として，治験実施計画書で規定した時点で以下の評価項目を評価した：

- X 線画像上で疾患進行が認められない被験者（SHS のベースラインからの変化量が 0 以下又は 0.5 以下と定義）の割合
- 関節裂隙狭小化スコア（JSN）及び骨びらんスコアのベースラインからの変化量
- ACR 反応率の個々の項目におけるベースラインからの変化量（TJC のベースラインからの変化量［0～68］，SJC のベースラインからの変化量［0～66］，疾患活動性 NRS の医師による全般的評価［PGA］のベースラインからの変化量，疾患活動性 NRS の患者による全般的評価［PtGA］のベースラインからの変化量，疼痛 NRS の患者による評価のベースラインからの変化量，HAQ-DI のベースラインからの変化量，hs-CRP のベースラインからの変化量）
- ACR20/50/70 反応率
- MDA を達成した被験者の割合
- LDI のベースラインからの変化量（ベースラインの LDI が 0 を超えていた被験者が対象）
- 指趾炎数のベースラインからの変化量（ベースラインの LDI が 0 を超えていた被験者が対象）
- 指趾炎数が消失した被験者の割合（ベースラインの LDI が 0 を超えていた被験者が対象）
- LEI のベースラインからの変化量（ベースラインの LEI が 0 を超えていた被験者が対象）
- 腱付着部炎が消失した被験者（LEI =0）の割合（ベースラインの LEI が 0 を超えていた被験者が対象）
- カナダ脊椎関節炎研究コンソーシアム（以下「SPARCC」）腱付着部炎指標のベースラインからの変化量（ベースラインの SPARCC 腱付着部炎指標が 0 を超えていた被験者が対象）
- 腱付着部炎が消失した被験者（SPARCC 腱付着部炎指標= 0）の割合（ベースラインの SPARCC 腱付着部炎指標が 0 を超えていた被験者が対象）
- 腱付着部炎総数のベースラインからの変化量（ベースラインの腱付着部炎総数が 0 を超えていた被験者が対象）
- 腱付着部炎が消失した被験者（腱付着部炎総数= 0）の割合（ベースラインの腱付着部炎総数が 0 を超えていた被験者が対象）
- PASI75/90/100 反応率（ベースラインで BSA の 3%以上の乾癬を有していた被験者が対象）
- 乾癬の sIGA スコアの 0 又は 1 を達成した被験者の割合（sIGA が 2 以上の被験者が対象）
- 体表面積－乾癬（以下「BSA-Ps」）のベースラインからの変化量（ベースラインで BSA-Ps が 0 を超えていた被験者が対象）
- 改変乾癬性関節炎反応基準（PsARC）に基づく奏効率
- 28 関節に基づく疾患活動性スコア（以下「DAS28」）（C-反応性蛋白［CRP］）のベースラインからの変化量
- DAS28（赤血球沈降速度［ESR］）のベースラインからの変化量
- 乾癬性関節炎疾患活動性スコア（PASDAS）のベースラインからの変化量
- 乾癬性関節炎疾患活動性（DAPSA）スコアのベースラインからの変化量
- SF-36 のベースラインからの変化量
- FACIT-F 質問票におけるベースラインからの変化量
- EuroQol 5 Dimensions 5 Levels（EQ-5D-5L）質問票及び EuroQol 視覚的アナログスケール（EQ-VAS）スコアにおけるベースラインからの変化
- 仕事の生産性及び活動障害（WPAI）質問票のベースラインからの変化量
- 健康資源活用（HRU）の累積数
- SAPS 質問票におけるベースラインからの変化量
- バース強直性脊椎炎疾患活動性指標（以下「BASDAI」）のベースラインからの変化量（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- BASDAI 50%改善（BASDAI50）反応率（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- 朝のこわばり（BASDAI 質問票 5 及び 6 の平均値）のベースラインからの変化量
- 朝のこわばりの重症度（BASDAI 質問票 5，0～10）のベースラインからの変化量
- 朝のこわばりの期間（BASDAI 質問票 6，0～10）のベースラインからの変化量

- 強直性脊椎炎疾患活動性スコア（以下「ASDAS」）のベースラインからの変化量（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- ASDAS における非活動性疾患を有する被験者の割合（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- ASDAS における主要改善を示した被験者の割合（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- ASDAS における臨床的に意義がある改善を示した被験者の割合（ベースラインに乾癬性脊椎炎を有していた被験者が対象）
- HAQ-DI で臨床的意義のある改善（0.35 以上）を認めた被験者の割合

薬物動態：
ウパダシチニブの血漿中濃度は，治験実施計画書で規定した時点に測定した。

安全性：
有害事象，バイタイルサイン，身体検査及び臨床検査（血液学的検査，血液生化学検査及び尿検査）

統計手法：
有効性：
主要評価項目：解析は最大の解析対象集団を対象として，ランダム化された投与群に基づいて実施した。主要解析にはノンレスポンダーインピュテーション（以下「NRI」）を用いた。主な層別化因子である DMARD の現在の使用の有無で調整した Cochran Mantel Haenszel（以下「CMH」）検定を用いて，主要評価項目についてウパダシチニブ各用量と併合したプラセボ群を比較した。点推定値，正規近似に基づく 95%信頼区間及び投与群の比較に関する *P* 値を示した。名目 *P* 値及び調整 *P* 値を示した。補足的な解析として，補完をせず，as observed（以下「AO」）データを用いて主要解析と同じ解析を実施した。missing not at random を含む，欠測値に関する様々な仮定について検討するため，ロジスティック回帰による多重補完により，ウパダシチニブ各用量群とプラセボ群のそれぞれで ACR 反応率を体系的に 0%から 100%まで変化させて補完することにより，tipping point analysis を実施した。また，補足的な解析として治験実施計画書に適合した解析対象集団を対象に，NRI を用いた CMH 解析も実施した。

主な副次評価項目：2 値変数について，各投与群の頻度とパーセンテージ（%）を示した。主要解析として，有効性の評価の定義を除き，主要評価項目と同様の解析を実施した。部分集団のみに適用される評価項目については，部分集団のみを対象に同じ解析を実施した。投与 24 週時の MDA を達成した被験者の割合，腱付着部炎が消失した被験者の割合及び指趾炎が消失した被験者の割合については，NRI を用いることに加え，救済療法基準に該当する被験者をノンレスポンダーとして取り扱った。ランダム化され，治験薬を 1 回以上投与された被験者を対象として，ウパダシチニブ各用量群とプラセボ群を比較した。補足的な解析として，2 値変数についても，AO データを用いて解析を実施した。ランダム化された各投与群の反応率について，点推定値及び正規近似に基づく 95%信頼区間を算出した。主要層別化因子である DMARD の現在の使用の有無で調整した CMH 検定を用いて，ウパダシチニブ各用量群と併合したプラセボ群を比較した。点推定値，正規近似に基づく 95%信頼区間及び投与群間差に関する *P* 値を示した。投与 12 週時の ARC20 反応率では，プラセボの効果を差し引いた投与群間差について，Koch の 3 群検定統計量を用いてアダリムマブに対するウパダシチニブの各用量の非劣性を検定した。本検定では，ウパダシチニブ投与によって，プラセボの効果を差し引いたアダリムマブの有効性の 50%以上が維持された場合に非劣性が示されるとした。非劣性検定が統計学的に有意であった場合，投与 12 週時の ARC20 反応率についてアダリムマブに対するウパダシチニブの優越性も検定することとした。
X 線画像データ以外の連続変数について，主要解析として，治療，来院，治療と来院の交互作用及び層別化因子である DMARD の現在の使用の有無を固定効果とし，ベースライン値を連続的固定共変量とする混合効果・反復測定モデル（以下「MMRM」）を用いて解析した。補足的な解析として，連続変数の順位付けした X 線画像データ以外の副次評価項目について，AO データを用い，また，投与群及び層別化因子である DMARD の現在の使用の有無を固定効果とし，対応するベースライン測定値を共変量とする共分散分析（以下「ANCOVA」）を用いて解析した。ランダム化された各投与群の最小二乗平均値及び 95%信頼区間，並びにウパダシチニブ各用量

群と併合したプラセボ群の投与群間差の最小二乗平均値，その 95%信頼区間及び *P* 値を示した。投与 12 週時の患者による疼痛度評価（NRS）及び HAQ-DI のベースラインからの変化量について，アダリムマブに対するウパダシチニブの優越性を同じ MMRM モデルを用いて検定した。順位付けした主な副次評価項目について，調整 *P* 値を示した。

X 線画像データの評価項目は，投与 24 週時の SHS のベースラインからの変化量について，投与群及び層別化因子である DMARD の現在の使用の有無を固定効果とし，対応するベースライン測定値を共変量とする ANCOVA を用い，統計的推定を行った。X 線画像データの主要解析として，投与 24 週時の SHS スコアのベースラインからの変化量の平均値の差を解析した。ランダム化され治験薬を 1 回以上投与された被験者を対象に，ウパダシチニブ各用量群とプラセボ群を比較した。

単一補完法の不確実性を考慮するため，感度分析として多重補完解析を実施した。各多重補完データセットに対して ANCOVA を行った。Rubin 法を用いて各多重補完データセットの結果を統合した。

補足的な解析として，ANCOVA と同じ解析を AO データを用いて実施した。

ランダム化された各投与群の最小二乗平均値及び 95%信頼区間，並びにウパダシチニブ各用量群と併合したプラセボ群間の投与群間差の最小二乗平均値，その 95%信頼区間及び *P* 値を示した。その他の感度分析として，ベースライン時点及びベースライン以降の測定値を含め，SHS 測定値を応答変数として用いたランダム係数モデルを適用した。

追加の評価項目については，主な副次評価項目と同じ解析を実施した。

薬物動態：

各来院時の被験者別のウパダシチニブ血漿中濃度を一覧表にし，適切な統計手法を用いて要約した。非線形混合効果モデルを用いた解析により，ウパダシチニブの見かけのクリアランス及び分布容積の母集団中心値及び経験的ベイズ推定法による個別値を推定した。

安全性：

投与 24 週時までの安全性解析及び長期安全性解析（20[redacted] 年 [redacted] 月 [redacted] 日の CSR W24 のデータカットオフ日まで）の 2 つの解析を行うこととした。

投与 24 週時まで：標準的な安全性解析として，有害事象，臨床検査及びバイタルサインを評価した。有害事象を発現した被験者数及び発現割合の表を，ICH 国際医薬用語集（以下「MedDRA」）の器官別大分類及び基本語別，投与群別に示した。各来院日の臨床検査値及びバイタルサインの連続変数は投与群別に要約した。臨床的に意義がある臨床検査値及びバイタルサインの基準に該当した被験者の集計表を実際に受けた投与に基づく投与群別に示した。安全性データの欠測値は補完しなかった。ウパダシチニブ群とプラセボ群又はアダリムマブ群との比較は，主な安全性評価項目である有害事象の概要，特に注目すべき有害事象の概要，特定の臨床検査パラメータのベースラインからの変化量及び臨床的に意義がある臨床検査値について示した。投与群間差及びその 95%信頼区間を示した。

治験実施計画書に規定した治療切替えを考慮した長期安全性解析として，累積曝露量で調整した有害事象の発現件数，来院日別の臨床検査値及びバイタルサインの要約，並びに臨床的に意義がある臨床検査値及びバイタルサインの発現割合を評価した。100 人年あたりの有害事象の発現件数は，有害事象が発現した時点の実際に受けた投与に基づく投与群別に示した。有害事象が発現した被験者の一覧を器官別大分類及び基本語別に示した。来院日別の臨床検査値及びバイタイルサインの要約は実際に受けた投与に基づく投与群の順序別に示した。臨床的に意義がある臨床検査値及びバイタルサインの基準に該当した被験者の集計及び一覧を，有害事象が発現した時点の実際に受けた投与に基づく投与群別に示した。安全性データの欠測値は補完しなかった。

実際に受けた投与に基づく投与群の順序は以下のとおり定義した。

1. プラセボ→ウパダシチニブ 15 mg 1 日 1 回
2. プラセボ→ウパダシチニブ 30 mg 1 日 1 回
3. ウパダシチニブ 15 mg 1 日 1 回
4. ウパダシチニブ 30 mg 1 日 1 回

5. アダリムマブ 40 mg 隔週

要約 / 結論：

有効性の結果：

継続中の本試験の二重盲検，プラセボ及び実薬対照の投与 24 週時の解析において，ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）は，non-bDMARD-IR（1 種類上）の中等度から高度の活動性乾癬性関節炎患者の治療において有効であった。本試験では主要評価項目が達成され，ACR20 反応率は，プラセボ群（36.2%）と比較してウパダシチニブ 15 mg 群（70.6%）及び 30 mg 群（78.5%）で統計学的に有意に大きかった（$P < 0.0001$）。更に，順位付けした副次評価項目（HAQ-DI，SF-36 PCS 及び FACIT-F のベースラインからの変化量，並びに sIGA スコアが 0 又は 1，PASI 75，MDA 及び腱付着部炎の消失を達成した被験者の割合）では，プラセボ群と比較してウパダシチニブ両用量群で統計学的に有意な有効性が認められた。SHS（改変トータルシャープスコアと同等）の測定により，プラセボ群と比較してウパダシチニブ 15 mg 及び 30 mg の両用量群で，X 線画像上での疾患進行の防止において統計学的に有意に高い有効性が示された。本試験では，投与 12 週時の ACR20 反応率について，非劣性検定でアダリムマブ群に対するウパダシチニブ両用量群の統計学的有意差が示され，ウパダシチニブ 30 mg 群ではアダリムマブ群に対する優越性が示された。HAQ-DI はアダリムマブ群と比較してウパダシチニブ両用量群で大きな改善が認められ，疼痛度評価ではアダリムマブ群と比較してウパダシチニブ 30 mg で大きな改善が認められた。また，指趾炎の消失及び SAPS により被験者が報告した乾癬の症状について，プラセボ群と比較してウパダシチニブ 15 mg 群及び 30 mg 群で大きな効果を示した。

筋骨格系症状（関節疾患，腱付着部炎，指趾炎及び脊椎疾患），身体機能，生活の質及びその他の患者報告健康アウトカムに対する有効性を評価した追加の有効性評価項目において，ウパダシチニブ両用量群ではプラセボ群を上回る大きな改善が認められ，アダリムマブ群との比較では同程度又は大きな改善が認められるという一貫した結果からも，ウパダシチニブ両用量群の有効性が支持された。更に，ウパダシチニブ両用量群では，乾癬の皮膚症状の治療に対しても一貫した有効性が示され，ウパダシチニブ 30 mg 群では，乾癬の皮膚症状の改善及び MDA 評価による包括的な疾患コントロールの達成において，アダリムマブ群よりも高い有効性を示した。ウパダシチニブ 15 mg 及び 30 mg の両用量群において，投与 2 週時にはいくつかの評価項目で速やかな有効性が確認され，投与 24 週時まで維持又は更なる改善が認められた。

薬物動態の結果：

投与後 24 時間以内でのウパダシチニブの平均血漿中濃度は，15 mg（1 日 1 回）では 7.21～33.0 ng/mL，30 mg（1 日 1 回）では 11.2～59.1 ng/mL であった。ウパダシチニブ濃度の実測値は，既存の薬物動態の結果から予測される濃度と一致した。

安全性の結果：

ウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）の投与は，CSR W24 のデータカットオフ日まで，忍容性はおおむね良好であった。本試験でのウパダシチニブの観察された安全性プロファイルは，関節リウマチ試験で観察されたものとおおむね一致していた。新規の安全性リスクは確認されなかった。主な安全性データの要約を以下に示した：

- 投与 24 週時までの有害事象の発現割合は，プラセボ群が最も低く，ウパダシチニブ 15 mg 群とアダリムマブ群で同程度であり，ウパダシチニブ 30 mg 群が最も高かった。重篤な有害事象の発現割合は，ウパダシチニブ 15 mg 群，アダリムマブ群及びプラセボ群で同程度であり，ウパダシチニブ 30 mg 群で高かった。高度の有害事象及び治験薬投与中止に至った有害事象の発現割合は，ウパダシチニブ 15 mg 群とプラセボ群で同程度であり，ウパダシチニブ 30 mg 群及びアダリムマブ群で高かった。
- CSR W24 のデータカットオフ日までの 100 人年あたりの有害事象の発現件数及び 100 人年あたりの高度の有害事象の発現件数は，ウパダシチニブ 15 mg 群とアダリムマブ群で同程度であったが，ウパダシチニブ 30 mg 群で多かった。重篤な有害事象の発現件数は，ウパダシチニブ 15 mg 群で最も少なく，ウパダシチニブ 30 mg 群で最も多かったが，治験薬の投与中止に至った有害事象は，ウパダシチニブ 15 mg 群で最も少なく，アダリムマブ群で最も多かった。
- 投与 24 週時までの主な有害事象（ウパダシチニブの各用量群で発現割合 5%以上）は，上気道感染，上

咽頭炎，血中クレアチンホスホキナーゼ増加，アラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加であった。

- 投与 24 週時まで，大部分の特に注目すべき有害事象の発現割合は低かった。CSR W24 のデータカットオフ日まで，大部分の特に注目すべき有害事象では投与群間で特記すべき 100 人年あたりの発現件数/発現被験者数の差はなかった。多く認められた特に注目すべき有害事象のうち，重篤な感染症，帯状疱疹，貧血，好中球減少症，リンパ球減少症及びクレアチンホスホキナーゼ（以下「CPK」）増加の 100 人年あたりの発現件数は，ウパダシチニブ 15 mg 群と比較してウパダシチニブ 30 mg 群で多かった。その他の特に注目すべき有害事象（日和見感染［結核及び帯状疱疹を除く］，悪性腫瘍，肝障害，消化管穿孔と判定された事象，腎障害，主要血管イベント［以下「MACE」］と判定された事象及び静脈血栓塞栓症［以下「VTE」］）の 100 人年あたりの発現件数 / 発現被験者数は，ウパダシチニブの両用量群で同程度であった。アダリムマブ群との比較では，ウパダシチニブの両用量群で帯状疱疹，貧血，リンパ球減少症及び CPK 増加の発現割合が高く，肝機能障害の発現割合が低かった。また，重篤な感染症及び好中球減少症は，アダリムマブ群に比べてウパダシチニブ 30 mg 群で高かった。
- CSR W24 のデータカットオフ日まで，曝露量で調整した帯状疱疹の 100 人年あたりの発現件数はウパダシチニブ 30 mg と比較してウパダシチニブ 15 mg 群で少なく，アダリムマブ群と比較してウパダシチニブの両用量群で多かった。帯状疱疹の多くは，非播種性（皮膚分節が 1～2 箇所に限定），重症度は軽度又は中等度であり，治験薬の投与中止には至らなかった。中枢神経系又はその他の内臓器官の症状を伴う帯状疱疹は報告されなかった。
- 日和見感染（結核及び帯状疱疹を除く）の発現は少なく（1.0 件/100 人年以下），CSR W24 のデータカットオフ日まで，ウパダシチニブ 15 mg 及び 30 mg 群のみで発現した。
- CSR W24 のデータカットオフ日までに，消化管穿孔と判定されたのはウパダシチニブ 15 mg 群の 1 件（穿孔性胃潰瘍）で，非ステロイド系抗炎症薬とメトトレキサートの併用投与の影響が考えられた。
- CSR W24 のデータカットオフ日まで，肝障害の多くは ALT 又は AST 増加であった。アダリムマブ群の 1 件を除き，肝障害はいずれも非重篤であり，治験薬の投与中止に至った事象はほとんどなかった。グレード 3 又グレード 4 の ALT 又は AST 増加の発現は少なかった。グレード 3 の血液生化学検査値の上昇の多くは一時的であり，再検査では確認されなかった。Hy's law に該当する被験者はいなかった。
- CSR W24 のデータカットオフ日まで，貧血，好中球減少症及びリンパ球減少症の多くは，重症度が軽度であった。グレード 3 の血液学的検査値の発現割合は，ウパダシチニブの両用量群で低かった。グレード 3 の血液学的検査値の減少の多くは一時的であり，再検査では確認されなかった。グレード 4 のヘモグロビン，好中球数及び白血球数の異常は認められなかった。グレード 3 の好中球数減少及びリンパ球数減少は，おおむね感染症の合併を伴うものではなかった。
- CSR W24 のデータカットオフ日まで，グレード 3 又はグレード 4 の CPK 増加の発現割合は低かった（いずれの投与群でも 2%以下）。ウパダシチニブ 30 mg 群の 2 名にグレード 3 又はグレード 4 の CPK 増加に伴う筋肉関連の症状が認められた。1 名は筋肉痛であり，もう 1 名は，治験薬投与中止後，複数回の来院時にグレード 4 の CPK 増加（ULN の 10 倍超）が認められ，皮膚筋炎との診断に至り，下肢脱力及び筋浮腫の筋肉関連の症状を示した。CPK 増加の事象はいずれも，非重篤であり，重症度はほとんどが軽度から中等度であった。治験薬の投与中止に至った事象はほとんどなかった。横紋筋融解症が認められた被験者はいなかった。
- CSR W24 のデータカットオフ日まで，悪性腫瘍の発現被験者数は少なく，各投与群で同程度であった。非黒色腫皮膚癌を除き，ほとんどの悪性腫瘍は 1 名の被験者に認められた。
- MACE 及び VTE と判定された事象は，CSR W24 のデータカットオフ日まで，ウパダシチニブ 15 mg 群及び 30 mg 群，並びにアダリムマブ群で同程度であった。
- 投与 24 週時までに，総コレステロール，高比重リポ蛋白コレステロール（以下「HDL-C」）及び低比重リポ蛋白コレステロール（以下「LDL-C」）の増加がウパダシチニブ投与で認められた。LDL-C /HDL-C 比及び総コレステロール/HDL-C 比にベースラインからの本質的な変化はなかった。
- 投与 24 週時までに，プラセボ群 1 名に治療下で発現した死亡（心停止）が認められ，死因不明と判断された。投与 24 週から CSR W24 のデータカットオフ日までに，ウパダシチニブ群の 2 名がいずれも治験薬の最終投与後 31 日以降に死亡した。うち 1 名はウパダシチニブ 15 mg 群で，遠隔転移を伴う肺癌

と診断されたために同意を撤回し，その約 2 ヵ月後に死亡した。もう 1 名はウパダシチニブ 30 mg 群で，間質性肺疾患で死亡した。

- 活動性結核又はリンパ腫はいずれの投与群でも報告されなかった。
- ウパダシチニブを投与された被験者の体重増加を除き，バイタルサインに重要な変化は認められなかった。

結論：

本試験（M15-572 試験）の投与 24 週時（第 1 ピリオド）までの解析において，non-bDMARD-IR（1 種類以上）の中等症から重症の活動性乾癬性関節炎患者における，乾癬性関節炎の臨床関連症状（筋骨格系症状［関節疾患，腱付着部炎，指趾炎及び脊椎疾患］，乾癬，身体機能，疼痛，疲労及びその他の患者報告健康アウトカム，並びに X 線画像上での疾患進行防止を含む）について，プラセボと比較してウパダシチニブ 15 mg 及び 30 mg（いずれも 1 日 1 回）の有効性が示された。投与 12 週時の ACR20 反応率において，ウパダシチニブ両用量群でアダリムマブ群に対する非劣性が示され，ウパダシチニブ 30 mg ではアダリムマブ群に対する優越性が示された。CSR W24 のデータカットオフ日まで，安全性では，ウパダシチニブ 15 mg 及び 30 mg の忍容性はおおむね良好であった。重篤な感染，帯状疱疹，貧血，好中球減少症，リンパ球減少症及び CPK 増加の発現件数は，ウパダシチニブ 15 mg と比較してウパダシチニブ 30 mg 群で多かった。アダリムマブ群と比較して，帯状疱疹の発現件数はウパダシチニブ 15 mg 及び 30 mg 群で多く，一方，重篤な感染の発現件数はウパダシチニブ 30 mg で多かった。これらは，ウパダシチニブで特定されていたリスクであった。本試験の投与 24 週時までの有効性の結果及び CSR W24 のデータカットオフ日までの安全性の結果より，ウパダシチニブの両用量のベネフィット・リスクのプロファイルは良好と考えられた。

表 1. 投与 24 週時までの有害事象を発現した被験者数及び発現割合：MedDRA のプライマリー器官別大分類及び基本語別（安全性解析対象集団）

相互参照：M15-572 試験 CSR W24 Table 14.3__1.2.1

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| Any adverse event | 252 (59.6) | 278 (64.8) | 287 (66.9) | 306 (72.3) |
| 血液およびリンパ系障害 | 16 (3.8) | 15 (3.5) | 20 (4.7) | 42 (9.9) |
| 貧血 | 3 (0.7) | 0 | 3 (0.7) | 10 (2.4) |
| 大球性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 自己免疫性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 失血性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 骨髄浮腫 | 0 | 0 | 0 | 1 (0.2) |
| 赤血球減少症 | 0 | 0 | 0 | 1 (0.2) |
| 顆粒球減少症 | 0 | 0 | 0 | 1 (0.2) |
| 内出血発生の増加傾向 | 0 | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| 鉄欠乏性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 白血球増加症 | 2 (0.5) | 0 | 0 | 1 (0.2) |
| 白血球減少症 | 4 (0.9) | 5 (1.2) | 10 (2.3) | 11 (2.6) |
| リンパ節症 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 0 |
| リンパ組織過形成 | 0 | 0 | 0 | 1 (0.2) |
| リンパ球減少症 | 5 (1.2) | 1 (0.2) | 5 (1.2) | 13 (3.1) |
| 大赤血球症 | 0 | 1 (0.2) | 0 | 0 |
| 好中球減少症 | 1 (0.2) | 8 (1.9) | 4 (0.9) | 16 (3.8) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports two or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.

Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 血液およびリンパ系障害 (Cont.) | | | | |
| 好中球増加症 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 正色素性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 血小板減少症 | 1 (0.2) | 1 (0.2) | 0 | 2 (0.5) |
| 血小板増加症 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 心臓障害 | 2 (0.5) | 6 (1.4) | 6 (1.4) | 6 (1.4) |
| 急性心筋梗塞 | 0 | 1 (0.2) | 0 | 0 |
| 大動脈弁硬化症 | 0 | 0 | 1 (0.2) | 0 |
| 心房細動 | 0 | 2 (0.5) | 0 | 1 (0.2) |
| 心房粗動 | 0 | 0 | 0 | 1 (0.2) |
| 左脚ブロック | 0 | 1 (0.2) | 0 | 0 |
| 右脚ブロック | 0 | 0 | 1 (0.2) | 0 |
| 心停止 | 1 (0.2) | 0 | 0 | 0 |
| 心不全 | 0 | 0 | 1 (0.2) | 0 |
| 心臓弁硬化症 | 0 | 0 | 0 | 1 (0.2) |
| 心室血栓症 | 0 | 1 (0.2) | 0 | 0 |
| 冠動脈疾患 | 0 | 0 | 0 | 1 (0.2) |
| 左室機能不全 | 0 | 1 (0.2) | 0 | 0 |
| 心筋虚血 | 0 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports two or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.

Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 心臓障害 (Cont.) | | | | |
| 動悸 | 1 (0.2) | 0 | 2 (0.5) | 1 (0.2) |
| 肺動脈弁閉鎖不全症 | 0 | 0 | 1 (0.2) | 0 |
| 頻脈 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 発作性頻脈 | 0 | 0 | 0 | 1 (0.2) |
| 三尖弁閉鎖不全症 | 0 | 0 | 1 (0.2) | 0 |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 0 | 1 (0.2) |
| 2a型高脂血症 | 0 | 0 | 0 | 1 (0.2) |
| 耳および迷路障害 | 7 (1.7) | 4 (0.9) | 1 (0.2) | 3 (0.7) |
| 耳閉 | 0 | 0 | 0 | 1 (0.2) |
| 耳痛 | 3 (0.7) | 0 | 0 | 0 |
| 乗物酔い | 1 (0.2) | 0 | 0 | 0 |
| 耳鳴 | 2 (0.5) | 3 (0.7) | 0 | 0 |
| 回転性めまい | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |
| 頭位性回転性めまい | 0 | 0 | 0 | 1 (0.2) |
| 前庭障害 | 0 | 0 | 0 | 1 (0.2) |
| 内分泌障害 | 2 (0.5) | 0 | 3 (0.7) | 0 |
| アンドロゲン欠乏症 | 0 | 0 | 1 (0.2) | 0 |
| 自己免疫性甲状腺炎 | 0 | 0 | 1 (0.2) | 0 |

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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 内分泌障害 (Cont.) | | | | |
| 受胎能増加 | 1 (0.2) | 0 | 0 | 0 |
| 甲状腺腫 | 0 | 0 | 1 (0.2) | 0 |
| 甲状腺機能低下症 | 1 (0.2) | 0 | 0 | 0 |
| 眼障害 | 6 (1.4) | 6 (1.4) | 6 (1.4) | 9 (2.1) |
| 動脈硬化性網膜症 | 0 | 0 | 1 (0.2) | 0 |
| 眼瞼痙攣 | 0 | 0 | 1 (0.2) | 0 |
| 白内障 | 0 | 2 (0.5) | 0 | 3 (0.7) |
| 嚢下白内障 | 1 (0.2) | 0 | 0 | 0 |
| 霰粒腫 | 0 | 0 | 0 | 1 (0.2) |
| 結膜刺激 | 1 (0.2) | 0 | 0 | 0 |
| 角膜代償不全 | 1 (0.2) | 0 | 0 | 0 |
| ドライアイ | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 眼痛 | 0 | 0 | 1 (0.2) | 0 |
| 眼瞼下垂 | 0 | 0 | 0 | 1 (0.2) |
| 緑内障 | 0 | 0 | 0 | 2 (0.5) |
| 虹彩毛様体炎 | 0 | 0 | 0 | 1 (0.2) |
| 角膜炎 | 0 | 0 | 0 | 1 (0.2) |
| 瞼板腺炎 | 0 | 1 (0.2) | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 眼障害 (Cont.) | | | | |
| 眼充血 | 1 (0.2) | 0 | 0 | 0 |
| 眼窩周囲浮腫 | 0 | 2 (0.5) | 0 | 0 |
| 眼瞼腫脹 | 0 | 0 | 1 (0.2) | 0 |
| ぶどう膜炎 | 1 (0.2) | 0 | 0 | 0 |
| 霧視 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 視力低下 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 視力障害 | 0 | 0 | 1 (0.2) | 0 |
| 硝子体剥離 | 1 (0.2) | 0 | 0 | 0 |
| 胃腸障害 | 43 (10.2) | 51 (11.9) | 58 (13.5) | 62 (14.7) |
| 腹部不快感 | 4 (0.9) | 2 (0.5) | 2 (0.5) | 2 (0.5) |
| 腹部膨満 | 0 | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 腹痛 | 1 (0.2) | 4 (0.9) | 1 (0.2) | 2 (0.5) |
| 下腹部痛 | 0 | 1 (0.2) | 0 | 0 |
| 上腹部痛 | 3 (0.7) | 4 (0.9) | 6 (1.4) | 4 (0.9) |
| 裂肛 | 0 | 0 | 0 | 1 (0.2) |
| 口角口唇炎 | 0 | 0 | 1 (0.2) | 0 |
| アフタ性潰瘍 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 根尖肉芽腫 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| 腹水 | 0 | 1 (0.2) | 0 | 0 |
| 大腸炎 | 0 | 0 | 1 (0.2) | 0 |
| 便秘 | 3 (0.7) | 5 (1.2) | 3 (0.7) | 2 (0.5) |
| 齲歯 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 下痢 | 10 (2.4) | 9 (2.1) | 18 (4.2) | 14 (3.3) |
| 憩室 | 1 (0.2) | 0 | 0 | 0 |
| 腸憩室 | 0 | 1 (0.2) | 0 | 0 |
| 食道憩室 | 0 | 0 | 0 | 1 (0.2) |
| 後天性過長結腸 | 0 | 1 (0.2) | 0 | 0 |
| 口内乾燥 | 1 (0.2) | 1 (0.2) | 0 | 1 (0.2) |
| 十二指腸潰瘍 | 0 | 1 (0.2) | 0 | 0 |
| 排便困難 | 0 | 0 | 0 | 1 (0.2) |
| 消化不良 | 2 (0.5) | 2 (0.5) | 4 (0.9) | 2 (0.5) |
| 嚥下障害 | 0 | 0 | 0 | 1 (0.2) |
| 小腸炎 | 0 | 1 (0.2) | 0 | 0 |
| 心窩部不快感 | 0 | 1 (0.2) | 0 | 0 |
| 腹膜垂炎 | 1 (0.2) | 0 | 0 | 0 |
| びらん性十二指腸炎 | 0 | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| おくび | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 変色便 | 0 | 0 | 1 (0.2) | 0 |
| 鼓腸 | 3 (0.7) | 2 (0.5) | 0 | 1 (0.2) |
| 食中毒 | 2 (0.5) | 1 (0.2) | 0 | 2 (0.5) |
| 胃ポリープ | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 胃潰瘍 | 0 | 1 (0.2) | 0 | 0 |
| 胃炎 | 2 (0.5) | 2 (0.5) | 2 (0.5) | 4 (0.9) |
| びらん性胃炎 | 0 | 0 | 2 (0.5) | 0 |
| 胃十二指腸出血 | 0 | 0 | 1 (0.2) | 0 |
| 胃十二指腸潰瘍 | 0 | 0 | 0 | 1 (0.2) |
| 胃食道逆流性疾患 | 2 (0.5) | 3 (0.7) | 3 (0.7) | 4 (0.9) |
| 舌炎 | 1 (0.2) | 0 | 0 | 0 |
| 血便排泄 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 痔核 | 0 | 2 (0.5) | 1 (0.2) | 0 |
| 裂孔ヘルニア | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 腸閉塞 | 0 | 0 | 1 (0.2) | 0 |
| 腸管ポリープ | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 過敏性腸症候群 | 1 (0.2) | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| 大腸ポリープ | 0 | 0 | 1 (0.2) | 0 |
| 口腔内白斑症 | 0 | 1 (0.2) | 0 | 0 |
| 口唇潰瘍 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 口腔嚢胞 | 0 | 0 | 0 | 1 (0.2) |
| 口腔内潰瘍形成 | 3 (0.7) | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 悪心 | 8 (1.9) | 10 (2.3) | 9 (2.1) | 13 (3.1) |
| 食道痙攣 | 0 | 0 | 0 | 1 (0.2) |
| 食道潰瘍 | 0 | 0 | 0 | 1 (0.2) |
| 口腔挫傷 | 0 | 0 | 1 (0.2) | 0 |
| 口腔障害 | 0 | 0 | 0 | 1 (0.2) |
| 口腔粘膜水疱形成 | 0 | 0 | 0 | 1 (0.2) |
| 膵臓障害 | 0 | 0 | 0 | 1 (0.2) |
| 膵炎 | 0 | 0 | 1 (0.2) | 0 |
| 歯周の炎症 | 0 | 0 | 1 (0.2) | 0 |
| 直腸出血 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 吐き戻し | 0 | 0 | 0 | 1 (0.2) |
| 口内炎 | 0 | 1 (0.2) | 0 | 3 (0.7) |
| 舌障害 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| 舌潰瘍 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 歯の障害 | 0 | 0 | 1 (0.2) | 0 |
| 歯の脱落 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 歯痛 | 0 | 0 | 3 (0.7) | 1 (0.2) |
| 嘔吐 | 5 (1.2) | 7 (1.6) | 8 (1.9) | 4 (0.9) |
| 一般・全身障害および投与部位の状態 | 21 (5.0) | 35 (8.2) | 25 (5.8) | 35 (8.3) |
| 医薬品副作用 | 0 | 1 (0.2) | 0 | 0 |
| 無力症 | 2 (0.5) | 0 | 3 (0.7) | 1 (0.2) |
| 胸痛 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 悪寒 | 1 (0.2) | 0 | 2 (0.5) | 0 |
| 不快感 | 0 | 0 | 1 (0.2) | 0 |
| 薬物不耐性 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 顔面痛 | 0 | 0 | 0 | 1 (0.2) |
| 疲労 | 6 (1.4) | 7 (1.6) | 5 (1.2) | 4 (0.9) |
| 歩行障害 | 0 | 0 | 0 | 1 (0.2) |
| 高熱 | 0 | 0 | 1 (0.2) | 0 |
| 低体温 | 0 | 0 | 0 | 1 (0.2) |
| インフルエンザ様疾患 | 4 (0.9) | 1 (0.2) | 2 (0.5) | 4 (0.9) |

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|---|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | | |
| 注射部位湿疹 | 0 | 1 (0.2) | 0 | 0 |
| 注射部位紅斑 | 0 | 4 (0.9) | 0 | 0 |
| 注射部位血腫 | 1 (0.2) | 0 | 0 | 0 |
| 注射部位過敏反応 | 0 | 1 (0.2) | 0 | 0 |
| 注射部位硬結 | 0 | 1 (0.2) | 0 | 0 |
| 注射部位疼痛 | 1 (0.2) | 4 (0.9) | 0 | 1 (0.2) |
| 注射部位そう痒感 | 0 | 2 (0.5) | 0 | 0 |
| 注射部位反応 | 0 | 12 (2.8) | 0 | 2 (0.5) |
| 注射部位蕁麻疹 | 0 | 2 (0.5) | 0 | 0 |
| 倦怠感 | 0 | 1 (0.2) | 3 (0.7) | 0 |
| 非心臓性胸痛 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 浮腫 | 0 | 0 | 1 (0.2) | 0 |
| 末梢性浮腫 | 2 (0.5) | 3 (0.7) | 1 (0.2) | 4 (0.9) |
| 疼痛 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 末梢腫脹 | 0 | 2 (0.5) | 4 (0.9) | 0 |
| 発熱 | 5 (1.2) | 2 (0.5) | 3 (0.7) | 12 (2.8) |
| 腫脹 | 0 | 0 | 0 | 1 (0.2) |
| 口渇 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | | |
| ワクチン接種部位そう痒感 | 0 | 1 (0.2) | 0 | 0 |
| 血管穿刺部位血腫 | 1 (0.2) | 0 | 0 | 0 |
| 肝胆道系障害 | 5 (1.2) | 18 (4.2) | 13 (3.0) | 14 (3.3) |
| 胆管結石 | 0 | 0 | 0 | 1 (0.2) |
| 胆道仙痛 | 1 (0.2) | 0 | 0 | 0 |
| 胆石症 | 2 (0.5) | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| 薬物性肝障害 | 0 | 2 (0.5) | 0 | 0 |
| 肝嚢胞 | 0 | 1 (0.2) | 0 | 0 |
| 肝線維症 | 0 | 1 (0.2) | 0 | 0 |
| 肝機能異常 | 0 | 3 (0.7) | 4 (0.9) | 4 (0.9) |
| 脂肪肝 | 0 | 5 (1.2) | 2 (0.5) | 4 (0.9) |
| 肝毒性 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 高ビリルビン血症 | 0 | 0 | 2 (0.5) | 1 (0.2) |
| 高トランスアミナーゼ血症 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 肝障害 | 0 | 2 (0.5) | 0 | 2 (0.5) |
| 非アルコール性脂肪性肝炎 | 1 (0.2) | 0 | 0 | 0 |
| 非アルコール性脂肪性肝疾患 | 1 (0.2) | 0 | 0 | 0 |
| 門脈血栓症 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 肝胆道系障害 (Cont.) | | | | |
| 脂肪性肝炎 | 0 | 0 | 2 (0.5) | 0 |
| 免疫系障害 | 4 (0.9) | 4 (0.9) | 3 (0.7) | 3 (0.7) |
| 節足動物咬傷アレルギー | 0 | 0 | 0 | 1 (0.2) |
| 節足動物刺傷アレルギー | 1 (0.2) | 0 | 0 | 0 |
| 薬物過敏症 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 食物アレルギー | 0 | 0 | 0 | 1 (0.2) |
| 過敏症 | 0 | 2 (0.5) | 0 | 1 (0.2) |
| 季節性アレルギー | 2 (0.5) | 2 (0.5) | 2 (0.5) | 0 |
| 感染症および寄生虫症 | 138 (32.6) | 146 (34.0) | 167 (38.9) | 182 (43.0) |
| 腹部膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| 膿瘍 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 口腔膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| 急性副鼻腔炎 | 0 | 0 | 1 (0.2) | 0 |
| 歯槽骨炎 | 0 | 1 (0.2) | 0 | 0 |
| 肛門膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| 虫垂炎 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 異型肺炎 | 0 | 0 | 0 | 2 (0.5) |
| 菌血症 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 細菌感染 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 細菌性前立腺炎 | 1 (0.2) | 0 | 0 | 0 |
| 細菌性膣症 | 0 | 1 (0.2) | 0 | 0 |
| 細菌尿 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 体部白癬 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 骨膿瘍 | 0 | 1 (0.2) | 0 | 0 |
| 乳房蜂巣炎 | 1 (0.2) | 0 | 0 | 0 |
| 気管支炎 | 9 (2.1) | 9 (2.1) | 14 (3.3) | 19 (4.5) |
| 細菌性気管支炎 | 0 | 0 | 0 | 1 (0.2) |
| ウイルス性気管支炎 | 1 (0.2) | 0 | 0 | 0 |
| カンジダ性尿道炎 | 0 | 0 | 1 (0.2) | 0 |
| 蜂巣炎 | 0 | 2 (0.5) | 3 (0.7) | 1 (0.2) |
| 慢性副鼻腔炎 | 0 | 2 (0.5) | 0 | 0 |
| 結膜炎 | 2 (0.5) | 2 (0.5) | 2 (0.5) | 1 (0.2) |
| ウイルス性結膜炎 | 1 (0.2) | 0 | 0 | 0 |
| 膀胱炎 | 6 (1.4) | 5 (1.2) | 4 (0.9) | 5 (1.2) |
| サイトメガロウイルス感染 | 0 | 0 | 0 | 1 (0.2) |
| 毛嚢虫症 | 0 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| デング熱 | 1 (0.2) | 0 | 0 | 0 |
| 憩室炎 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 耳感染 | 0 | 2 (0.5) | 2 (0.5) | 1 (0.2) |
| エンテロウイルス感染 | 0 | 1 (0.2) | 0 | 0 |
| 丹毒 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 紅色陰癬 | 0 | 1 (0.2) | 0 | 0 |
| 大腸菌性尿路感染 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 毛包炎 | 1 (0.2) | 1 (0.2) | 8 (1.9) | 3 (0.7) |
| 皮膚真菌感染 | 1 (0.2) | 3 (0.7) | 3 (0.7) | 4 (0.9) |
| せつ | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 胃腸炎 | 5 (1.2) | 7 (1.6) | 5 (1.2) | 13 (3.1) |
| ウイルス性胃腸炎 | 3 (0.7) | 3 (0.7) | 0 | 6 (1.4) |
| 消化管感染 | 2 (0.5) | 0 | 1 (0.2) | 0 |
| ウイルス性消化管感染 | 0 | 0 | 0 | 1 (0.2) |
| 陰部ヘルペス | 0 | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 歯肉炎 | 0 | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 鼡径部膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| 手足口病 | 0 | 0 | 1 (0.2) | 0 |

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TABLE 14.3__1.2.1

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| ヘリコバクター感染 | 0 | 1 (0.2) | 0 | 0 |
| B型肝炎再活性化 | 0 | 0 | 1 (0.2) | 0 |
| C型肝炎 | 1 (0.2) | 0 | 0 | 0 |
| E型肝炎 | 0 | 1 (0.2) | 0 | 0 |
| 単純ヘルペス | 2 (0.5) | 1 (0.2) | 1 (0.2) | 8 (1.9) |
| ヘルペスウイルス感染 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 帯状疱疹 | 3 (0.7) | 0 | 4 (0.9) | 5 (1.2) |
| 麦粒腫 | 0 | 0 | 3 (0.7) | 0 |
| 膿痂疹 | 0 | 0 | 0 | 1 (0.2) |
| インフルエンザ | 5 (1.2) | 2 (0.5) | 11 (2.6) | 6 (1.4) |
| 喉頭炎 | 3 (0.7) | 0 | 3 (0.7) | 1 (0.2) |
| 限局性感染 | 0 | 0 | 0 | 1 (0.2) |
| 下気道感染 | 3 (0.7) | 2 (0.5) | 4 (0.9) | 2 (0.5) |
| 肺感染 | 0 | 0 | 0 | 1 (0.2) |
| ライム病 | 0 | 1 (0.2) | 0 | 0 |
| 爪床感染 | 0 | 0 | 0 | 2 (0.5) |
| 爪感染 | 1 (0.2) | 0 | 0 | 0 |
| 鼻ヘルペス | 0 | 1 (0.2) | 0 | 2 (0.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 上咽頭炎 | 21 (5.0) | 29 (6.8) | 21 (4.9) | 26 (6.1) |
| 爪真菌症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 口腔カンジダ症 | 0 | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 口腔ヘルペス | 4 (0.9) | 6 (1.4) | 7 (1.6) | 19 (4.5) |
| 口腔感染 | 1 (0.2) | 0 | 0 | 0 |
| 精巣炎 | 0 | 1 (0.2) | 0 | 0 |
| 骨髄炎 | 0 | 1 (0.2) | 0 | 0 |
| 外耳炎 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 急性中耳炎 | 0 | 2 (0.5) | 0 | 2 (0.5) |
| 爪囲炎 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 2 (0.5) |
| 軟骨膜炎 | 0 | 0 | 0 | 1 (0.2) |
| 歯周炎 | 1 (0.2) | 0 | 1 (0.2) | 2 (0.5) |
| 扁桃周囲膿瘍 | 1 (0.2) | 0 | 0 | 0 |
| 咽頭炎 | 4 (0.9) | 3 (0.7) | 4 (0.9) | 6 (1.4) |
| レンサ球菌性咽頭炎 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 咽頭扁桃炎 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 0 | 0 | 0 | 1 (0.2) |
| 肺炎 | 2 (0.5) | 4 (0.9) | 3 (0.7) | 4 (0.9) |

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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 歯髄炎 | 0 | 0 | 2 (0.5) | 0 |
| 化膿性分泌物 | 0 | 0 | 0 | 1 (0.2) |
| 急性腎盂腎炎 | 0 | 0 | 0 | 1 (0.2) |
| 膿疱性皮疹 | 0 | 0 | 0 | 2 (0.5) |
| 気道感染 | 2 (0.5) | 4 (0.9) | 9 (2.1) | 8 (1.9) |
| ウイルス性気道感染 | 3 (0.7) | 4 (0.9) | 4 (0.9) | 4 (0.9) |
| 鼻炎 | 7 (1.7) | 1 (0.2) | 2 (0.5) | 5 (1.2) |
| サルモネラ症 | 0 | 1 (0.2) | 0 | 0 |
| 敗血症 | 0 | 0 | 2 (0.5) | 0 |
| 副鼻腔炎 | 6 (1.4) | 5 (1.2) | 7 (1.6) | 7 (1.7) |
| 皮膚細菌感染 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 皮膚感染 | 0 | 2 (0.5) | 1 (0.2) | 0 |
| 軟部組織感染 | 0 | 2 (0.5) | 0 | 0 |
| ブドウ球菌感染 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| ブドウ球菌皮膚感染 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 皮下組織膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| 股部白癬 | 0 | 1 (0.2) | 0 | 0 |
| 白癬感染 | 0 | 1 (0.2) | 1 (0.2) | 0 |

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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 足部白癬 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 癜風 | 0 | 0 | 2 (0.5) | 0 |
| 扁桃炎 | 0 | 5 (1.2) | 3 (0.7) | 3 (0.7) |
| 細菌性扁桃炎 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 歯膿瘍 | 0 | 0 | 2 (0.5) | 0 |
| 歯感染 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 気管炎 | 1 (0.2) | 0 | 0 | 3 (0.7) |
| 気管気管支炎 | 2 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| トリコモナス症 | 0 | 1 (0.2) | 0 | 0 |
| 上気道感染 | 34 (8.0) | 30 (7.0) | 44 (10.3) | 39 (9.2) |
| 尿路感染 | 10 (2.4) | 14 (3.3) | 18 (4.2) | 15 (3.5) |
| 尿路性敗血症 | 0 | 0 | 0 | 1 (0.2) |
| 腟感染 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| ウイルス感染 | 5 (1.2) | 2 (0.5) | 4 (0.9) | 5 (1.2) |
| ウイルス性咽頭炎 | 0 | 0 | 0 | 1 (0.2) |
| ウイルス性気管炎 | 0 | 0 | 1 (0.2) | 0 |
| ウイルス性上気道感染 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 2 (0.5) |
| 外陰部炎 | 0 | 0 | 1 (0.2) | 0 |

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TABLE 14.3__1.2.1

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 外陰部腟カンジダ症 | 0 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 外陰腟真菌感染 | 0 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 創傷感染 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 傷害、中毒および処置合併症 | 17 (4.0) | 17 (4.0) | 24 (5.6) | 20 (4.7) |
| 偶発的過量投与 | 0 | 1 (0.2) | 0 | 0 |
| 動物咬傷 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 足関節部骨折 | 0 | 0 | 0 | 1 (0.2) |
| 節足動物咬傷 | 1 (0.2) | 2 (0.5) | 1 (0.2) | 2 (0.5) |
| 節足動物刺傷 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 第1度熱傷 | 0 | 0 | 0 | 1 (0.2) |
| 第2度熱傷 | 1 (0.2) | 0 | 0 | 0 |
| 粉砕骨折 | 0 | 0 | 0 | 1 (0.2) |
| 挫傷 | 1 (0.2) | 3 (0.7) | 1 (0.2) | 2 (0.5) |
| 上顎炎 | 0 | 1 (0.2) | 0 | 0 |
| 眼挫傷 | 1 (0.2) | 0 | 0 | 0 |
| 転倒 | 2 (0.5) | 2 (0.5) | 3 (0.7) | 1 (0.2) |
| 腓骨骨折 | 0 | 0 | 1 (0.2) | 0 |
| 仙骨骨折 | 0 | 0 | 0 | 1 (0.2) |

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TABLE 14.3__1.2.1

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|---|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | | |
| 手骨折 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 頭部損傷 | 1 (0.2) | 0 | 0 | 0 |
| 上腕骨骨折 | 0 | 0 | 0 | 1 (0.2) |
| 腸脛靭帯症候群 | 0 | 1 (0.2) | 0 | 0 |
| 注射に伴う反応 | 0 | 1 (0.2) | 0 | 0 |
| 関節脱臼 | 0 | 0 | 1 (0.2) | 0 |
| 関節損傷 | 0 | 0 | 1 (0.2) | 0 |
| 靭帯捻挫 | 3 (0.7) | 0 | 0 | 2 (0.5) |
| 四肢損傷 | 0 | 1 (0.2) | 3 (0.7) | 0 |
| 半月板損傷 | 1 (0.2) | 0 | 0 | 0 |
| 椎弓切除後症候群 | 0 | 0 | 0 | 1 (0.2) |
| 処置後出血 | 0 | 0 | 0 | 1 (0.2) |
| 処置後炎症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 外傷後疼痛 | 1 (0.2) | 0 | 0 | 0 |
| 肋骨骨折 | 0 | 0 | 0 | 2 (0.5) |
| 交通事故 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 皮膚擦過傷 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |
| 皮膚裂傷 | 2 (0.5) | 0 | 3 (0.7) | 1 (0.2) |

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TABLE 14.3__1.2.1

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|---|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | | |
| ストレス骨折 | 0 | 1 (0.2) | 0 | 0 |
| 腱断裂 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 熱傷 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 歯牙破折 | 0 | 1 (0.2) | 5 (1.2) | 0 |
| 各種物質毒性 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 上肢骨折 | 1 (0.2) | 0 | 0 | 0 |
| 創傷 | 0 | 0 | 0 | 1 (0.2) |
| 臨床検査 | 36 (8.5) | 80 (18.6) | 72 (16.8) | 90 (21.3) |
| アラニンアミノトランスフェラーゼ増加 | 12 (2.8) | 32 (7.5) | 19 (4.4) | 27 (6.4) |
| アルドラーゼ増加 | 0 | 0 | 0 | 1 (0.2) |
| αヒドロキシ酪酸脱水素酵素増加 | 0 | 0 | 0 | 1 (0.2) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 8 (1.9) | 22 (5.1) | 14 (3.3) | 15 (3.5) |
| 血中アルカリホスファターゼ増加 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 血中重炭酸塩減少 | 1 (0.2) | 0 | 0 | 0 |
| 血中ビリルビン増加 | 1 (0.2) | 3 (0.7) | 1 (0.2) | 0 |
| 血中コレステロール減少 | 1 (0.2) | 0 | 0 | 0 |
| 血中コレステロール増加 | 0 | 0 | 4 (0.9) | 2 (0.5) |
| 血中クレアチンホスホキナーゼ増加 | 6 (1.4) | 24 (5.6) | 38 (8.9) | 41 (9.7) |

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TABLE 14.3__1.2.1

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- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| 血中クレアチニン増加 | 1 (0.2) | 3 (0.7) | 2 (0.5) | 4 (0.9) |
| 血中ブドウ糖増加 | 2 (0.5) | 2 (0.5) | 3 (0.7) | 1 (0.2) |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 0 | 1 (0.2) |
| 血中リン減少 | 0 | 0 | 0 | 1 (0.2) |
| 血中カリウム増加 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 血圧上昇 | 4 (0.9) | 3 (0.7) | 5 (1.2) | 3 (0.7) |
| 血中トリグリセリド増加 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 血中尿素増加 | 0 | 0 | 0 | 3 (0.7) |
| 血中尿酸増加 | 0 | 0 | 0 | 3 (0.7) |
| γ-グルタミルトランスフェラーゼ増加 | 0 | 0 | 0 | 1 (0.2) |
| ヘモグロビン減少 | 1 (0.2) | 0 | 0 | 5 (1.2) |
| 肝酵素上昇 | 3 (0.7) | 7 (1.6) | 2 (0.5) | 4 (0.9) |
| 高比重リポ蛋白減少 | 1 (0.2) | 0 | 0 | 0 |
| 高比重リポ蛋白増加 | 0 | 1 (0.2) | 2 (0.5) | 0 |
| 未熟顆粒球数増加 | 0 | 0 | 1 (0.2) | 0 |
| 肝機能検査値上昇 | 0 | 1 (0.2) | 5 (1.2) | 1 (0.2) |
| 低比重リポ蛋白増加 | 0 | 0 | 2 (0.5) | 1 (0.2) |
| リンパ球数減少 | 0 | 0 | 1 (0.2) | 2 (0.5) |

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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| 平均赤血球容積増加 | 0 | 1 (0.2) | 0 | 4 (0.9) |
| 筋酵素上昇 | 0 | 0 | 1 (0.2) | 0 |
| 骨髄球存在 | 0 | 0 | 0 | 1 (0.2) |
| 好中球数減少 | 0 | 3 (0.7) | 0 | 4 (0.9) |
| 好中球数増加 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 好中球百分率増加 | 0 | 1 (0.2) | 0 | 0 |
| 血小板数増加 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 前立腺特異性抗原異常 | 0 | 0 | 1 (0.2) | 0 |
| 尿中蛋白陽性 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 0 |
| 赤血球数減少 | 0 | 1 (0.2) | 0 | 3 (0.7) |
| 血沈亢進 | 2 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| 尿中赤血球 | 1 (0.2) | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 10 (2.3) | 2 (0.5) | 7 (1.7) |
| 超音波スキャン異常 | 0 | 1 (0.2) | 0 | 0 |
| 尿中白血球エステラーゼ陽性 | 0 | 1 (0.2) | 0 | 0 |
| 超低比重リポ蛋白増加 | 0 | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| ビタミンB12減少 | 0 | 1 (0.2) | 0 | 0 |
| 体重減少 | 1 (0.2) | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| 体重増加 | 0 | 3 (0.7) | 0 | 3 (0.7) |
| 白血球数減少 | 0 | 2 (0.5) | 0 | 6 (1.4) |
| 白血球数増加 | 1 (0.2) | 0 | 0 | 0 |
| 尿中白血球陽性 | 0 | 1 (0.2) | 0 | 0 |
| 代謝および栄養障害 | 20 (4.7) | 27 (6.3) | 25 (5.8) | 36 (8.5) |
| 炭水化物不耐症 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 糖尿病 | 1 (0.2) | 5 (1.2) | 3 (0.7) | 1 (0.2) |
| コントロール不良の糖尿病 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 脂質異常症 | 2 (0.5) | 2 (0.5) | 3 (0.7) | 7 (1.7) |
| 体液貯留 | 0 | 1 (0.2) | 0 | 0 |
| 耐糖能障害 | 0 | 2 (0.5) | 1 (0.2) | 0 |
| 痛風 | 0 | 1 (0.2) | 0 | 0 |
| 高カルシウム血症 | 0 | 0 | 0 | 1 (0.2) |
| 高コレステロール血症 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 10 (2.4) |
| 高血糖 | 6 (1.4) | 7 (1.6) | 3 (0.7) | 3 (0.7) |
| 高カリウム血症 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 高脂血症 | 3 (0.7) | 1 (0.2) | 1 (0.2) | 3 (0.7) |
| 高トリグリセリド血症 | 3 (0.7) | 5 (1.2) | 1 (0.2) | 2 (0.5) |

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TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
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| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 代謝および栄養障害 (Cont.) | | | | |
| 高尿酸血症 | 1 (0.2) | 3 (0.7) | 3 (0.7) | 5 (1.2) |
| 低カルシウム血症 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 低血糖 | 0 | 1 (0.2) | 0 | 0 |
| 低カリウム血症 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 低リン酸血症 | 0 | 0 | 1 (0.2) | 0 |
| 空腹時血中ブドウ糖不良 | 1 (0.2) | 0 | 0 | 0 |
| 食欲亢進 | 0 | 0 | 1 (0.2) | 0 |
| インスリン抵抗性 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 鉄欠乏 | 0 | 0 | 1 (0.2) | 0 |
| 肥満 | 0 | 0 | 2 (0.5) | 0 |
| 2型糖尿病 | 0 | 0 | 3 (0.7) | 2 (0.5) |
| ビタミンB群欠乏 | 0 | 0 | 1 (0.2) | 0 |
| ビタミンD欠乏 | 0 | 0 | 2 (0.5) | 2 (0.5) |
| 筋骨格系および結合組織障害 | 49 (11.6) | 36 (8.4) | 35 (8.2) | 37 (8.7) |
| 関節痛 | 2 (0.5) | 2 (0.5) | 3 (0.7) | 3 (0.7) |
| 背部痛 | 7 (1.7) | 8 (1.9) | 6 (1.4) | 9 (2.1) |
| 滑液包炎 | 0 | 0 | 2 (0.5) | 0 |
| 軟骨疾患 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | | |
| 肋軟骨炎 | 0 | 1 (0.2) | 0 | 0 |
| デュプイトラン拘縮 | 1 (0.2) | 0 | 0 | 0 |
| 椎間関節症候群 | 1 (0.2) | 0 | 0 | 0 |
| 線維筋痛 | 0 | 1 (0.2) | 0 | 0 |
| 側腹部痛 | 0 | 0 | 0 | 1 (0.2) |
| 足変形 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 高クレアチン血症 | 0 | 0 | 0 | 1 (0.2) |
| 椎間板圧迫 | 1 (0.2) | 0 | 0 | 0 |
| 椎間板変性症 | 0 | 0 | 0 | 1 (0.2) |
| 椎間板障害 | 1 (0.2) | 1 (0.2) | 0 | 1 (0.2) |
| 椎間板突出 | 1 (0.2) | 3 (0.7) | 1 (0.2) | 1 (0.2) |
| 関節雑音 | 0 | 0 | 0 | 1 (0.2) |
| 関節硬直 | 0 | 0 | 1 (0.2) | 0 |
| 関節腫脹 | 0 | 1 (0.2) | 0 | 0 |
| 腰部脊柱管狭窄症 | 0 | 1 (0.2) | 0 | 0 |
| 咀嚼障害 | 0 | 1 (0.2) | 0 | 0 |
| 中足骨痛 | 1 (0.2) | 0 | 0 | 0 |
| 筋肉疲労 | 0 | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | | |
| 筋痙縮 | 4 (0.9) | 3 (0.7) | 5 (1.2) | 2 (0.5) |
| 筋力低下 | 0 | 0 | 0 | 1 (0.2) |
| 筋骨格系胸痛 | 0 | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| 筋骨格痛 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |
| 筋骨格硬直 | 0 | 0 | 0 | 1 (0.2) |
| 筋肉痛 | 2 (0.5) | 2 (0.5) | 2 (0.5) | 0 |
| 頚部痛 | 1 (0.2) | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| 変形性関節症 | 2 (0.5) | 2 (0.5) | 0 | 4 (0.9) |
| 骨端症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 骨粗鬆症 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 四肢痛 | 4 (0.9) | 0 | 3 (0.7) | 2 (0.5) |
| 関節周囲炎 | 1 (0.2) | 0 | 0 | 0 |
| 骨膜炎 | 1 (0.2) | 0 | 0 | 0 |
| 足底筋膜炎 | 3 (0.7) | 2 (0.5) | 0 | 1 (0.2) |
| 乾癬性関節症 | 13 (3.1) | 5 (1.2) | 6 (1.4) | 7 (1.7) |
| 肩回旋筋腱板症候群 | 0 | 1 (0.2) | 0 | 0 |
| 仙腸骨炎 | 1 (0.2) | 0 | 0 | 0 |
| 軟部組織腫脹 | 0 | 0 | 1 (0.2) | 0 |

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TABLE 14.3__1.2.1

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|---|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | | |
| 変形性脊椎症 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 脊椎痛 | 1 (0.2) | 0 | 2 (0.5) | 0 |
| 脊柱管狭窄症 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |
| 脊椎すべり症 | 0 | 1 (0.2) | 0 | 0 |
| 滑液嚢腫 | 0 | 0 | 1 (0.2) | 0 |
| 腱痛 | 1 (0.2) | 0 | 0 | 0 |
| 腱鞘炎 | 0 | 0 | 1 (0.2) | 0 |
| 翼状肩甲骨 | 0 | 1 (0.2) | 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） | 5 (1.2) | 5 (1.2) | 5 (1.2) | 6 (1.4) |
| 肛門性器疣贅 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 基底細胞癌 | 1 (0.2) | 0 | 0 | 2 (0.5) |
| 乳腺線維腫 | 0 | 0 | 1 (0.2) | 0 |
| 大腸腺腫 | 0 | 0 | 0 | 1 (0.2) |
| 遠隔転移を伴う結腸癌 | 0 | 1 (0.2) | 0 | 0 |
| 肝臓血管腫 | 0 | 1 (0.2) | 0 | 0 |
| 脂肪腫 | 0 | 0 | 1 (0.2) | 0 |
| 乳房脂肪腫 | 0 | 0 | 1 (0.2) | 0 |
| 肺腺癌 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 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） (Cont.) | | | | |
| メラノサイト性母斑 | 1 (0.2) | 0 | 0 | 0 |
| 神経内分泌癌 | 0 | 0 | 1 (0.2) | 0 |
| 卵巣癌 | 0 | 1 (0.2) | 0 | 0 |
| 化膿性肉芽腫 | 1 (0.2) | 0 | 0 | 0 |
| 脂漏性角化症 | 2 (0.5) | 1 (0.2) | 0 | 0 |
| 皮膚乳頭腫 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 子宮癌 | 0 | 1 (0.2) | 0 | 0 |
| 神経系障害 | 27 (6.4) | 37 (8.6) | 34 (7.9) | 34 (8.0) |
| 筋萎縮性側索硬化症 | 0 | 1 (0.2) | 0 | 0 |
| 灼熱感 | 0 | 1 (0.2) | 0 | 0 |
| 手根管症候群 | 2 (0.5) | 1 (0.2) | 0 | 2 (0.5) |
| 脳血管発作 | 0 | 1 (0.2) | 0 | 0 |
| 頚髄神経根障害 | 0 | 0 | 1 (0.2) | 0 |
| 頚腕症候群 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 認知障害 | 0 | 0 | 1 (0.2) | 0 |
| 頚頭蓋症候群 | 0 | 1 (0.2) | 0 | 0 |
| 脱髄 | 0 | 0 | 0 | 1 (0.2) |
| 注意力障害 | 1 (0.2) | 0 | 0 | 0 |

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|---|---|---|---|---|
| 神経系障害 (Cont.) | | | | |
| 浮動性めまい | 4 (0.9) | 5 (1.2) | 2 (0.5) | 5 (1.2) |
| 味覚異常 | 0 | 0 | 1 (0.2) | 0 |
| 顔面麻痺 | 0 | 1 (0.2) | 0 | 0 |
| 頭痛 | 10 (2.4) | 18 (4.2) | 17 (4.0) | 17 (4.0) |
| 肝性脳症 | 0 | 1 (0.2) | 0 | 0 |
| 感覚鈍麻 | 2 (0.5) | 0 | 2 (0.5) | 1 (0.2) |
| 味覚減退 | 0 | 1 (0.2) | 0 | 0 |
| 肋間神経痛 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 虚血性ニューロパチー | 0 | 0 | 0 | 1 (0.2) |
| 嗜眠 | 0 | 0 | 1 (0.2) | 0 |
| 意識消失 | 1 (0.2) | 0 | 0 | 0 |
| 腰髄神経根障害 | 0 | 0 | 1 (0.2) | 0 |
| 記憶障害 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 片頭痛 | 2 (0.5) | 2 (0.5) | 1 (0.2) | 2 (0.5) |
| 神経圧迫 | 1 (0.2) | 0 | 0 | 0 |
| 神経痛 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 末梢性ニューロパチー | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 錯感覚 | 1 (0.2) | 0 | 1 (0.2) | 3 (0.7) |

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TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 神経系障害 (Cont.) | | | | |
| 神経周囲嚢胞 | 0 | 1 (0.2) | 0 | 0 |
| 末梢性感覚ニューロパチー | 0 | 0 | 0 | 1 (0.2) |
| 睡眠の質低下 | 0 | 2 (0.5) | 0 | 0 |
| ヘルペス後神経痛 | 1 (0.2) | 0 | 0 | 0 |
| 神経根障害 | 0 | 1 (0.2) | 0 | 0 |
| 坐骨神経痛 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 0 |
| 感覚障害 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 1 (0.2) | 0 |
| 傾眠 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 失神 | 0 | 1 (0.2) | 0 | 0 |
| 緊張性頭痛 | 0 | 0 | 1 (0.2) | 0 |
| 胸髄神経根障害 | 1 (0.2) | 0 | 0 | 0 |
| 一過性脳虚血発作 | 0 | 1 (0.2) | 0 | 0 |
| 三叉神経痛 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 製品の問題 | 0 | 0 | 1 (0.2) | 0 |
| 医療機器破損 | 0 | 0 | 1 (0.2) | 0 |
| 精神障害 | 3 (0.7) | 8 (1.9) | 15 (3.5) | 9 (2.1) |
| 不安 | 0 | 4 (0.9) | 1 (0.2) | 2 (0.5) |

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|---|---|---|---|---|
| 精神障害 (Cont.) | | | | |
| 不安障害 | 0 | 0 | 2 (0.5) | 0 |
| 燃え尽き症候群 | 0 | 0 | 1 (0.2) | 0 |
| 抑うつ気分 | 0 | 1 (0.2) | 0 | 0 |
| うつ病 | 0 | 1 (0.2) | 1 (0.2) | 3 (0.7) |
| 不眠症 | 2 (0.5) | 2 (0.5) | 10 (2.3) | 4 (0.9) |
| 気分動揺 | 1 (0.2) | 0 | 0 | 0 |
| 睡眠障害 | 0 | 0 | 1 (0.2) | 0 |
| ストレス | 0 | 0 | 1 (0.2) | 0 |
| 腎および尿路障害 | 4 (0.9) | 10 (2.3) | 15 (3.5) | 8 (1.9) |
| 急性腎障害 | 1 (0.2) | 0 | 0 | 0 |
| 膀胱脱 | 0 | 0 | 1 (0.2) | 0 |
| 尿路結石 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 慢性腎臓病 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 結晶尿 | 0 | 0 | 0 | 1 (0.2) |
| 排尿困難 | 0 | 0 | 1 (0.2) | 0 |
| 糖尿 | 0 | 1 (0.2) | 0 | 0 |
| 血尿 | 2 (0.5) | 1 (0.2) | 5 (1.2) | 4 (0.9) |
| 緊張性膀胱 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 腎および尿路障害 (Cont.) | | | | |
| 白血球尿 | 0 | 0 | 2 (0.5) | 1 (0.2) |
| 腎結石症 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 腎症 | 0 | 0 | 1 (0.2) | 0 |
| 頻尿 | 0 | 0 | 0 | 1 (0.2) |
| 蛋白尿 | 2 (0.5) | 3 (0.7) | 2 (0.5) | 2 (0.5) |
| 腎嚢胞 | 0 | 0 | 1 (0.2) | 0 |
| 腎不全 | 1 (0.2) | 0 | 0 | 0 |
| 無菌性膿尿 | 0 | 1 (0.2) | 0 | 0 |
| 尿管結石症 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 尿失禁 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 尿閉 | 0 | 0 | 1 (0.2) | 0 |
| 尿路の炎症 | 0 | 1 (0.2) | 0 | 0 |
| 生殖系および乳房障害 | 6 (1.4) | 6 (1.4) | 16 (3.7) | 8 (1.9) |
| 腺筋症 | 0 | 0 | 0 | 1 (0.2) |
| 無月経 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 良性前立腺肥大症 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 乳房障害 | 0 | 0 | 1 (0.2) | 0 |
| 乳房形成異常 | 1 (0.2) | 0 | 0 | 0 |

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|---|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | | |
| 乳房線維化 | 0 | 0 | 1 (0.2) | 0 |
| 前立腺結石 | 0 | 0 | 1 (0.2) | 0 |
| 子宮頚管ポリープ | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 月経困難症 | 0 | 1 (0.2) | 0 | 0 |
| 子宮頚外反 | 0 | 0 | 0 | 1 (0.2) |
| 子宮内膜増殖症 | 0 | 0 | 1 (0.2) | 0 |
| 子宮内膜症 | 0 | 1 (0.2) | 0 | 0 |
| 勃起不全 | 0 | 0 | 0 | 1 (0.2) |
| 線維嚢胞性乳腺疾患 | 0 | 0 | 0 | 1 (0.2) |
| 月経過多 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 不規則月経 | 0 | 0 | 4 (0.9) | 0 |
| 不正子宮出血 | 2 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| 卵巣嚢胞 | 0 | 0 | 1 (0.2) | 0 |
| 骨盤痛 | 1 (0.2) | 0 | 0 | 0 |
| ペイロニー病 | 1 (0.2) | 0 | 0 | 0 |
| 前立腺閉塞 | 0 | 0 | 1 (0.2) | 0 |
| 前立腺炎 | 0 | 0 | 1 (0.2) | 0 |
| 精巣障害 | 0 | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | | |
| 精巣腫脹 | 0 | 1 (0.2) | 0 | 0 |
| 子宮出血 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 子宮ポリープ | 0 | 0 | 1 (0.2) | 0 |
| 子宮脱 | 0 | 0 | 1 (0.2) | 0 |
| 膣出血 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 呼吸器、胸郭および縦隔障害 | 19 (4.5) | 31 (7.2) | 30 (7.0) | 34 (8.0) |
| 喘息 | 0 | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| 無気肺 | 0 | 0 | 0 | 1 (0.2) |
| 気管支痙攣 | 0 | 0 | 1 (0.2) | 0 |
| カタル | 0 | 1 (0.2) | 0 | 0 |
| 息詰まり | 0 | 1 (0.2) | 0 | 0 |
| 慢性閉塞性肺疾患 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 咳嗽 | 5 (1.2) | 7 (1.6) | 11 (2.6) | 14 (3.3) |
| 発声障害 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 呼吸困難 | 1 (0.2) | 0 | 5 (1.2) | 2 (0.5) |
| 肺気腫 | 1 (0.2) | 0 | 0 | 0 |
| 鼻出血 | 4 (0.9) | 1 (0.2) | 0 | 1 (0.2) |
| 喀血 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | | |
| 肺浸潤 | 0 | 1 (0.2) | 0 | 0 |
| 鼻閉 | 0 | 2 (0.5) | 0 | 2 (0.5) |
| 鼻部不快感 | 0 | 0 | 1 (0.2) | 0 |
| 鼻の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 鼻閉塞 | 0 | 0 | 1 (0.2) | 0 |
| 鼻潰瘍 | 0 | 0 | 0 | 2 (0.5) |
| 閉塞性気道障害 | 1 (0.2) | 0 | 0 | 0 |
| 口腔咽頭不快感 | 0 | 1 (0.2) | 0 | 0 |
| 口腔咽頭痛 | 3 (0.7) | 8 (1.9) | 6 (1.4) | 5 (1.2) |
| 咽頭の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 胸水 | 0 | 1 (0.2) | 0 | 0 |
| 胸膜炎 | 0 | 0 | 1 (0.2) | 0 |
| 肺臓炎 | 0 | 1 (0.2) | 0 | 0 |
| 湿性咳嗽 | 1 (0.2) | 0 | 0 | 0 |
| 肺塞栓症 | 0 | 0 | 0 | 1 (0.2) |
| 肺線維症 | 0 | 0 | 0 | 1 (0.2) |
| 肺水腫 | 1 (0.2) | 0 | 0 | 0 |
| 気道うっ血 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | | |
| アレルギー性鼻炎 | 1 (0.2) | 1 (0.2) | 3 (0.7) | 0 |
| 鼻漏 | 4 (0.9) | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| 副鼻腔うっ血 | 0 | 1 (0.2) | 0 | 0 |
| 睡眠時無呼吸症候群 | 0 | 0 | 1 (0.2) | 0 |
| 喀痰増加 | 0 | 0 | 1 (0.2) | 0 |
| 咽喉刺激感 | 0 | 0 | 0 | 2 (0.5) |
| 扁桃の炎症 | 0 | 1 (0.2) | 0 | 0 |
| 上気道の炎症 | 0 | 1 (0.2) | 2 (0.5) | 0 |
| 皮膚および皮下組織障害 | 28 (6.6) | 43 (10.0) | 28 (6.5) | 41 (9.7) |
| 黒色表皮腫 | 0 | 0 | 1 (0.2) | 0 |
| ざ瘡 | 1 (0.2) | 0 | 5 (1.2) | 6 (1.4) |
| 光線角化症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 脱毛症 | 1 (0.2) | 7 (1.6) | 1 (0.2) | 1 (0.2) |
| 水疱 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 皮膚嚢腫 | 0 | 0 | 2 (0.5) | 1 (0.2) |
| 皮膚炎 | 0 | 3 (0.7) | 1 (0.2) | 2 (0.5) |
| ざ瘡様皮膚炎 | 0 | 0 | 0 | 3 (0.7) |
| アレルギー性皮膚炎 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 1 (0.2) |

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|---|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | | |
| 接触皮膚炎 | 0 | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| 薬疹 | 0 | 1 (0.2) | 0 | 0 |
| 皮膚乾燥 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 湿疹 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 紅斑 | 1 (0.2) | 3 (0.7) | 2 (0.5) | 2 (0.5) |
| 環状紅斑 | 0 | 1 (0.2) | 0 | 0 |
| 毛髪成長異常 | 0 | 0 | 1 (0.2) | 0 |
| 多汗症 | 1 (0.2) | 0 | 2 (0.5) | 1 (0.2) |
| 過角化 | 2 (0.5) | 1 (0.2) | 0 | 0 |
| 嵌入爪 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 0 |
| 間擦疹 | 0 | 0 | 1 (0.2) | 0 |
| 爪郭の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 爪成長異常 | 0 | 0 | 1 (0.2) | 0 |
| 爪破損 | 1 (0.2) | 0 | 0 | 0 |
| 爪甲脱落症 | 0 | 0 | 1 (0.2) | 0 |
| 口囲皮膚炎 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 光線過敏性反応 | 0 | 1 (0.2) | 0 | 0 |
| そう痒症 | 1 (0.2) | 7 (1.6) | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | | |
| 全身性そう痒症 | 0 | 1 (0.2) | 0 | 0 |
| 乾癬 | 7 (1.7) | 9 (2.1) | 3 (0.7) | 4 (0.9) |
| 膿疱性乾癬 | 0 | 0 | 0 | 1 (0.2) |
| 発疹 | 8 (1.9) | 5 (1.2) | 0 | 4 (0.9) |
| 紅斑性皮疹 | 0 | 1 (0.2) | 0 | 2 (0.5) |
| 全身性皮疹 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 斑状皮疹 | 0 | 0 | 0 | 1 (0.2) |
| 斑状丘疹状皮疹 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 丘疹性皮疹 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| そう痒性皮疹 | 0 | 2 (0.5) | 0 | 0 |
| 酒さ | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 脂漏性皮膚炎 | 1 (0.2) | 0 | 0 | 0 |
| 皮膚変色 | 0 | 0 | 1 (0.2) | 0 |
| 皮膚剥脱 | 0 | 1 (0.2) | 0 | 0 |
| 皮膚亀裂 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 皮膚色素過剰 | 0 | 0 | 1 (0.2) | 0 |
| 皮膚色素減少 | 0 | 0 | 0 | 1 (0.2) |
| 皮膚刺激 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | | |
| 皮膚病変 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 顔面腫脹 | 0 | 0 | 1 (0.2) | 0 |
| 蕁麻疹 | 0 | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| 社会環境 | 0 | 0 | 1 (0.2) | 0 |
| 閉経 | 0 | 0 | 1 (0.2) | 0 |
| 血管障害 | 16 (3.8) | 15 (3.5) | 23 (5.4) | 15 (3.5) |
| 大動脈瘤 | 0 | 0 | 0 | 1 (0.2) |
| 深部静脈血栓症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 本態性高血圧症 | 2 (0.5) | 0 | 0 | 0 |
| 血腫 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |
| ほてり | 1 (0.2) | 0 | 3 (0.7) | 1 (0.2) |
| 高血圧 | 10 (2.4) | 8 (1.9) | 16 (3.7) | 12 (2.8) |
| 高血圧クリーゼ | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 高血圧切迫症 | 0 | 0 | 0 | 1 (0.2) |
| 起立性低血圧 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 末梢冷感 | 0 | 1 (0.2) | 0 | 0 |
| 末梢静脈疾患 | 0 | 0 | 1 (0.2) | 0 |
| 血栓性静脈炎 | 0 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Program Source Code: [redacted]

TABLE 14.3__1.2.1

Subjects with Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
- up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 血管障害 (Cont.) | | | | |
| 表在性血栓性静脈炎 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 静脈瘤 | 0 | 0 | 0 | 1 (0.2) |
| 血管炎 | 0 | 1 (0.2) | 0 | 0 |
| 静脈性高血圧 | 0 | 0 | 1 (0.2) | 0 |

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Program Source Code: [redacted]

表 2.　投与 24 週時までの治験薬と関連ありの有害事象を発現した被験者数及び発現割合：MedDRA のプライマリー器官別大分類及び基本語別（安全性解析対象集団）

相互参照：M15-572 試験 CSR W24 Table 14.3__1.6.1

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| Any adverse event | 120 (28.4) | 168 (39.2) | 157 (36.6) | 186 (44.0) |
| 血液およびリンパ系障害 | 10 (2.4) | 11 (2.6) | 18 (4.2) | 34 (8.0) |
| 貧血 | 2 (0.5) | 0 | 2 (0.5) | 6 (1.4) |
| 大球性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 骨髄浮腫 | 0 | 0 | 0 | 1 (0.2) |
| 赤血球減少症 | 0 | 0 | 0 | 1 (0.2) |
| 顆粒球減少症 | 0 | 0 | 0 | 1 (0.2) |
| 内出血発生の増加傾向 | 0 | 0 | 0 | 1 (0.2) |
| 鉄欠乏性貧血 | 0 | 0 | 0 | 1 (0.2) |
| 白血球増加症 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 白血球減少症 | 2 (0.5) | 4 (0.9) | 10 (2.3) | 9 (2.1) |
| リンパ節症 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 0 |
| リンパ組織過形成 | 0 | 0 | 0 | 1 (0.2) |
| リンパ球減少症 | 3 (0.7) | 1 (0.2) | 5 (1.2) | 11 (2.6) |
| 大赤血球症 | 0 | 1 (0.2) | 0 | 0 |
| 好中球減少症 | 1 (0.2) | 6 (1.4) | 4 (0.9) | 15 (3.5) |
| 好中球増加症 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 正色素性貧血 | 0 | 0 | 0 | 1 (0.2) |

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Program Source Code: [redacted]

TABLE 14.3__1.6.1

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(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 血液およびリンパ系障害 (Cont.) | | | | |
| 血小板減少症 | 1 (0.2) | 1 (0.2) | 0 | 1 (0.2) |
| 血小板増加症 | 1 (0.2) | 0 | 0 | 0 |
| 心臓障害 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 心房細動 | 0 | 1 (0.2) | 0 | 0 |
| 動悸 | 0 | 0 | 1 (0.2) | 0 |
| 発作性頻脈 | 0 | 0 | 0 | 1 (0.2) |
| 耳および迷路障害 | 3 (0.7) | 2 (0.5) | 0 | 0 |
| 耳痛 | 3 (0.7) | 0 | 0 | 0 |
| 耳鳴 | 0 | 1 (0.2) | 0 | 0 |
| 回転性めまい | 0 | 1 (0.2) | 0 | 0 |
| 内分泌障害 | 0 | 0 | 1 (0.2) | 0 |
| アンドロゲン欠乏症 | 0 | 0 | 1 (0.2) | 0 |
| 眼障害 | 2 (0.5) | 1 (0.2) | 3 (0.7) | 2 (0.5) |
| 眼瞼痙攣 | 0 | 0 | 1 (0.2) | 0 |
| ドライアイ | 0 | 0 | 0 | 1 (0.2) |
| 眼痛 | 0 | 0 | 1 (0.2) | 0 |
| 虹彩毛様体炎 | 0 | 0 | 0 | 1 (0.2) |
| 瞼板腺炎 | 0 | 1 (0.2) | 1 (0.2) | 0 |

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Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

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|---|---|---|---|---|
| 眼障害 (Cont.) | | | | |
| 眼充血 | 1 (0.2) | 0 | 0 | 0 |
| 霧視 | 0 | 0 | 1 (0.2) | 0 |
| 視力障害 | 0 | 0 | 1 (0.2) | 0 |
| 硝子体剥離 | 1 (0.2) | 0 | 0 | 0 |
| 胃腸障害 | 21 (5.0) | 21 (4.9) | 28 (6.5) | 24 (5.7) |
| 腹部不快感 | 2 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| 腹部膨満 | 0 | 0 | 0 | 2 (0.5) |
| 上腹部痛 | 1 (0.2) | 3 (0.7) | 4 (0.9) | 3 (0.7) |
| 口角口唇炎 | 0 | 0 | 1 (0.2) | 0 |
| アフタ性潰瘍 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 根尖肉芽腫 | 0 | 0 | 0 | 1 (0.2) |
| 便秘 | 2 (0.5) | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| 下痢 | 5 (1.2) | 3 (0.7) | 7 (1.6) | 4 (0.9) |
| 口内乾燥 | 1 (0.2) | 1 (0.2) | 0 | 1 (0.2) |
| 十二指腸潰瘍 | 0 | 1 (0.2) | 0 | 0 |
| 消化不良 | 2 (0.5) | 0 | 2 (0.5) | 1 (0.2) |
| 小腸炎 | 0 | 1 (0.2) | 0 | 0 |
| びらん性十二指腸炎 | 0 | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| 変色便 | 0 | 0 | 1 (0.2) | 0 |
| 鼓腸 | 2 (0.5) | 0 | 0 | 1 (0.2) |
| 胃炎 | 0 | 1 (0.2) | 0 | 2 (0.5) |
| びらん性胃炎 | 0 | 0 | 2 (0.5) | 0 |
| 胃十二指腸出血 | 0 | 0 | 1 (0.2) | 0 |
| 胃十二指腸潰瘍 | 0 | 0 | 0 | 1 (0.2) |
| 胃食道逆流性疾患 | 0 | 0 | 1 (0.2) | 0 |
| 舌炎 | 1 (0.2) | 0 | 0 | 0 |
| 痔核 | 0 | 0 | 1 (0.2) | 0 |
| 腸管ポリープ | 0 | 1 (0.2) | 0 | 0 |
| 過敏性腸症候群 | 1 (0.2) | 0 | 0 | 0 |
| 口腔内白斑症 | 0 | 1 (0.2) | 0 | 0 |
| 口腔内潰瘍形成 | 2 (0.5) | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 悪心 | 5 (1.2) | 5 (1.2) | 6 (1.4) | 5 (1.2) |
| 食道潰瘍 | 0 | 0 | 0 | 1 (0.2) |
| 口腔障害 | 0 | 0 | 0 | 1 (0.2) |
| 口腔粘膜水疱形成 | 0 | 0 | 0 | 1 (0.2) |
| 膵炎 | 0 | 0 | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 胃腸障害 (Cont.) | | | | |
| 歯周の炎症 | 0 | 0 | 1 (0.2) | 0 |
| 口内炎 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 舌障害 | 0 | 1 (0.2) | 0 | 0 |
| 舌潰瘍 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 歯の障害 | 0 | 0 | 1 (0.2) | 0 |
| 歯痛 | 0 | 0 | 1 (0.2) | 0 |
| 嘔吐 | 1 (0.2) | 4 (0.9) | 0 | 2 (0.5) |
| 一般・全身障害および投与部位の状態 | 9 (2.1) | 26 (6.1) | 10 (2.3) | 15 (3.5) |
| 医薬品副作用 | 0 | 1 (0.2) | 0 | 0 |
| 無力症 | 2 (0.5) | 0 | 1 (0.2) | 1 (0.2) |
| 悪寒 | 0 | 0 | 2 (0.5) | 0 |
| 疲労 | 2 (0.5) | 2 (0.5) | 3 (0.7) | 2 (0.5) |
| インフルエンザ様疾患 | 2 (0.5) | 0 | 0 | 2 (0.5) |
| 注射部位湿疹 | 0 | 1 (0.2) | 0 | 0 |
| 注射部位紅斑 | 0 | 4 (0.9) | 0 | 0 |
| 注射部位血腫 | 1 (0.2) | 0 | 0 | 0 |
| 注射部位過敏反応 | 0 | 1 (0.2) | 0 | 0 |
| 注射部位硬結 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | | |
| 注射部位疼痛 | 1 (0.2) | 3 (0.7) | 0 | 1 (0.2) |
| 注射部位そう痒感 | 0 | 2 (0.5) | 0 | 0 |
| 注射部位反応 | 0 | 10 (2.3) | 0 | 1 (0.2) |
| 注射部位蕁麻疹 | 0 | 2 (0.5) | 0 | 0 |
| 倦怠感 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 疼痛 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 末梢腫脹 | 0 | 0 | 1 (0.2) | 0 |
| 発熱 | 2 (0.5) | 1 (0.2) | 2 (0.5) | 6 (1.4) |
| 腫脹 | 0 | 0 | 0 | 1 (0.2) |
| 肝胆道系障害 | 2 (0.5) | 5 (1.2) | 7 (1.6) | 7 (1.7) |
| 胆道仙痛 | 1 (0.2) | 0 | 0 | 0 |
| 胆石症 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 肝機能異常 | 0 | 2 (0.5) | 3 (0.7) | 3 (0.7) |
| 脂肪肝 | 0 | 0 | 0 | 1 (0.2) |
| 肝毒性 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 高ビリルビン血症 | 0 | 0 | 2 (0.5) | 1 (0.2) |
| 肝障害 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 門脈血栓症 | 0 | 1 (0.2) | 0 | 0 |

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|---|---|---|---|---|
| 肝胆道系障害 (Cont.) | | | | |
| 脂肪性肝炎 | 0 | 0 | 1 (0.2) | 0 |
| 免疫系障害 | 0 | 2 (0.5) | 0 | 2 (0.5) |
| 食物アレルギー | 0 | 0 | 0 | 1 (0.2) |
| 過敏症 | 0 | 2 (0.5) | 0 | 1 (0.2) |
| 感染症および寄生虫症 | 58 (13.7) | 83 (19.3) | 90 (21.0) | 89 (21.0) |
| 歯槽骨炎 | 0 | 1 (0.2) | 0 | 0 |
| 虫垂炎 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 異型肺炎 | 0 | 0 | 0 | 1 (0.2) |
| 菌血症 | 0 | 0 | 0 | 1 (0.2) |
| 細菌感染 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 細菌性前立腺炎 | 1 (0.2) | 0 | 0 | 0 |
| 体部白癬 | 0 | 0 | 1 (0.2) | 0 |
| 骨膿瘍 | 0 | 1 (0.2) | 0 | 0 |
| 乳房蜂巣炎 | 1 (0.2) | 0 | 0 | 0 |
| 気管支炎 | 2 (0.5) | 5 (1.2) | 3 (0.7) | 9 (2.1) |
| 細菌性気管支炎 | 0 | 0 | 0 | 1 (0.2) |
| 蜂巣炎 | 0 | 2 (0.5) | 2 (0.5) | 0 |
| 結膜炎 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 膀胱炎 | 2 (0.5) | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| サイトメガロウイルス感染 | 0 | 0 | 0 | 1 (0.2) |
| 毛嚢虫症 | 0 | 0 | 1 (0.2) | 0 |
| 憩室炎 | 0 | 1 (0.2) | 0 | 0 |
| 耳感染 | 0 | 1 (0.2) | 0 | 0 |
| 丹毒 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 大腸菌性尿路感染 | 0 | 0 | 1 (0.2) | 0 |
| 毛包炎 | 0 | 0 | 5 (1.2) | 2 (0.5) |
| 皮膚真菌感染 | 0 | 3 (0.7) | 2 (0.5) | 2 (0.5) |
| せつ | 0 | 0 | 1 (0.2) | 0 |
| 胃腸炎 | 2 (0.5) | 2 (0.5) | 1 (0.2) | 3 (0.7) |
| ウイルス性胃腸炎 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 消化管感染 | 1 (0.2) | 0 | 0 | 0 |
| 陰部ヘルペス | 0 | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 歯肉炎 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 鼠径部膿瘍 | 0 | 0 | 0 | 1 (0.2) |
| B型肝炎再活性化 | 0 | 0 | 1 (0.2) | 0 |
| C型肝炎 | 1 (0.2) | 0 | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 単純ヘルペス | 1 (0.2) | 1 (0.2) | 1 (0.2) | 5 (1.2) |
| ヘルペスウイルス感染 | 0 | 0 | 1 (0.2) | 0 |
| 帯状疱疹 | 2 (0.5) | 0 | 4 (0.9) | 4 (0.9) |
| 麦粒腫 | 0 | 0 | 1 (0.2) | 0 |
| インフルエンザ | 0 | 1 (0.2) | 6 (1.4) | 3 (0.7) |
| 喉頭炎 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 下気道感染 | 3 (0.7) | 1 (0.2) | 3 (0.7) | 1 (0.2) |
| 肺感染 | 0 | 0 | 0 | 1 (0.2) |
| 爪感染 | 1 (0.2) | 0 | 0 | 0 |
| 鼻ヘルペス | 0 | 1 (0.2) | 0 | 0 |
| 上咽頭炎 | 7 (1.7) | 19 (4.4) | 7 (1.6) | 9 (2.1) |
| 爪真菌症 | 0 | 1 (0.2) | 0 | 0 |
| 口腔カンジダ症 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 口腔ヘルペス | 4 (0.9) | 5 (1.2) | 5 (1.2) | 18 (4.3) |
| 口腔感染 | 1 (0.2) | 0 | 0 | 0 |
| 外耳炎 | 0 | 0 | 0 | 1 (0.2) |
| 急性中耳炎 | 0 | 1 (0.2) | 0 | 2 (0.5) |
| 爪囲炎 | 0 | 1 (0.2) | 2 (0.5) | 2 (0.5) |

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 歯周炎 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 咽頭炎 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| レンサ球菌性咽頭炎 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 0 | 0 | 0 | 1 (0.2) |
| 肺炎 | 0 | 3 (0.7) | 2 (0.5) | 2 (0.5) |
| 歯髄炎 | 0 | 0 | 1 (0.2) | 0 |
| 化膿性分泌物 | 0 | 0 | 0 | 1 (0.2) |
| 膿疱性皮疹 | 0 | 0 | 0 | 2 (0.5) |
| 気道感染 | 2 (0.5) | 2 (0.5) | 7 (1.6) | 7 (1.7) |
| 鼻炎 | 3 (0.7) | 1 (0.2) | 0 | 3 (0.7) |
| サルモネラ症 | 0 | 1 (0.2) | 0 | 0 |
| 敗血症 | 0 | 0 | 2 (0.5) | 0 |
| 副鼻腔炎 | 1 (0.2) | 4 (0.9) | 2 (0.5) | 2 (0.5) |
| 皮膚感染 | 0 | 0 | 1 (0.2) | 0 |
| 軟部組織感染 | 0 | 2 (0.5) | 0 | 0 |
| ブドウ球菌感染 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| ブドウ球菌皮膚感染 | 0 | 0 | 1 (0.2) | 0 |
| 皮下組織膿瘍 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 白癬感染 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 足部白癬 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 癜風 | 0 | 0 | 1 (0.2) | 0 |
| 扁桃炎 | 0 | 2 (0.5) | 1 (0.2) | 3 (0.7) |
| 細菌性扁桃炎 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 歯膿瘍 | 0 | 0 | 1 (0.2) | 0 |
| 歯感染 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 気管炎 | 0 | 0 | 0 | 2 (0.5) |
| 気管気管支炎 | 0 | 0 | 1 (0.2) | 0 |
| トリコモナス症 | 0 | 1 (0.2) | 0 | 0 |
| 上気道感染 | 18 (4.3) | 21 (4.9) | 24 (5.6) | 17 (4.0) |
| 尿路感染 | 6 (1.4) | 8 (1.9) | 10 (2.3) | 6 (1.4) |
| 尿路性敗血症 | 0 | 0 | 0 | 1 (0.2) |
| 腟感染 | 1 (0.2) | 0 | 0 | 0 |
| ウイルス感染 | 2 (0.5) | 1 (0.2) | 0 | 1 (0.2) |
| ウイルス性咽頭炎 | 0 | 0 | 0 | 1 (0.2) |
| ウイルス性気管炎 | 0 | 0 | 1 (0.2) | 0 |
| ウイルス性上気道感染 | 1 (0.2) | 2 (0.5) | 0 | 0 |

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|---|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | | |
| 外陰部炎 | 0 | 0 | 1 (0.2) | 0 |
| 外陰部腟カンジダ症 | 0 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 外陰腟真菌感染 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 創傷感染 | 0 | 1 (0.2) | 0 | 0 |
| 傷害、中毒および処置合併症 | 1 (0.2) | 2 (0.5) | 1 (0.2) | 3 (0.7) |
| 偶発的過量投与 | 0 | 1 (0.2) | 0 | 0 |
| 節足動物咬傷 | 0 | 0 | 0 | 1 (0.2) |
| 挫傷 | 0 | 0 | 0 | 1 (0.2) |
| 仙骨骨折 | 0 | 0 | 0 | 1 (0.2) |
| 注射に伴う反応 | 0 | 1 (0.2) | 0 | 0 |
| 皮膚擦過傷 | 0 | 0 | 1 (0.2) | 0 |
| 各種物質毒性 | 1 (0.2) | 0 | 0 | 0 |
| 臨床検査 | 21 (5.0) | 58 (13.5) | 47 (11.0) | 64 (15.1) |
| アラニンアミノトランスフェラーゼ増加 | 7 (1.7) | 24 (5.6) | 18 (4.2) | 21 (5.0) |
| αヒドロキシ酪酸脱水素酵素増加 | 0 | 0 | 0 | 1 (0.2) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 4 (0.9) | 18 (4.2) | 13 (3.0) | 12 (2.8) |
| 血中アルカリホスファターゼ増加 | 1 (0.2) | 0 | 0 | 0 |
| 血中ビリルビン増加 | 0 | 3 (0.7) | 1 (0.2) | 0 |

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|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| 血中コレステロール減少 | 1 (0.2) | 0 | 0 | 0 |
| 血中コレステロール増加 | 0 | 0 | 3 (0.7) | 2 (0.5) |
| 血中クレアチンホスホキナーゼ増加 | 4 (0.9) | 17 (4.0) | 28 (6.5) | 33 (7.8) |
| 血中クレアチニン増加 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 2 (0.5) |
| 血中ブドウ糖増加 | 0 | 2 (0.5) | 0 | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 0 | 1 (0.2) |
| 血中カリウム増加 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 血圧上昇 | 1 (0.2) | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| 血中トリグリセリド増加 | 0 | 0 | 0 | 1 (0.2) |
| 血中尿素増加 | 0 | 0 | 0 | 1 (0.2) |
| 血中尿酸増加 | 0 | 0 | 0 | 3 (0.7) |
| ヘモグロビン減少 | 1 (0.2) | 0 | 0 | 3 (0.7) |
| 肝酵素上昇 | 2 (0.5) | 4 (0.9) | 1 (0.2) | 2 (0.5) |
| 高比重リポ蛋白減少 | 1 (0.2) | 0 | 0 | 0 |
| 高比重リポ蛋白増加 | 0 | 1 (0.2) | 2 (0.5) | 0 |
| 未熟顆粒球数増加 | 0 | 0 | 1 (0.2) | 0 |
| 肝機能検査値上昇 | 0 | 1 (0.2) | 3 (0.7) | 1 (0.2) |
| 低比重リポ蛋白増加 | 0 | 0 | 2 (0.5) | 1 (0.2) |

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|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| リンパ球数減少 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 平均赤血球容積増加 | 0 | 1 (0.2) | 0 | 2 (0.5) |
| 筋酵素上昇 | 0 | 0 | 1 (0.2) | 0 |
| 骨髄球存在 | 0 | 0 | 0 | 1 (0.2) |
| 好中球数減少 | 0 | 2 (0.5) | 0 | 4 (0.9) |
| 好中球数増加 | 1 (0.2) | 0 | 0 | 0 |
| 血小板数増加 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| 尿中蛋白陽性 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 赤血球数減少 | 0 | 1 (0.2) | 0 | 3 (0.7) |
| 血沈亢進 | 1 (0.2) | 0 | 1 (0.2) | 0 |
| 尿中赤血球 | 1 (0.2) | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 7 (1.6) | 0 | 3 (0.7) |
| 尿中白血球エステラーゼ陽性 | 0 | 1 (0.2) | 0 | 0 |
| 超低比重リポ蛋白増加 | 0 | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 体重減少 | 1 (0.2) | 0 | 0 | 0 |
| 体重増加 | 0 | 2 (0.5) | 0 | 1 (0.2) |
| 白血球数減少 | 0 | 2 (0.5) | 0 | 6 (1.4) |
| 白血球数増加 | 1 (0.2) | 0 | 0 | 0 |

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|---|---|---|---|---|
| 臨床検査 (Cont.) | | | | |
| 尿中白血球陽性 | 0 | 1 (0.2) | 0 | 0 |
| 代謝および栄養障害 | 7 (1.7) | 12 (2.8) | 7 (1.6) | 17 (4.0) |
| 炭水化物不耐症 | 0 | 1 (0.2) | 0 | 0 |
| 糖尿病 | 0 | 1 (0.2) | 0 | 0 |
| コントロール不良の糖尿病 | 0 | 1 (0.2) | 0 | 0 |
| 脂質異常症 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 3 (0.7) |
| 耐糖能障害 | 0 | 1 (0.2) | 0 | 0 |
| 高カルシウム血症 | 0 | 0 | 0 | 1 (0.2) |
| 高コレステロール血症 | 0 | 0 | 1 (0.2) | 7 (1.7) |
| 高血糖 | 1 (0.2) | 3 (0.7) | 1 (0.2) | 1 (0.2) |
| 高カリウム血症 | 1 (0.2) | 0 | 0 | 0 |
| 高脂血症 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 3 (0.7) |
| 高トリグリセリド血症 | 2 (0.5) | 3 (0.7) | 0 | 0 |
| 高尿酸血症 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 低カリウム血症 | 0 | 1 (0.2) | 0 | 0 |
| 低リン酸血症 | 0 | 0 | 1 (0.2) | 0 |
| ビタミンD欠乏 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 筋骨格系および結合組織障害 | 5 (1.2) | 5 (1.2) | 7 (1.6) | 5 (1.2) |
| 背部痛 | 1 (0.2) | 2 (0.5) | 0 | 0 |
| 側腹部痛 | 0 | 0 | 0 | 1 (0.2) |
| 関節雑音 | 0 | 0 | 0 | 1 (0.2) |
| 関節硬直 | 0 | 0 | 1 (0.2) | 0 |
| 筋痙縮 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 筋力低下 | 0 | 0 | 0 | 1 (0.2) |
| 筋肉痛 | 0 | 0 | 2 (0.5) | 0 |
| 頚部痛 | 0 | 1 (0.2) | 0 | 0 |
| 四肢痛 | 0 | 0 | 1 (0.2) | 0 |
| 骨膜炎 | 1 (0.2) | 0 | 0 | 0 |
| 乾癬性関節症 | 2 (0.5) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| 脊椎痛 | 0 | 0 | 1 (0.2) | 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） | 1 (0.2) | 0 | 0 | 3 (0.7) |
| 肛門性器疣贅 | 0 | 0 | 0 | 1 (0.2) |
| 基底細胞癌 | 0 | 0 | 0 | 1 (0.2) |
| 化膿性肉芽腫 | 1 (0.2) | 0 | 0 | 0 |
| 皮膚乳頭腫 | 0 | 0 | 0 | 1 (0.2) |

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|---|---|---|---|---|
| 神経系障害 | 9 (2.1) | 8 (1.9) | 10 (2.3) | 16 (3.8) |
| 手根管症候群 | 0 | 0 | 0 | 1 (0.2) |
| 注意力障害 | 1 (0.2) | 0 | 0 | 0 |
| 浮動性めまい | 2 (0.5) | 1 (0.2) | 2 (0.5) | 2 (0.5) |
| 頭痛 | 6 (1.4) | 5 (1.2) | 6 (1.4) | 7 (1.7) |
| 肝性脳症 | 0 | 1 (0.2) | 0 | 0 |
| 感覚鈍麻 | 1 (0.2) | 0 | 0 | 0 |
| 嗜眠 | 0 | 0 | 1 (0.2) | 0 |
| 記憶障害 | 0 | 0 | 0 | 1 (0.2) |
| 片頭痛 | 0 | 0 | 0 | 1 (0.2) |
| 神経痛 | 0 | 0 | 0 | 1 (0.2) |
| 錯感覚 | 0 | 0 | 1 (0.2) | 1 (0.2) |
| 末梢性感覚ニューロパチー | 0 | 0 | 0 | 1 (0.2) |
| 睡眠の質低下 | 0 | 1 (0.2) | 0 | 0 |
| 感覚障害 | 0 | 0 | 0 | 1 (0.2) |
| 傾眠 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 精神障害 | 1 (0.2) | 2 (0.5) | 4 (0.9) | 3 (0.7) |
| 不安 | 0 | 0 | 0 | 2 (0.5) |
| 抑うつ気分 | 0 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 精神障害 (Cont.) | | | | |
| うつ病 | 0 | 0 | 1 (0.2) | 0 |
| 不眠症 | 1 (0.2) | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| 睡眠障害 | 0 | 0 | 1 (0.2) | 0 |
| 腎および尿路障害 | 2 (0.5) | 5 (1.2) | 2 (0.5) | 4 (0.9) |
| 尿路結石 | 0 | 0 | 0 | 1 (0.2) |
| 慢性腎臓病 | 0 | 0 | 0 | 1 (0.2) |
| 糖尿 | 0 | 1 (0.2) | 0 | 0 |
| 血尿 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 白血球尿 | 0 | 0 | 1 (0.2) | 0 |
| 頻尿 | 0 | 0 | 0 | 1 (0.2) |
| 蛋白尿 | 1 (0.2) | 2 (0.5) | 0 | 1 (0.2) |
| 尿路の炎症 | 0 | 1 (0.2) | 0 | 0 |
| 生殖系および乳房障害 | 1 (0.2) | 1 (0.2) | 5 (1.2) | 1 (0.2) |
| 無月経 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 前立腺結石 | 0 | 0 | 1 (0.2) | 0 |
| 線維嚢胞性乳腺疾患 | 0 | 0 | 0 | 1 (0.2) |
| 月経過多 | 0 | 0 | 1 (0.2) | 0 |
| 不規則月経 | 0 | 0 | 2 (0.5) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | | |
| 不正子宮出血 | 1 (0.2) | 0 | 0 | 0 |
| 子宮出血 | 1 (0.2) | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 7 (1.7) | 16 (3.7) | 8 (1.9) | 17 (4.0) |
| 喘息 | 0 | 1 (0.2) | 0 | 0 |
| 咳嗽 | 3 (0.7) | 1 (0.2) | 2 (0.5) | 8 (1.9) |
| 呼吸困難 | 0 | 0 | 1 (0.2) | 0 |
| 鼻出血 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| 肺浸潤 | 0 | 1 (0.2) | 0 | 0 |
| 鼻閉 | 0 | 2 (0.5) | 0 | 0 |
| 鼻部不快感 | 0 | 0 | 1 (0.2) | 0 |
| 鼻の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 鼻潰瘍 | 0 | 0 | 0 | 1 (0.2) |
| 閉塞性気道障害 | 1 (0.2) | 0 | 0 | 0 |
| 口腔咽頭不快感 | 0 | 1 (0.2) | 0 | 0 |
| 口腔咽頭痛 | 3 (0.7) | 6 (1.4) | 1 (0.2) | 2 (0.5) |
| 咽頭の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 胸膜炎 | 0 | 0 | 1 (0.2) | 0 |
| 肺臓炎 | 0 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | | |
| 肺塞栓症 | 0 | 0 | 0 | 1 (0.2) |
| 肺線維症 | 0 | 0 | 0 | 1 (0.2) |
| アレルギー性鼻炎 | 0 | 0 | 1 (0.2) | 0 |
| 鼻漏 | 1 (0.2) | 2 (0.5) | 2 (0.5) | 1 (0.2) |
| 咽喉刺激感 | 0 | 0 | 0 | 2 (0.5) |
| 上気道の炎症 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 皮膚および皮下組織障害 | 14 (3.3) | 21 (4.9) | 13 (3.0) | 16 (3.8) |
| ざ瘡 | 0 | 0 | 1 (0.2) | 2 (0.5) |
| 脱毛症 | 0 | 6 (1.4) | 1 (0.2) | 1 (0.2) |
| 水疱 | 0 | 0 | 0 | 1 (0.2) |
| 皮膚嚢腫 | 0 | 0 | 1 (0.2) | 0 |
| 皮膚炎 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| ざ瘡様皮膚炎 | 0 | 0 | 0 | 1 (0.2) |
| アレルギー性皮膚炎 | 0 | 1 (0.2) | 0 | 0 |
| 皮膚乾燥 | 1 (0.2) | 0 | 0 | 1 (0.2) |
| 湿疹 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 紅斑 | 0 | 1 (0.2) | 0 | 2 (0.5) |
| 環状紅斑 | 0 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | | |
| 毛髪成長異常 | 0 | 0 | 1 (0.2) | 0 |
| 多汗症 | 1 (0.2) | 0 | 2 (0.5) | 0 |
| 過角化 | 2 (0.5) | 0 | 0 | 0 |
| 間擦疹 | 0 | 0 | 1 (0.2) | 0 |
| 爪郭の炎症 | 0 | 0 | 0 | 1 (0.2) |
| 爪成長異常 | 0 | 0 | 1 (0.2) | 0 |
| 光線過敏性反応 | 0 | 1 (0.2) | 0 | 0 |
| そう痒症 | 0 | 3 (0.7) | 0 | 1 (0.2) |
| 全身性そう痒症 | 0 | 1 (0.2) | 0 | 0 |
| 乾癬 | 5 (1.2) | 4 (0.9) | 2 (0.5) | 1 (0.2) |
| 膿疱性乾癬 | 0 | 0 | 0 | 1 (0.2) |
| 発疹 | 5 (1.2) | 3 (0.7) | 0 | 3 (0.7) |
| 全身性皮疹 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| 斑状皮疹 | 0 | 0 | 0 | 1 (0.2) |
| 斑状丘疹状皮疹 | 0 | 0 | 1 (0.2) | 0 |
| 皮膚亀裂 | 1 (0.2) | 0 | 0 | 0 |
| 皮膚刺激 | 0 | 0 | 0 | 1 (0.2) |
| 皮膚病変 | 0 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports two or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Program Source Code: [redacted]

TABLE 14.3__1.6.1

Subjects with Treatment-Emergent Adverse Events with Reasonable Possibly Related to Study Drug
by Primary MedDRA System Organ Class and Preferred Term - up to Week 24
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | Placebo<br>(N = 423)<br>n (%) | ADA 40 mg EOW<br>(N = 429)<br>n (%) | UPA<br>15 mg QD<br>(N = 429)<br>n (%) | UPA<br>30 mg QD<br>(N = 423)<br>n (%) |
|---|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | | |
| 顔面腫脹 | 0 | 0 | 1 (0.2) | 0 |
| 蕁麻疹 | 0 | 3 (0.7) | 0 | 0 |
| 血管障害 | 3 (0.7) | 6 (1.4) | 6 (1.4) | 4 (0.9) |
| 深部静脈血栓症 | 1 (0.2) | 0 | 0 | 0 |
| 血腫 | 0 | 1 (0.2) | 0 | 0 |
| ほてり | 0 | 0 | 3 (0.7) | 0 |
| 高血圧 | 2 (0.5) | 2 (0.5) | 2 (0.5) | 3 (0.7) |
| 高血圧クリーゼ | 0 | 0 | 1 (0.2) | 0 |
| 血栓性静脈炎 | 0 | 1 (0.2) | 0 | 0 |
| 表在性血栓性静脈炎 | 0 | 1 (0.2) | 0 | 1 (0.2) |
| 血管炎 | 0 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 30 days after the last dose of placebo or UPA and up to 70 days for adalimumab, if subject discontinued study drug prematurely before Week 24 dosing.
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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Program Source Code: [redacted]

表 3.　　長期投与時の有害事象の 100 人年あたりの発現件数：MedDRA のプライマリー器官別大分類及び基本語別（安全性解析対象集団）

相互参照：M15-572 試験 CSR W24 Table 14.3__1.2.2

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| Any adverse event | 1683 (321.1) | 2015 (383.1) | 1294 (328.0) |
| 血液およびリンパ系障害 | 63 (12.0) | 120 (22.8) | 42 (10.6) |
| 貧血 | 10 (1.9) | 22 (4.2) | 3 (0.8) |
| 大球性貧血 | 1 (0.2) | 1 (0.2) | 0 |
| 自己免疫性貧血 | 0 | 2 (0.4) | 0 |
| 失血性貧血 | 0 | 1 (0.2) | 0 |
| 骨髄浮腫 | 0 | 1 (0.2) | 0 |
| 血球減少症 | 0 | 1 (0.2) | 0 |
| 赤血球減少症 | 0 | 1 (0.2) | 0 |
| 顆粒球減少症 | 0 | 3 (0.6) | 0 |
| 内出血発生の増加傾向 | 3 (0.6) | 1 (0.2) | 2 (0.5) |
| 鉄欠乏性貧血 | 1 (0.2) | 2 (0.4) | 0 |
| 白血球増加症 | 0 | 1 (0.2) | 1 (0.3) |
| 白血球減少症 | 16 (3.1) | 22 (4.2) | 9 (2.3) |
| リンパ節症 | 2 (0.4) | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 血液およびリンパ系障害 (Cont.) | | | |
| リンパ組織過形成 | 0 | 1 (0.2) | 0 |
| リンパ球減少症 | 15 (2.9) | 21 (4.0) | 1 (0.3) |
| 大赤血球症 | 0 | 0 | 1 (0.3) |
| 好中球減少症 | 12 (2.3) | 29 (5.5) | 18 (4.6) |
| 好中球増加症 | 1 (0.2) | 2 (0.4) | 2 (0.5) |
| 正色素性貧血 | 0 | 1 (0.2) | 0 |
| 正色素性正球性貧血 | 0 | 0 | 2 (0.5) |
| 血小板減少症 | 2 (0.4) | 5 (1.0) | 2 (0.5) |
| 血小板増加症 | 0 | 3 (0.6) | 0 |
| 心臓障害 | 20 (3.8) | 18 (3.4) | 14 (3.5) |
| 急性心筋梗塞 | 0 | 0 | 1 (0.3) |
| 狭心症 | 0 | 1 (0.2) | 0 |
| 大動脈弁硬化症 | 2 (0.4) | 0 | 0 |
| 不整脈 | 0 | 1 (0.2) | 0 |
| 冠動脈硬化症 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 心臓障害 (Cont.) | | | |
| 心房細動 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| 心房粗動 | 0 | 1 (0.2) | 0 |
| 房室ブロック | 0 | 0 | 1 (0.3) |
| 第一度房室ブロック | 1 (0.2) | 0 | 0 |
| 第二度房室ブロック | 0 | 1 (0.2) | 0 |
| 徐脈 | 0 | 0 | 1 (0.3) |
| 左脚ブロック | 0 | 0 | 1 (0.3) |
| 右脚ブロック | 1 (0.2) | 1 (0.2) | 0 |
| 心不全 | 1 (0.2) | 0 | 0 |
| うっ血性心不全 | 0 | 1 (0.2) | 0 |
| 心臓弁硬化症 | 0 | 1 (0.2) | 0 |
| 心室血栓症 | 0 | 0 | 1 (0.3) |
| 冠動脈疾患 | 0 | 1 (0.2) | 1 (0.3) |
| チアノーゼ | 0 | 1 (0.2) | 0 |
| 期外収縮 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 心臓障害 (Cont.) | | | |
| 左室機能不全 | 0 | 0 | 1 (0.3) |
| 僧帽弁閉鎖不全症 | 1 (0.2) | 0 | 0 |
| 僧帽弁硬化症 | 1 (0.2) | 0 | 0 |
| 心筋梗塞 | 1 (0.2) | 1 (0.2) | 0 |
| 心筋虚血 | 1 (0.2) | 0 | 0 |
| 動悸 | 5 (1.0) | 1 (0.2) | 0 |
| 心膜炎 | 0 | 0 | 1 (0.3) |
| 肺動脈弁閉鎖不全症 | 2 (0.4) | 0 | 0 |
| 洞性徐脈 | 0 | 2 (0.4) | 0 |
| 洞性頻脈 | 0 | 0 | 1 (0.3) |
| 頻脈 | 0 | 2 (0.4) | 2 (0.5) |
| 発作性頻脈 | 0 | 1 (0.2) | 0 |
| 三尖弁閉鎖不全症 | 1 (0.2) | 0 | 0 |
| 心室性期外収縮 | 0 | 0 | 1 (0.3) |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 先天性、家族性および遺伝性障害 | 2 (0.4) | 1 (0.2) | 0 |
| 発育性股関節形成不全 | 1 (0.2) | 0 | 0 |
| 陰嚢水瘤 | 1 (0.2) | 0 | 0 |
| 2a型高脂血症 | 0 | 1 (0.2) | 0 |
| 耳および迷路障害 | 6 (1.1) | 5 (1.0) | 5 (1.3) |
| 耳垢栓塞 | 0 | 2 (0.4) | 0 |
| 耳閉 | 0 | 1 (0.2) | 0 |
| 外耳の炎症 | 1 (0.2) | 0 | 0 |
| 耳鳴 | 1 (0.2) | 0 | 3 (0.8) |
| 回転性めまい | 2 (0.4) | 0 | 2 (0.5) |
| 頭位性回転性めまい | 2 (0.4) | 1 (0.2) | 0 |
| 前庭障害 | 0 | 1 (0.2) | 0 |
| 内分泌障害 | 4 (0.8) | 5 (1.0) | 1 (0.3) |
| 副腎石灰化 | 0 | 1 (0.2) | 0 |
| アンドロゲン欠乏症 | 1 (0.2) | 0 | 0 |
| 自己免疫性甲状腺炎 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 内分泌障害 (Cont.) | | | |
| 甲状腺腫 | 1 (0.2) | 1 (0.2) | 0 |
| 甲状腺機能亢進症 | 0 | 1 (0.2) | 0 |
| 甲状腺機能低下症 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 甲状腺腫瘤 | 0 | 1 (0.2) | 0 |
| 眼障害 | 25 (4.8) | 26 (4.9) | 10 (2.5) |
| 動脈硬化性網膜症 | 1 (0.2) | 0 | 0 |
| 眼瞼痙攣 | 1 (0.2) | 0 | 0 |
| 境界域緑内障 | 1 (0.2) | 0 | 0 |
| 白内障 | 2 (0.4) | 9 (1.7) | 3 (0.8) |
| 霰粒腫 | 0 | 1 (0.2) | 0 |
| 結膜出血 | 1 (0.2) | 0 | 1 (0.3) |
| 結膜充血 | 1 (0.2) | 0 | 0 |
| アレルギー性結膜炎 | 0 | 1 (0.2) | 0 |
| 糖尿病網膜症 | 1 (0.2) | 0 | 0 |
| 複視 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 眼障害 (Cont.) | | | |
| ドライアイ | 0 | 1 (0.2) | 0 |
| 眼痛 | 1 (0.2) | 1 (0.2) | 0 |
| 眼瞼下垂 | 2 (0.4) | 1 (0.2) | 0 |
| 緑内障 | 2 (0.4) | 5 (1.0) | 0 |
| 虹彩毛様体炎 | 0 | 1 (0.2) | 0 |
| 角膜炎 | 0 | 1 (0.2) | 0 |
| 流涙増加 | 0 | 1 (0.2) | 0 |
| 瞼板腺炎 | 1 (0.2) | 0 | 1 (0.3) |
| 眼部不快感 | 0 | 1 (0.2) | 0 |
| 眼窩周囲浮腫 | 0 | 0 | 2 (0.5) |
| 眼窩周囲腫脹 | 0 | 1 (0.2) | 0 |
| 光視症 | 1 (0.2) | 0 | 0 |
| 翼状片 | 0 | 0 | 1 (0.3) |
| 眼瞼腫脹 | 1 (0.2) | 0 | 0 |
| ぶどう膜炎 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 眼障害 (Cont.) | | | |
| 霧視 | 3 (0.6) | 0 | 2 (0.5) |
| 視力低下 | 1 (0.2) | 1 (0.2) | 0 |
| 視力障害 | 3 (0.6) | 0 | 0 |
| 硝子体浮遊物 | 1 (0.2) | 0 | 0 |
| 胃腸障害 | 157 (30.0) | 166 (31.6) | 118 (29.9) |
| 腹部不快感 | 4 (0.8) | 3 (0.6) | 2 (0.5) |
| 腹部膨満 | 2 (0.4) | 3 (0.6) | 1 (0.3) |
| 腹部腫瘤 | 1 (0.2) | 0 | 0 |
| 腹痛 | 5 (1.0) | 3 (0.6) | 4 (1.0) |
| 下腹部痛 | 2 (0.4) | 0 | 3 (0.8) |
| 上腹部痛 | 11 (2.1) | 9 (1.7) | 6 (1.5) |
| 腹壁嚢胞 | 0 | 1 (0.2) | 0 |
| 裂肛 | 0 | 1 (0.2) | 0 |
| 痔瘻 | 0 | 1 (0.2) | 0 |
| 口角口唇炎 | 1 (0.2) | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| アフタ性潰瘍 | 2 (0.4) | 2 (0.4) | 1 (0.3) |
| 根尖肉芽腫 | 0 | 1 (0.2) | 0 |
| 腹水 | 0 | 0 | 1 (0.3) |
| 慢性胃炎 | 0 | 2 (0.4) | 0 |
| 大腸炎 | 2 (0.4) | 0 | 0 |
| 結腸異形成 | 1 (0.2) | 0 | 0 |
| 便秘 | 4 (0.8) | 5 (1.0) | 7 (1.8) |
| 齲歯 | 1 (0.2) | 3 (0.6) | 0 |
| 下痢 | 26 (5.0) | 28 (5.3) | 18 (4.6) |
| 憩室 | 2 (0.4) | 2 (0.4) | 0 |
| 腸憩室 | 0 | 2 (0.4) | 1 (0.3) |
| 食道憩室 | 0 | 1 (0.2) | 0 |
| 後天性過長結腸 | 0 | 0 | 1 (0.3) |
| 口内乾燥 | 0 | 2 (0.4) | 2 (0.5) |
| 十二指腸潰瘍 | 0 | 2 (0.4) | 2 (0.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 出血性十二指腸潰瘍 | 0 | 1 (0.2) | 0 |
| 十二指腸炎 | 0 | 1 (0.2) | 0 |
| 排便困難 | 0 | 1 (0.2) | 0 |
| 消化不良 | 7 (1.3) | 5 (1.0) | 3 (0.8) |
| 嚥下障害 | 0 | 1 (0.2) | 0 |
| 小腸炎 | 0 | 2 (0.4) | 2 (0.5) |
| 腸炎 | 0 | 2 (0.4) | 0 |
| 心窩部不快感 | 1 (0.2) | 0 | 1 (0.3) |
| びらん性十二指腸炎 | 1 (0.2) | 0 | 0 |
| びらん性食道炎 | 0 | 1 (0.2) | 0 |
| おくび | 1 (0.2) | 0 | 0 |
| 変色便 | 1 (0.2) | 0 | 0 |
| 鼓腸 | 1 (0.2) | 2 (0.4) | 2 (0.5) |
| 食中毒 | 0 | 2 (0.4) | 3 (0.8) |
| 胃ポリープ | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 胃潰瘍 | 0 | 0 | 1 (0.3) |
| 穿孔性胃潰瘍 | 1 (0.2) | 0 | 0 |
| 胃炎 | 8 (1.5) | 6 (1.1) | 4 (1.0) |
| びらん性胃炎 | 3 (0.6) | 1 (0.2) | 2 (0.5) |
| 胃十二指腸出血 | 1 (0.2) | 0 | 0 |
| 胃十二指腸潰瘍 | 0 | 1 (0.2) | 0 |
| 胃腸出血 | 1 (0.2) | 0 | 1 (0.3) |
| 胃食道逆流性疾患 | 5 (1.0) | 6 (1.1) | 4 (1.0) |
| 歯肉腫脹 | 0 | 1 (0.2) | 0 |
| 血便排泄 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 痔核 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| 裂孔ヘルニア | 3 (0.6) | 3 (0.6) | 1 (0.3) |
| 鼠径ヘルニア | 0 | 1 (0.2) | 0 |
| 腸閉塞 | 1 (0.2) | 0 | 0 |
| 腸管ポリープ | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 過敏性腸症候群 | 0 | 0 | 1 (0.3) |
| 大腸ポリープ | 2 (0.4) | 0 | 1 (0.3) |
| 口腔内白斑症 | 0 | 0 | 1 (0.3) |
| 口唇乾燥 | 1 (0.2) | 0 | 0 |
| 口唇潰瘍 | 1 (0.2) | 1 (0.2) | 0 |
| 口腔嚢胞 | 0 | 1 (0.2) | 0 |
| 口腔内潰瘍形成 | 3 (0.6) | 6 (1.1) | 1 (0.3) |
| 悪心 | 16 (3.1) | 23 (4.4) | 18 (4.6) |
| 食道痙攣 | 0 | 1 (0.2) | 0 |
| 食道潰瘍 | 0 | 1 (0.2) | 0 |
| 食道潰瘍出血 | 1 (0.2) | 0 | 0 |
| 口腔挫傷 | 1 (0.2) | 0 | 0 |
| 口腔障害 | 0 | 1 (0.2) | 0 |
| 口腔粘膜びらん | 0 | 1 (0.2) | 0 |
| 口腔粘膜水疱形成 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 膵臓障害 | 0 | 1 (0.2) | 1 (0.3) |
| 膵脂肪変性 | 0 | 1 (0.2) | 0 |
| 膵炎 | 1 (0.2) | 0 | 0 |
| 消化性潰瘍 | 1 (0.2) | 0 | 0 |
| 歯周の炎症 | 1 (0.2) | 0 | 0 |
| 直腸出血 | 1 (0.2) | 2 (0.4) | 0 |
| 吐き戻し | 0 | 1 (0.2) | 0 |
| レッチング | 1 (0.2) | 0 | 0 |
| 口内炎 | 3 (0.6) | 3 (0.6) | 1 (0.3) |
| 舌障害 | 0 | 0 | 1 (0.3) |
| 舌潰瘍 | 1 (0.2) | 2 (0.4) | 0 |
| 変色歯 | 0 | 0 | 1 (0.3) |
| 歯の障害 | 1 (0.2) | 1 (0.2) | 0 |
| 歯の脱落 | 0 | 0 | 1 (0.3) |
| 歯痛 | 6 (1.1) | 2 (0.4) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 上部消化管出血 | 1 (0.2) | 0 | 0 |
| 嘔吐 | 13 (2.5) | 6 (1.1) | 13 (3.3) |
| 一般・全身障害および投与部位の状態 | 43 (8.2) | 59 (11.2) | 81 (20.5) |
| 医薬品副作用 | 1 (0.2) | 0 | 1 (0.3) |
| 無力症 | 3 (0.6) | 3 (0.6) | 0 |
| 胸痛 | 2 (0.4) | 2 (0.4) | 3 (0.8) |
| 悪寒 | 2 (0.4) | 0 | 0 |
| 不快感 | 1 (0.2) | 0 | 0 |
| 薬物不耐性 | 1 (0.2) | 3 (0.6) | 0 |
| 顔面痛 | 0 | 1 (0.2) | 0 |
| 疲労 | 10 (1.9) | 6 (1.1) | 9 (2.3) |
| 歩行障害 | 0 | 2 (0.4) | 0 |
| 高熱 | 1 (0.2) | 0 | 0 |
| 低体温 | 0 | 1 (0.2) | 0 |
| 炎症 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | |
| インフルエンザ様疾患 | 4 (0.8) | 4 (0.8) | 1 (0.3) |
| 注射部位内出血 | 0 | 1 (0.2) | 1 (0.3) |
| 注射部位湿疹 | 0 | 0 | 3 (0.8) |
| 注射部位紅斑 | 0 | 0 | 5 (1.3) |
| 注射部位過敏反応 | 0 | 0 | 1 (0.3) |
| 注射部位硬結 | 0 | 0 | 1 (0.3) |
| 注射部位疼痛 | 0 | 1 (0.2) | 5 (1.3) |
| 注射部位そう痒感 | 0 | 0 | 2 (0.5) |
| 注射部位反応 | 0 | 2 (0.4) | 24 (6.1) |
| 注射部位蕁麻疹 | 0 | 0 | 3 (0.8) |
| 倦怠感 | 4 (0.8) | 0 | 2 (0.5) |
| 小結節 | 0 | 1 (0.2) | 1 (0.3) |
| 非心臓性胸痛 | 0 | 1 (0.2) | 0 |
| 浮腫 | 1 (0.2) | 0 | 0 |
| 末梢性浮腫 | 4 (0.8) | 6 (1.1) | 8 (2.0) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | |
| 疼痛 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 末梢腫脹 | 4 (0.8) | 3 (0.6) | 2 (0.5) |
| 発熱 | 4 (0.8) | 19 (3.6) | 5 (1.3) |
| 腫脹 | 0 | 1 (0.2) | 0 |
| 口渇 | 0 | 0 | 1 (0.3) |
| ワクチン接種部位そう痒感 | 0 | 0 | 1 (0.3) |
| 肝胆道系障害 | 28 (5.3) | 37 (7.0) | 28 (7.1) |
| 胆管結石 | 0 | 1 (0.2) | 0 |
| 胆道仙痛 | 1 (0.2) | 0 | 0 |
| 胆道ジスキネジア | 0 | 0 | 1 (0.3) |
| 胆石症 | 2 (0.4) | 4 (0.8) | 3 (0.8) |
| 薬物性肝障害 | 0 | 1 (0.2) | 2 (0.5) |
| 肝嚢胞 | 0 | 1 (0.2) | 1 (0.3) |
| 肝線維症 | 0 | 0 | 1 (0.3) |
| 肝機能異常 | 12 (2.3) | 12 (2.3) | 3 (0.8) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 肝胆道系障害 (Cont.) | | | |
| 肝腫瘤 | 0 | 1 (0.2) | 0 |
| 脂肪肝 | 4 (0.8) | 9 (1.7) | 8 (2.0) |
| 肝炎 | 1 (0.2) | 0 | 0 |
| 肝腫大 | 0 | 1 (0.2) | 2 (0.5) |
| 肝毒性 | 1 (0.2) | 1 (0.2) | 0 |
| 高ビリルビン血症 | 2 (0.4) | 1 (0.2) | 0 |
| 高トランスアミナーゼ血症 | 0 | 1 (0.2) | 2 (0.5) |
| 肝障害 | 0 | 3 (0.6) | 3 (0.8) |
| 肝損傷 | 0 | 0 | 1 (0.3) |
| 非アルコール性脂肪性肝炎 | 1 (0.2) | 0 | 0 |
| 非アルコール性脂肪性肝疾患 | 2 (0.4) | 1 (0.2) | 0 |
| 門脈血栓症 | 0 | 0 | 1 (0.3) |
| 脂肪性肝炎 | 2 (0.4) | 0 | 0 |
| 免疫系障害 | 4 (0.8) | 8 (1.5) | 5 (1.3) |
| 節足動物咬傷アレルギー | 0 | 2 (0.4) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 免疫系障害 (Cont.) | | | |
| 薬物過敏症 | 1 (0.2) | 1 (0.2) | 0 |
| 食物アレルギー | 0 | 1 (0.2) | 0 |
| 過敏症 | 0 | 1 (0.2) | 3 (0.8) |
| ダニアレルギー | 0 | 2 (0.4) | 0 |
| 季節性アレルギー | 3 (0.6) | 1 (0.2) | 2 (0.5) |
| 感染症および寄生虫症 | 527 (100.6) | 669 (127.2) | 340 (86.2) |
| 腹部膿瘍 | 0 | 2 (0.4) | 0 |
| 膿瘍 | 0 | 1 (0.2) | 0 |
| 四肢膿瘍 | 0 | 3 (0.6) | 1 (0.3) |
| 口腔膿瘍 | 0 | 1 (0.2) | 0 |
| ダニ皮膚炎 | 1 (0.2) | 0 | 0 |
| 急性副鼻腔炎 | 3 (0.6) | 0 | 2 (0.5) |
| 歯槽骨炎 | 0 | 0 | 1 (0.3) |
| 肛門膿瘍 | 0 | 1 (0.2) | 0 |
| 虫垂炎 | 1 (0.2) | 2 (0.4) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 細菌性関節炎 | 1 (0.2) | 0 | 0 |
| 無症候性細菌尿 | 1 (0.2) | 0 | 0 |
| 異型肺炎 | 0 | 2 (0.4) | 0 |
| バベシア症 | 0 | 1 (0.2) | 0 |
| 菌血症 | 0 | 1 (0.2) | 0 |
| 細菌感染 | 1 (0.2) | 0 | 1 (0.3) |
| 細菌性膣症 | 1 (0.2) | 0 | 1 (0.3) |
| 細菌尿 | 1 (0.2) | 1 (0.2) | 0 |
| 体部白癬 | 2 (0.4) | 2 (0.4) | 0 |
| 骨膿瘍 | 0 | 0 | 1 (0.3) |
| 気管支炎 | 30 (5.7) | 42 (8.0) | 12 (3.0) |
| 細菌性気管支炎 | 1 (0.2) | 1 (0.2) | 0 |
| マイコプラズマ性気管支炎 | 0 | 0 | 1 (0.3) |
| 気管支肺アスペルギルス症 | 1 (0.2) | 0 | 0 |
| カンジダ感染 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| カンジダ性尿道炎 | 1 (0.2) | 0 | 0 |
| 蜂巣炎 | 3 (0.6) | 2 (0.4) | 8 (2.0) |
| 慢性副鼻腔炎 | 0 | 0 | 2 (0.5) |
| 慢性扁桃炎 | 0 | 0 | 1 (0.3) |
| 結膜炎 | 6 (1.1) | 2 (0.4) | 5 (1.3) |
| 膀胱炎 | 9 (1.7) | 8 (1.5) | 11 (2.8) |
| サイトメガロウイルス感染 | 0 | 1 (0.2) | 0 |
| 毛嚢虫症 | 1 (0.2) | 0 | 0 |
| 爪の皮膚糸状菌症 | 1 (0.2) | 0 | 0 |
| 憩室炎 | 1 (0.2) | 0 | 1 (0.3) |
| 耳感染 | 7 (1.3) | 1 (0.2) | 4 (1.0) |
| エンテロウイルス感染 | 0 | 0 | 1 (0.3) |
| 丹毒 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 紅色陰癬 | 0 | 0 | 3 (0.8) |
| 大腸菌性尿路感染 | 2 (0.4) | 1 (0.2) | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 眼感染 | 0 | 0 | 1 (0.3) |
| 毛包炎 | 9 (1.7) | 8 (1.5) | 2 (0.5) |
| 真菌感染 | 1 (0.2) | 0 | 0 |
| 皮膚真菌感染 | 3 (0.6) | 8 (1.5) | 3 (0.8) |
| せつ | 1 (0.2) | 0 | 1 (0.3) |
| 胃腸炎 | 17 (3.2) | 23 (4.4) | 12 (3.0) |
| ウイルス性胃腸炎 | 2 (0.4) | 12 (2.3) | 3 (0.8) |
| 消化管感染 | 3 (0.6) | 0 | 0 |
| ウイルス性消化管感染 | 0 | 1 (0.2) | 0 |
| 性器カンジダ症 | 1 (0.2) | 0 | 0 |
| 陰部ヘルペス | 4 (0.8) | 3 (0.6) | 1 (0.3) |
| 陰部帯状疱疹 | 1 (0.2) | 0 | 0 |
| 泌尿生殖器感染 | 1 (0.2) | 0 | 0 |
| 歯肉炎 | 3 (0.6) | 5 (1.0) | 2 (0.5) |
| 肛径部膿瘍 | 0 | 1 (0.2) | 0 |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| H1N1インフルエンザ | 1 (0.2) | 0 | 0 |
| 手足口病 | 1 (0.2) | 0 | 0 |
| ヘリコバクター感染 | 1 (0.2) | 0 | 1 (0.3) |
| B型肝炎再活性化 | 1 (0.2) | 0 | 0 |
| E型肝炎 | 0 | 0 | 1 (0.3) |
| 単純ヘルペス | 4 (0.8) | 17 (3.2) | 1 (0.3) |
| ヘルペスウイルス感染 | 1 (0.2) | 1 (0.2) | 0 |
| 帯状疱疹 | 16 (3.1) | 32 (6.1) | 2 (0.5) |
| 麦粒腫 | 4 (0.8) | 1 (0.2) | 0 |
| 膿痂疹 | 0 | 1 (0.2) | 0 |
| 伝染性単核症 | 0 | 1 (0.2) | 0 |
| インフルエンザ | 18 (3.4) | 19 (3.6) | 3 (0.8) |
| クレブシエラ感染 | 1 (0.2) | 0 | 0 |
| 喉頭炎 | 4 (0.8) | 5 (1.0) | 1 (0.3) |
| 潜伏結核 | 7 (1.3) | 2 (0.4) | 3 (0.8) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 限局性感染 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 下気道感染 | 5 (1.0) | 4 (0.8) | 5 (1.3) |
| 肺感染 | 0 | 2 (0.4) | 0 |
| ライム病 | 0 | 0 | 2 (0.5) |
| リンパ管炎 | 0 | 1 (0.2) | 0 |
| 爪床感染 | 0 | 2 (0.4) | 0 |
| 爪感染 | 1 (0.2) | 5 (1.0) | 0 |
| 鼻ヘルペス | 0 | 2 (0.4) | 2 (0.5) |
| 上咽頭炎 | 51 (9.7) | 64 (12.2) | 52 (13.2) |
| 爪真菌症 | 0 | 1 (0.2) | 1 (0.3) |
| 口腔カンジダ症 | 4 (0.8) | 6 (1.1) | 1 (0.3) |
| 口腔真菌感染 | 0 | 2 (0.4) | 0 |
| 口腔ヘルペス | 13 (2.5) | 46 (8.7) | 15 (3.8) |
| 口腔感染 | 0 | 1 (0.2) | 0 |
| 精巣炎 | 0 | 0 | 1 (0.3) |

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Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 中咽頭カンジダ症 | 0 | 1 (0.2) | 0 |
| 骨髄炎 | 0 | 0 | 1 (0.3) |
| 外耳炎 | 0 | 1 (0.2) | 1 (0.3) |
| 中耳炎 | 0 | 1 (0.2) | 2 (0.5) |
| 急性中耳炎 | 0 | 3 (0.6) | 2 (0.5) |
| 子宮傍組織炎 | 1 (0.2) | 0 | 0 |
| 爪囲炎 | 3 (0.6) | 4 (0.8) | 2 (0.5) |
| パルボウイルス感染 | 0 | 0 | 1 (0.3) |
| 軟骨膜炎 | 0 | 1 (0.2) | 0 |
| 歯周炎 | 4 (0.8) | 2 (0.4) | 0 |
| 咽頭炎 | 16 (3.1) | 14 (2.7) | 10 (2.5) |
| レンサ球菌性咽頭炎 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 咽頭扁桃炎 | 2 (0.4) | 0 | 0 |
| ニューモシスチス・イロベチイ肺炎 | 0 | 1 (0.2) | 0 |
| 肺炎 | 9 (1.7) | 7 (1.3) | 7 (1.8) |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| レンサ球菌性肺炎 | 0 | 1 (0.2) | 0 |
| 前立腺感染 | 0 | 1 (0.2) | 0 |
| 歯髄炎 | 2 (0.4) | 0 | 0 |
| 化膿性分泌物 | 0 | 1 (0.2) | 0 |
| 腎盂腎炎 | 0 | 1 (0.2) | 0 |
| 急性腎盂腎炎 | 0 | 1 (0.2) | 0 |
| 膿尿 | 0 | 0 | 1 (0.3) |
| 膿疱性皮疹 | 0 | 4 (0.8) | 0 |
| 気道感染 | 15 (2.9) | 12 (2.3) | 8 (2.0) |
| ウイルス性気道感染 | 5 (1.0) | 12 (2.3) | 5 (1.3) |
| 鼻炎 | 4 (0.8) | 8 (1.5) | 4 (1.0) |
| サルモネラ症 | 0 | 0 | 1 (0.3) |
| 卵管炎 | 0 | 1 (0.2) | 0 |
| 敗血症 | 2 (0.4) | 0 | 0 |
| 副鼻腔炎 | 15 (2.9) | 18 (3.4) | 9 (2.3) |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 細菌性副鼻腔炎 | 1 (0.2) | 0 | 0 |
| 皮膚細菌感染 | 1 (0.2) | 1 (0.2) | 0 |
| 皮膚感染 | 3 (0.6) | 2 (0.4) | 3 (0.8) |
| 軟部組織感染 | 0 | 0 | 3 (0.8) |
| ブドウ球菌性菌血症 | 0 | 1 (0.2) | 0 |
| ブドウ球菌感染 | 1 (0.2) | 0 | 1 (0.3) |
| ブドウ球菌性敗血症 | 0 | 1 (0.2) | 0 |
| ブドウ球菌皮膚感染 | 1 (0.2) | 1 (0.2) | 0 |
| 皮下組織膿瘍 | 0 | 1 (0.2) | 0 |
| 股部白癬 | 0 | 0 | 1 (0.3) |
| 白癬感染 | 1 (0.2) | 0 | 1 (0.3) |
| 手白癬 | 0 | 1 (0.2) | 0 |
| 足部白癬 | 2 (0.4) | 7 (1.3) | 1 (0.3) |
| 癜風 | 2 (0.4) | 0 | 0 |
| 扁桃炎 | 7 (1.3) | 6 (1.1) | 6 (1.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 細菌性扁桃炎 | 3 (0.6) | 1 (0.2) | 0 |
| 歯膿瘍 | 7 (1.3) | 0 | 0 |
| 歯感染 | 2 (0.4) | 5 (1.0) | 2 (0.5) |
| 気管炎 | 2 (0.4) | 4 (0.8) | 0 |
| 気管気管支炎 | 3 (0.6) | 1 (0.2) | 0 |
| トリコモナス症 | 0 | 0 | 1 (0.3) |
| 上気道感染 | 91 (17.4) | 98 (18.6) | 62 (15.7) |
| 尿路感染 | 39 (7.4) | 55 (10.5) | 18 (4.6) |
| 尿路性敗血症 | 0 | 1 (0.2) | 0 |
| 腟感染 | 0 | 1 (0.2) | 1 (0.3) |
| ウイルス感染 | 4 (0.8) | 7 (1.3) | 2 (0.5) |
| ウイルス性咽頭炎 | 0 | 2 (0.4) | 0 |
| ウイルス性副鼻腔炎 | 0 | 1 (0.2) | 0 |
| ウイルス性気管炎 | 1 (0.2) | 0 | 0 |
| ウイルス性上気道感染 | 11 (2.1) | 8 (1.5) | 5 (1.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 外陰部炎 | 1 (0.2) | 0 | 0 |
| 外陰部腟カンジダ症 | 4 (0.8) | 3 (0.6) | 1 (0.3) |
| 外陰腟真菌感染 | 4 (0.8) | 11 (2.1) | 2 (0.5) |
| 創傷感染 | 0 | 0 | 1 (0.3) |
| 傷害、中毒および処置合併症 | 59 (11.3) | 66 (12.5) | 51 (12.9) |
| 偶発的過量投与 | 0 | 0 | 1 (0.3) |
| 動物咬傷 | 1 (0.2) | 2 (0.4) | 0 |
| 足関節部骨折 | 0 | 1 (0.2) | 0 |
| 節足動物咬傷 | 4 (0.8) | 2 (0.4) | 4 (1.0) |
| 節足動物刺傷 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 背部損傷 | 1 (0.2) | 0 | 0 |
| 第1度熱傷 | 0 | 1 (0.2) | 0 |
| 軟骨損傷 | 0 | 1 (0.2) | 0 |
| 鎖骨骨折 | 0 | 1 (0.2) | 0 |
| 粉砕骨折 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | |
| 脳振盪 | 0 | 1 (0.2) | 0 |
| 挫傷 | 6 (1.1) | 5 (1.0) | 8 (2.0) |
| 角膜擦過傷 | 0 | 0 | 1 (0.3) |
| 上顆炎 | 0 | 1 (0.2) | 1 (0.3) |
| 転倒 | 4 (0.8) | 7 (1.3) | 5 (1.3) |
| 大腿骨骨折 | 0 | 1 (0.2) | 0 |
| 腓骨骨折 | 1 (0.2) | 0 | 1 (0.3) |
| 足骨折 | 4 (0.8) | 0 | 0 |
| 仙骨骨折 | 0 | 1 (0.2) | 0 |
| 手骨折 | 1 (0.2) | 2 (0.4) | 0 |
| 上腕骨骨折 | 1 (0.2) | 2 (0.4) | 0 |
| 腸脛靱帯症候群 | 0 | 0 | 1 (0.3) |
| 注射に伴う反応 | 0 | 0 | 1 (0.3) |
| 関節脱臼 | 1 (0.2) | 1 (0.2) | 0 |
| 関節損傷 | 2 (0.4) | 2 (0.4) | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | |
| 靭帯損傷 | 0 | 1 (0.2) | 0 |
| 靭帯断裂 | 0 | 2 (0.4) | 0 |
| 靭帯捻挫 | 2 (0.4) | 4 (0.8) | 2 (0.5) |
| 四肢損傷 | 3 (0.6) | 0 | 2 (0.5) |
| 口唇損傷 | 0 | 1 (0.2) | 0 |
| 半月板損傷 | 0 | 1 (0.2) | 1 (0.3) |
| 筋損傷 | 0 | 1 (0.2) | 0 |
| 筋断裂 | 2 (0.4) | 0 | 0 |
| 肉離れ | 1 (0.2) | 3 (0.6) | 3 (0.8) |
| 椎弓切除後症候群 | 0 | 1 (0.2) | 0 |
| 処置後出血 | 0 | 1 (0.2) | 0 |
| 処置後炎症 | 0 | 0 | 1 (0.3) |
| 外傷後頚部症候群 | 1 (0.2) | 0 | 0 |
| 処置による疼痛 | 0 | 1 (0.2) | 0 |
| 橈骨骨折 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | |
| 肋骨骨折 | 0 | 2 (0.4) | 0 |
| 交通事故 | 1 (0.2) | 2 (0.4) | 0 |
| 引っかき傷 | 1 (0.2) | 0 | 0 |
| 皮膚擦過傷 | 2 (0.4) | 1 (0.2) | 4 (1.0) |
| 皮膚裂傷 | 4 (0.8) | 1 (0.2) | 1 (0.3) |
| ストレス骨折 | 0 | 1 (0.2) | 1 (0.3) |
| 滑膜断裂 | 1 (0.2) | 0 | 0 |
| 腱断裂 | 0 | 2 (0.4) | 2 (0.5) |
| 熱傷 | 2 (0.4) | 1 (0.2) | 3 (0.8) |
| 脛骨骨折 | 1 (0.2) | 0 | 0 |
| 歯牙破折 | 6 (1.1) | 1 (0.2) | 2 (0.5) |
| 各種物質毒性 | 1 (0.2) | 1 (0.2) | 0 |
| 外傷性血腫 | 2 (0.4) | 0 | 0 |
| 上肢骨折 | 0 | 2 (0.4) | 1 (0.3) |
| 創傷 | 1 (0.2) | 2 (0.4) | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | |
| 創離開 | 0 | 0 | 1 (0.3) |
| 手首関節骨折 | 1 (0.2) | 1 (0.2) | 0 |
| 臨床検査 | 227 (43.3) | 303 (57.6) | 177 (44.9) |
| アラニンアミノトランスフェラーゼ増加 | 46 (8.8) | 43 (8.2) | 44 (11.2) |
| アルドラーゼ増加 | 0 | 1 (0.2) | 0 |
| αヒドロキシ酪酸脱水素酵素増加 | 0 | 1 (0.2) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 32 (6.1) | 30 (5.7) | 27 (6.8) |
| 細菌検査陽性 | 1 (0.2) | 1 (0.2) | 0 |
| 血中アルカリホスファターゼ増加 | 2 (0.4) | 0 | 1 (0.3) |
| 血中ビリルビン増加 | 1 (0.2) | 0 | 4 (1.0) |
| 血中コレステロール増加 | 5 (1.0) | 4 (0.8) | 0 |
| 血中クレアチンホスホキナーゼ増加 | 75 (14.3) | 113 (21.5) | 36 (9.1) |
| 血中クレアチニン増加 | 5 (1.0) | 6 (1.1) | 3 (0.8) |
| 血中ブドウ糖異常 | 2 (0.4) | 0 | 0 |
| 血中ブドウ糖増加 | 5 (1.0) | 1 (0.2) | 3 (0.8) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| 血中乳酸脱水素酵素増加 | 0 | 1 (0.2) | 0 |
| 血中リン減少 | 1 (0.2) | 1 (0.2) | 0 |
| 血中カリウム増加 | 1 (0.2) | 5 (1.0) | 1 (0.3) |
| 血圧上昇 | 6 (1.1) | 5 (1.0) | 5 (1.3) |
| 血中甲状腺刺激ホルモン減少 | 1 (0.2) | 0 | 0 |
| 血中トリグリセリド減少 | 0 | 0 | 1 (0.3) |
| 血中トリグリセリド増加 | 2 (0.4) | 1 (0.2) | 0 |
| 血中尿素増加 | 0 | 4 (0.8) | 0 |
| 血中尿酸増加 | 1 (0.2) | 3 (0.6) | 0 |
| 心電図T波逆転 | 0 | 1 (0.2) | 0 |
| 心電図異常 | 0 | 0 | 1 (0.3) |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 1 (0.2) | 0 |
| ヘモグロビン減少 | 1 (0.2) | 5 (1.0) | 0 |
| ヘリコバクター検査陽性 | 0 | 1 (0.2) | 0 |
| 肝酵素上昇 | 3 (0.6) | 5 (1.0) | 9 (2.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| 高比重リポ蛋白増加 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| 未熟顆粒球数増加 | 1 (0.2) | 0 | 0 |
| 眼圧上昇 | 0 | 1 (0.2) | 0 |
| 肝機能検査値上昇 | 6 (1.1) | 6 (1.1) | 1 (0.3) |
| 低比重リポ蛋白減少 | 0 | 0 | 1 (0.3) |
| 低比重リポ蛋白増加 | 3 (0.6) | 2 (0.4) | 0 |
| リンパ球数減少 | 2 (0.4) | 4 (0.8) | 0 |
| 平均赤血球容積増加 | 2 (0.4) | 6 (1.1) | 1 (0.3) |
| 筋酵素上昇 | 1 (0.2) | 0 | 0 |
| 骨髄球存在 | 0 | 1 (0.2) | 0 |
| 好中球数減少 | 2 (0.4) | 7 (1.3) | 5 (1.3) |
| 好中球数増加 | 0 | 0 | 1 (0.3) |
| 好中球百分率増加 | 0 | 0 | 1 (0.3) |
| 血小板数増加 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 前立腺特異性抗原異常 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| 総蛋白増加 | 1 (0.2) | 0 | 0 |
| 尿中蛋白陽性 | 1 (0.2) | 0 | 1 (0.3) |
| 赤血球数減少 | 0 | 4 (0.8) | 1 (0.3) |
| 血沈亢進 | 1 (0.2) | 1 (0.2) | 0 |
| 血清フェリチン減少 | 0 | 1 (0.2) | 0 |
| トランスアミナーゼ上昇 | 5 (1.0) | 11 (2.1) | 11 (2.8) |
| 超音波スキャン異常 | 0 | 0 | 1 (0.3) |
| 尿検査異常 | 0 | 1 (0.2) | 0 |
| 尿中白血球エステラーゼ陽性 | 0 | 0 | 2 (0.5) |
| 超低比重リポ蛋白増加 | 2 (0.4) | 5 (1.0) | 1 (0.3) |
| ビタミンB12減少 | 0 | 0 | 1 (0.3) |
| 体重減少 | 2 (0.4) | 0 | 1 (0.3) |
| 体重増加 | 3 (0.6) | 4 (0.8) | 3 (0.8) |
| 白血球数減少 | 1 (0.2) | 13 (2.5) | 6 (1.5) |
| 尿中白血球陽性 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 代謝および栄養障害 | 61 (11.6) | 62 (11.8) | 46 (11.7) |
| 炭水化物不耐症 | 1 (0.2) | 0 | 1 (0.3) |
| 糖尿病 | 7 (1.3) | 3 (0.6) | 5 (1.3) |
| コントロール不良の糖尿病 | 1 (0.2) | 0 | 1 (0.3) |
| 脂質異常症 | 6 (1.1) | 11 (2.1) | 4 (1.0) |
| 体液貯留 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 耐糖能障害 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| グルテン過敏症 | 0 | 1 (0.2) | 0 |
| 痛風 | 1 (0.2) | 0 | 1 (0.3) |
| 高カルシウム血症 | 0 | 1 (0.2) | 0 |
| 高コレステロール血症 | 4 (0.8) | 12 (2.3) | 4 (1.0) |
| 高血糖 | 7 (1.3) | 7 (1.3) | 8 (2.0) |
| 高カリウム血症 | 1 (0.2) | 1 (0.2) | 0 |
| 高脂血症 | 1 (0.2) | 6 (1.1) | 1 (0.3) |
| 高トリグリセリド血症 | 1 (0.2) | 2 (0.4) | 6 (1.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 代謝および栄養障害 (Cont.) | | | |
| 高尿酸血症 | 7 (1.3) | 9 (1.7) | 4 (1.0) |
| 低カルシウム血症 | 1 (0.2) | 0 | 0 |
| 低血糖 | 1 (0.2) | 0 | 1 (0.3) |
| 低カリウム血症 | 2 (0.4) | 0 | 1 (0.3) |
| 低ナトリウム血症 | 0 | 1 (0.2) | 0 |
| 低リン酸血症 | 1 (0.2) | 0 | 0 |
| 空腹時血中ブドウ糖不良 | 0 | 1 (0.2) | 0 |
| 食欲亢進 | 1 (0.2) | 0 | 0 |
| インスリン抵抗性 | 1 (0.2) | 1 (0.2) | 0 |
| 鉄欠乏 | 1 (0.2) | 0 | 1 (0.3) |
| 代謝性アシドーシス | 0 | 0 | 1 (0.3) |
| 肥満 | 2 (0.4) | 0 | 0 |
| 2型糖尿病 | 6 (1.1) | 2 (0.4) | 2 (0.5) |
| ビタミンB群欠乏 | 2 (0.4) | 0 | 0 |
| ビタミンB12欠乏 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 代謝および栄養障害 (Cont.) | | | |
| ビタミンD欠乏 | 3 (0.6) | 2 (0.4) | 1 (0.3) |
| 筋骨格系および結合組織障害 | 98 (18.7) | 115 (21.9) | 85 (21.5) |
| 関節痛 | 7 (1.3) | 8 (1.5) | 5 (1.3) |
| 背部痛 | 9 (1.7) | 18 (3.4) | 15 (3.8) |
| 滑液包炎 | 4 (0.8) | 4 (0.8) | 2 (0.5) |
| 頚部脊柱管狭窄症 | 1 (0.2) | 0 | 0 |
| 軟骨疾患 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 肋軟骨炎 | 1 (0.2) | 0 | 1 (0.3) |
| デュプイトラン拘縮 | 0 | 0 | 1 (0.3) |
| 線維筋痛 | 0 | 0 | 1 (0.3) |
| 側腹部痛 | 0 | 1 (0.2) | 0 |
| 足変形 | 1 (0.2) | 0 | 0 |
| 出血性関節症 | 1 (0.2) | 0 | 0 |
| 高クレアチン血症 | 0 | 1 (0.2) | 0 |
| 椎間板線維輪断裂 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | |
| 椎間板変性症 | 0 | 2 (0.4) | 0 |
| 椎間板障害 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 椎間板突出 | 1 (0.2) | 3 (0.6) | 5 (1.3) |
| 関節過伸展 | 1 (0.2) | 0 | 0 |
| 関節雑音 | 0 | 1 (0.2) | 0 |
| 関節硬直 | 1 (0.2) | 0 | 0 |
| 関節腫脹 | 1 (0.2) | 0 | 2 (0.5) |
| 腰部脊柱管狭窄症 | 1 (0.2) | 0 | 1 (0.3) |
| 咀嚼障害 | 0 | 0 | 1 (0.3) |
| 筋肉疲労 | 1 (0.2) | 0 | 0 |
| 筋痙縮 | 6 (1.1) | 6 (1.1) | 4 (1.0) |
| 筋緊張 | 1 (0.2) | 0 | 0 |
| 筋力低下 | 1 (0.2) | 2 (0.4) | 0 |
| 筋骨格系胸痛 | 2 (0.4) | 4 (0.8) | 2 (0.5) |
| 筋骨格痛 | 4 (0.8) | 3 (0.6) | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | |
| 筋骨格硬直 | 0 | 1 (0.2) | 0 |
| 筋肉痛 | 3 (0.6) | 1 (0.2) | 2 (0.5) |
| 筋膜疼痛症候群 | 0 | 1 (0.2) | 0 |
| 筋炎 | 1 (0.2) | 0 | 0 |
| 頚部痛 | 1 (0.2) | 3 (0.6) | 2 (0.5) |
| 変形性関節症 | 4 (0.8) | 4 (0.8) | 5 (1.3) |
| 骨端症 | 2 (0.4) | 0 | 1 (0.3) |
| 骨壊死 | 0 | 4 (0.8) | 0 |
| 骨粗鬆症 | 2 (0.4) | 1 (0.2) | 1 (0.3) |
| 四肢痛 | 5 (1.0) | 3 (0.6) | 0 |
| 関節周囲炎 | 0 | 1 (0.2) | 0 |
| 足底筋膜炎 | 0 | 4 (0.8) | 3 (0.8) |
| 乾癬性関節症 | 19 (3.6) | 25 (4.8) | 19 (4.8) |
| 肩回旋筋腱板症候群 | 2 (0.4) | 0 | 3 (0.8) |
| 仙腸骨炎 | 1 (0.2) | 0 | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | |
| 軟部組織腫脹 | 1 (0.2) | 0 | 0 |
| 脊椎不安定 | 0 | 1 (0.2) | 0 |
| 変形性脊椎症 | 4 (0.8) | 4 (0.8) | 1 (0.3) |
| 脊椎痛 | 2 (0.4) | 1 (0.2) | 0 |
| 脊椎後方すべり症 | 0 | 1 (0.2) | 0 |
| 脊柱管狭窄症 | 1 (0.2) | 0 | 1 (0.3) |
| 脊椎すべり症 | 0 | 0 | 2 (0.5) |
| 滑液嚢腫 | 1 (0.2) | 2 (0.4) | 0 |
| 滑膜炎 | 1 (0.2) | 0 | 0 |
| 腱障害 | 0 | 0 | 1 (0.3) |
| 腱鞘炎 | 1 (0.2) | 0 | 0 |
| 狭窄性腱鞘炎 | 0 | 1 (0.2) | 0 |
| 弾発指 | 1 (0.2) | 0 | 0 |
| 椎間孔狭窄 | 0 | 1 (0.2) | 0 |
| 翼状肩甲骨 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 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） | 16 (3.1) | 16 (3.0) | 9 (2.3) |
| 肛門性器疣贅 | 2 (0.4) | 1 (0.2) | 0 |
| 基底細胞癌 | 1 (0.2) | 2 (0.4) | 2 (0.5) |
| 肺の良性新生物 | 0 | 0 | 1 (0.3) |
| 副腎の良性新生物 | 0 | 1 (0.2) | 0 |
| ボーエン病 | 0 | 1 (0.2) | 0 |
| 乳腺線維腫 | 1 (0.2) | 0 | 0 |
| 大腸腺腫 | 1 (0.2) | 1 (0.2) | 0 |
| 遠隔転移を伴う結腸癌 | 0 | 0 | 1 (0.3) |
| 肝臓血管腫 | 0 | 0 | 1 (0.3) |
| 脂肪腫 | 1 (0.2) | 0 | 0 |
| 乳房脂肪腫 | 1 (0.2) | 0 | 0 |
| 肺腺癌 | 0 | 1 (0.2) | 0 |
| 遠隔転移を伴う肺癌 | 1 (0.2) | 0 | 0 |
| 悪性黒色腫 | 1 (0.2) | 0 | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 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）<br>(Cont.) | | | |
| メラノサイト性母斑 | 0 | 1 (0.2) | 0 |
| 単クローン性免疫グロブリン血症 | 0 | 1 (0.2) | 0 |
| 骨髄異形成症候群 | 1 (0.2) | 0 | 0 |
| 神経内分泌癌 | 1 (0.2) | 0 | 0 |
| 卵巣癌 | 0 | 0 | 1 (0.3) |
| 遠隔転移を伴う膵癌 | 0 | 0 | 1 (0.3) |
| 脂漏性角化症 | 1 (0.2) | 0 | 1 (0.3) |
| 皮膚乳頭腫 | 3 (0.6) | 4 (0.8) | 0 |
| 扁平上皮癌 | 0 | 1 (0.2) | 0 |
| 皮膚有棘細胞癌 | 1 (0.2) | 1 (0.2) | 0 |
| 子宮癌 | 0 | 0 | 1 (0.3) |
| 子宮平滑筋腫 | 0 | 1 (0.2) | 0 |
| 神経系障害 | 68 (13.0) | 69 (13.1) | 69 (17.5) |
| 健忘 | 0 | 1 (0.2) | 0 |
| 筋萎縮性側索硬化症 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 灼熱感 | 0 | 0 | 1 (0.3) |
| 手根管症候群 | 0 | 3 (0.6) | 2 (0.5) |
| 中枢性肺胞性低換気 | 1 (0.2) | 0 | 0 |
| 脳血管発作 | 0 | 0 | 2 (0.5) |
| 頚髄神経根障害 | 1 (0.2) | 0 | 0 |
| 頚腕症候群 | 1 (0.2) | 0 | 0 |
| 認知障害 | 1 (0.2) | 0 | 0 |
| 頚頭蓋症候群 | 0 | 0 | 2 (0.5) |
| 認知症 | 0 | 0 | 1 (0.3) |
| 脱髄 | 0 | 1 (0.2) | 0 |
| 糖尿病性ニューロパチー | 0 | 1 (0.2) | 0 |
| 注意力障害 | 1 (0.2) | 0 | 0 |
| 浮動性めまい | 3 (0.6) | 5 (1.0) | 6 (1.5) |
| 体位性めまい | 0 | 1 (0.2) | 1 (0.3) |
| 異常感覚 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 味覚異常 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 顔面麻痺 | 0 | 0 | 1 (0.3) |
| 蟻走感 | 1 (0.2) | 0 | 0 |
| 頭痛 | 31 (5.9) | 24 (4.6) | 25 (6.3) |
| 肝性脳症 | 0 | 0 | 1 (0.3) |
| 感覚鈍麻 | 2 (0.4) | 2 (0.4) | 3 (0.8) |
| 味覚減退 | 0 | 0 | 1 (0.3) |
| 肋間神経痛 | 1 (0.2) | 1 (0.2) | 0 |
| 虚血性ニューロパチー | 0 | 1 (0.2) | 0 |
| 虚血性脳卒中 | 1 (0.2) | 0 | 0 |
| ラクナ脳卒中 | 1 (0.2) | 0 | 0 |
| 嗜眠 | 1 (0.2) | 1 (0.2) | 0 |
| 腰髄神経根障害 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 記憶障害 | 2 (0.4) | 2 (0.4) | 0 |
| 片頭痛 | 2 (0.4) | 6 (1.1) | 4 (1.0) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 神経痛 | 0 | 1 (0.2) | 0 |
| 末梢性ニューロパチー | 0 | 1 (0.2) | 0 |
| 錯感覚 | 2 (0.4) | 5 (1.0) | 0 |
| 神経周囲嚢胞 | 0 | 0 | 1 (0.3) |
| 末梢性感覚ニューロパチー | 0 | 2 (0.4) | 0 |
| 睡眠の質低下 | 0 | 0 | 2 (0.5) |
| ヘルペス後神経痛 | 1 (0.2) | 2 (0.4) | 0 |
| 神経根痛 | 1 (0.2) | 0 | 0 |
| 神経根障害 | 0 | 0 | 1 (0.3) |
| 坐骨神経痛 | 6 (1.1) | 1 (0.2) | 4 (1.0) |
| 感覚障害 | 0 | 2 (0.4) | 0 |
| 副鼻腔炎に伴う頭痛 | 1 (0.2) | 0 | 1 (0.3) |
| 傾眠 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 失神 | 0 | 0 | 1 (0.3) |
| 緊張性頭痛 | 3 (0.6) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 一過性脳虚血発作 | 0 | 1 (0.2) | 1 (0.3) |
| 振戦 | 0 | 1 (0.2) | 1 (0.3) |
| 三叉神経痛 | 1 (0.2) | 0 | 1 (0.3) |
| 椎骨脳底動脈不全 | 0 | 1 (0.2) | 0 |
| 製品の問題 | 1 (0.2) | 0 | 0 |
| 医療機器破損 | 1 (0.2) | 0 | 0 |
| 精神障害 | 29 (5.5) | 21 (4.0) | 12 (3.0) |
| 不安 | 3 (0.6) | 5 (1.0) | 4 (1.0) |
| 不安障害 | 3 (0.6) | 1 (0.2) | 0 |
| 燃え尽き症候群 | 1 (0.2) | 0 | 0 |
| 抑うつ気分 | 0 | 0 | 3 (0.8) |
| うつ病 | 5 (1.0) | 7 (1.3) | 2 (0.5) |
| 全般性不安障害 | 1 (0.2) | 0 | 0 |
| 不眠症 | 13 (2.5) | 8 (1.5) | 3 (0.8) |
| 睡眠障害 | 2 (0.4) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 精神障害 (Cont.) | | | |
| ストレス | 1 (0.2) | 0 | 0 |
| 腎および尿路障害 | 36 (6.9) | 33 (6.3) | 23 (5.8) |
| 膀胱脱 | 1 (0.2) | 0 | 0 |
| 尿路結石 | 2 (0.4) | 1 (0.2) | 0 |
| 慢性腎臓病 | 2 (0.4) | 2 (0.4) | 0 |
| 結晶尿 | 0 | 1 (0.2) | 0 |
| 腺性膀胱炎 | 1 (0.2) | 0 | 0 |
| 糖尿病性腎症 | 0 | 1 (0.2) | 0 |
| 排尿困難 | 1 (0.2) | 3 (0.6) | 2 (0.5) |
| 糖尿 | 0 | 0 | 1 (0.3) |
| 血尿 | 7 (1.3) | 8 (1.5) | 3 (0.8) |
| 緊張性膀胱 | 1 (0.2) | 1 (0.2) | 0 |
| 白血球尿 | 4 (0.8) | 2 (0.4) | 0 |
| 尿意切迫 | 1 (0.2) | 0 | 0 |
| 腎結石症 | 4 (0.8) | 4 (0.8) | 3 (0.8) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 腎および尿路障害 (Cont.) | | | |
| 腎症 | 1 (0.2) | 0 | 0 |
| 頻尿 | 0 | 1 (0.2) | 0 |
| 多尿 | 0 | 0 | 1 (0.3) |
| 蛋白尿 | 4 (0.8) | 6 (1.1) | 5 (1.3) |
| 腎盂腎杯拡張症 | 0 | 1 (0.2) | 0 |
| 腎仙痛 | 1 (0.2) | 0 | 2 (0.5) |
| 腎嚢胞 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 腎機能障害 | 1 (0.2) | 0 | 0 |
| 腎静脈圧迫 | 0 | 1 (0.2) | 0 |
| 無菌性膿尿 | 0 | 0 | 1 (0.3) |
| 腹圧性尿失禁 | 0 | 0 | 1 (0.3) |
| 尿管結石症 | 2 (0.4) | 0 | 1 (0.3) |
| 尿失禁 | 1 (0.2) | 0 | 1 (0.3) |
| 尿閉 | 1 (0.2) | 0 | 0 |
| 尿路の炎症 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 生殖系および乳房障害 | 31 (5.9) | 18 (3.4) | 11 (2.8) |
| 腺筋症 | 0 | 1 (0.2) | 0 |
| 無月経 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 良性前立腺肥大症 | 1 (0.2) | 4 (0.8) | 1 (0.3) |
| 乳房嚢胞 | 1 (0.2) | 0 | 0 |
| 乳房障害 | 1 (0.2) | 0 | 0 |
| 乳房線維化 | 1 (0.2) | 0 | 0 |
| 乳房腫瘤 | 0 | 0 | 2 (0.5) |
| 前立腺結石 | 1 (0.2) | 0 | 0 |
| 子宮頚部上皮異形成 | 1 (0.2) | 0 | 0 |
| 子宮頚管ポリープ | 0 | 1 (0.2) | 1 (0.3) |
| 膀胱瘤 | 1 (0.2) | 0 | 0 |
| 月経困難症 | 0 | 0 | 1 (0.3) |
| 子宮頚外反 | 0 | 1 (0.2) | 0 |
| 子宮内膜増殖症 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | |
| 子宮内膜症 | 0 | 0 | 1 (0.3) |
| 精巣上体嚢胞 | 1 (0.2) | 0 | 0 |
| 勃起不全 | 0 | 1 (0.2) | 0 |
| 線維嚢胞性乳腺疾患 | 0 | 1 (0.2) | 0 |
| 閉経期症状 | 0 | 1 (0.2) | 0 |
| 月経過多 | 3 (0.6) | 0 | 0 |
| 不規則月経 | 4 (0.8) | 1 (0.2) | 0 |
| 不正子宮出血 | 1 (0.2) | 1 (0.2) | 0 |
| 卵巣嚢胞 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 骨盤痛 | 1 (0.2) | 0 | 0 |
| 前立腺閉塞 | 1 (0.2) | 0 | 0 |
| 前立腺炎 | 3 (0.6) | 0 | 1 (0.3) |
| 前立腺腫大 | 0 | 1 (0.2) | 0 |
| 精巣障害 | 1 (0.2) | 0 | 0 |
| 精巣腫脹 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | |
| 子宮出血 | 1 (0.2) | 0 | 0 |
| 子宮ポリープ | 1 (0.2) | 0 | 0 |
| 子宮脱 | 2 (0.4) | 0 | 0 |
| 膣出血 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 外陰膣そう痒症 | 1 (0.2) | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 60 (11.4) | 79 (15.0) | 55 (13.9) |
| アレルギー性咽頭炎 | 1 (0.2) | 0 | 0 |
| 喘息 | 2 (0.4) | 2 (0.4) | 2 (0.5) |
| 無気肺 | 0 | 1 (0.2) | 1 (0.3) |
| 慢性気管支炎 | 0 | 2 (0.4) | 0 |
| 気管支痙攣 | 2 (0.4) | 1 (0.2) | 0 |
| カタル | 0 | 0 | 1 (0.3) |
| 息詰まり | 0 | 0 | 1 (0.3) |
| 慢性閉塞性肺疾患 | 3 (0.6) | 4 (0.8) | 1 (0.3) |
| 咳嗽 | 14 (2.7) | 28 (5.3) | 9 (2.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | |
| 発声障害 | 1 (0.2) | 2 (0.4) | 0 |
| 呼吸困難 | 5 (1.0) | 6 (1.1) | 2 (0.5) |
| 労作性呼吸困難 | 1 (0.2) | 1 (0.2) | 0 |
| 鼻出血 | 3 (0.6) | 1 (0.2) | 2 (0.5) |
| 喀血 | 0 | 0 | 1 (0.3) |
| 下気道の炎症 | 0 | 0 | 1 (0.3) |
| 肺浸潤 | 0 | 0 | 1 (0.3) |
| 鼻閉 | 0 | 2 (0.4) | 3 (0.8) |
| 鼻部不快感 | 1 (0.2) | 0 | 0 |
| 鼻の炎症 | 0 | 1 (0.2) | 0 |
| 鼻閉塞 | 1 (0.2) | 0 | 0 |
| 鼻潰瘍 | 0 | 3 (0.6) | 0 |
| 口腔咽頭不快感 | 0 | 0 | 1 (0.3) |
| 口腔咽頭痛 | 7 (1.3) | 8 (1.5) | 12 (3.0) |
| 咽頭の炎症 | 0 | 1 (0.2) | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | |
| 胸水 | 0 | 0 | 2 (0.5) |
| 胸膜炎 | 1 (0.2) | 0 | 0 |
| 肺臓炎 | 0 | 0 | 1 (0.3) |
| 自然気胸 | 0 | 1 (0.2) | 0 |
| 肺塞栓症 | 2 (0.4) | 2 (0.4) | 0 |
| 肺線維症 | 0 | 1 (0.2) | 0 |
| 肺高血圧症 | 1 (0.2) | 0 | 0 |
| 肺腫瘤 | 0 | 2 (0.4) | 1 (0.3) |
| 呼吸窮迫 | 1 (0.2) | 0 | 0 |
| 気道うっ血 | 0 | 0 | 1 (0.3) |
| アレルギー性鼻炎 | 5 (1.0) | 2 (0.4) | 1 (0.3) |
| 鼻漏 | 3 (0.6) | 2 (0.4) | 3 (0.8) |
| 副鼻腔うっ血 | 0 | 1 (0.2) | 1 (0.3) |
| 副鼻腔障害 | 1 (0.2) | 0 | 0 |
| 睡眠時無呼吸症候群 | 2 (0.4) | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | |
| 喀痰増加 | 1 (0.2) | 0 | 0 |
| 咽喉刺激感 | 0 | 3 (0.6) | 0 |
| 扁桃肥大 | 0 | 0 | 2 (0.5) |
| 扁桃の炎症 | 0 | 0 | 2 (0.5) |
| 上気道の炎症 | 2 (0.4) | 2 (0.4) | 1 (0.3) |
| 皮膚および皮下組織障害 | 75 (14.3) | 80 (15.2) | 86 (21.8) |
| 黒色表皮腫 | 1 (0.2) | 0 | 0 |
| ざ瘡 | 6 (1.1) | 8 (1.5) | 0 |
| 光線性口唇炎 | 0 | 1 (0.2) | 0 |
| 光線角化症 | 1 (0.2) | 0 | 1 (0.3) |
| 脱毛症 | 2 (0.4) | 1 (0.2) | 8 (2.0) |
| 血管浮腫 | 1 (0.2) | 0 | 0 |
| 水疱 | 3 (0.6) | 3 (0.6) | 1 (0.3) |
| 肝斑 | 0 | 1 (0.2) | 0 |
| 皮膚嚢腫 | 2 (0.4) | 2 (0.4) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 皮膚炎 | 2 (0.4) | 3 (0.6) | 4 (1.0) |
| ざ瘡様皮膚炎 | 0 | 3 (0.6) | 0 |
| アレルギー性皮膚炎 | 3 (0.6) | 4 (0.8) | 3 (0.8) |
| アトピー性皮膚炎 | 1 (0.2) | 0 | 0 |
| 接触皮膚炎 | 1 (0.2) | 1 (0.2) | 4 (1.0) |
| 薬疹 | 0 | 1 (0.2) | 1 (0.3) |
| 皮膚乾燥 | 0 | 3 (0.6) | 0 |
| 異汗性湿疹 | 1 (0.2) | 1 (0.2) | 0 |
| 湿疹 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 紅斑 | 2 (0.4) | 5 (1.0) | 4 (1.0) |
| 環状紅斑 | 0 | 0 | 1 (0.3) |
| 毛髪成長異常 | 1 (0.2) | 0 | 0 |
| 多汗症 | 2 (0.4) | 1 (0.2) | 0 |
| 過角化 | 0 | 0 | 2 (0.5) |
| 嵌入爪 | 2 (0.4) | 0 | 4 (1.0) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 間擦疹 | 1 (0.2) | 0 | 0 |
| 爪郭の炎症 | 0 | 1 (0.2) | 0 |
| 爪成長異常 | 1 (0.2) | 0 | 0 |
| 爪破損 | 1 (0.2) | 0 | 0 |
| 爪甲脱落症 | 2 (0.4) | 0 | 0 |
| 丘疹 | 0 | 1 (0.2) | 1 (0.3) |
| 口囲皮膚炎 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 光線過敏性反応 | 0 | 0 | 1 (0.3) |
| そう痒症 | 0 | 3 (0.6) | 10 (2.5) |
| 全身性そう痒症 | 1 (0.2) | 0 | 1 (0.3) |
| 乾癬 | 7 (1.3) | 7 (1.3) | 19 (4.8) |
| 膿疱性乾癬 | 0 | 1 (0.2) | 1 (0.3) |
| 発疹 | 3 (0.6) | 8 (1.5) | 5 (1.3) |
| 紅斑性皮疹 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 毛孔性皮疹 | 1 (0.2) | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 全身性皮疹 | 1 (0.2) | 0 | 2 (0.5) |
| 斑状皮疹 | 2 (0.4) | 1 (0.2) | 0 |
| 斑状丘疹状皮疹 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 丘疹性皮疹 | 1 (0.2) | 0 | 0 |
| そう痒性皮疹 | 0 | 0 | 2 (0.5) |
| 酒さ | 5 (1.0) | 2 (0.4) | 0 |
| 痂皮 | 0 | 1 (0.2) | 0 |
| 皮膚変色 | 1 (0.2) | 0 | 0 |
| 皮膚障害 | 0 | 1 (0.2) | 0 |
| 皮膚剥脱 | 0 | 1 (0.2) | 1 (0.3) |
| 皮膚亀裂 | 0 | 1 (0.2) | 0 |
| 皮膚出血 | 1 (0.2) | 0 | 0 |
| 皮膚色素過剰 | 1 (0.2) | 0 | 0 |
| 皮膚色素減少 | 0 | 1 (0.2) | 0 |
| 皮膚刺激 | 1 (0.2) | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 皮膚病変 | 4 (0.8) | 2 (0.4) | 2 (0.5) |
| 顔面腫脹 | 1 (0.2) | 0 | 0 |
| 蕁麻疹 | 5 (1.0) | 4 (0.8) | 3 (0.8) |
| 社会環境 | 3 (0.6) | 0 | 0 |
| 閉経 | 2 (0.4) | 0 | 0 |
| 職場でのストレス | 1 (0.2) | 0 | 0 |
| 血管障害 | 40 (7.6) | 39 (7.4) | 26 (6.6) |
| 大動脈瘤 | 0 | 1 (0.2) | 1 (0.3) |
| 大動脈硬化症 | 0 | 1 (0.2) | 0 |
| 動脈硬化症 | 0 | 1 (0.2) | 0 |
| 深部静脈血栓症 | 2 (0.4) | 0 | 1 (0.3) |
| 四肢壊死 | 0 | 1 (0.2) | 0 |
| 血腫 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| ほてり | 3 (0.6) | 1 (0.2) | 0 |
| 高血圧 | 31 (5.9) | 20 (3.8) | 13 (3.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.2.2

Treatment-Emergent Adverse Events per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 血管障害 (Cont.) | | | |
| 高血圧クリーゼ | 1 (0.2) | 0 | 1 (0.3) |
| 高血圧切迫症 | 0 | 1 (0.2) | 0 |
| リンパ浮腫 | 0 | 1 (0.2) | 1 (0.3) |
| 起立性低血圧 | 0 | 3 (0.6) | 0 |
| 末梢冷感 | 0 | 0 | 2 (0.5) |
| 末梢静脈疾患 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| レイノー現象 | 0 | 0 | 2 (0.5) |
| 血栓性静脈炎 | 0 | 0 | 1 (0.3) |
| 表在性血栓性静脈炎 | 0 | 3 (0.6) | 1 (0.3) |
| 静脈瘤 | 0 | 3 (0.6) | 0 |
| 血管炎 | 0 | 0 | 1 (0.3) |
| 血管拡張 | 0 | 1 (0.2) | 0 |
| 静脈性高血圧 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

表 4. 長期投与時の治験薬と関連ありの有害事象の 100 人年あたりの発現件数：MedDRA のプライマリー器官別大分類及び基本語別（安全性解析対象集団）

相互参照：M15-572 試験 CSR W24 Table 14.3__1.6.2

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| Any adverse event | 694 (132.4) | 910 (173.0) | 594 (150.6) |
| 血液およびリンパ系障害 | 54 (10.3) | 93 (17.7) | 34 (8.6) |
| 貧血 | 8 (1.5) | 12 (2.3) | 2 (0.5) |
| 大球性貧血 | 1 (0.2) | 1 (0.2) | 0 |
| 骨髄浮腫 | 0 | 1 (0.2) | 0 |
| 血球減少症 | 0 | 1 (0.2) | 0 |
| 赤血球減少症 | 0 | 1 (0.2) | 0 |
| 顆粒球減少症 | 0 | 3 (0.6) | 0 |
| 内出血発生の増加傾向 | 1 (0.2) | 1 (0.2) | 0 |
| 鉄欠乏性貧血 | 0 | 2 (0.4) | 0 |
| 白血球増加症 | 0 | 1 (0.2) | 0 |
| 白血球減少症 | 15 (2.9) | 20 (3.8) | 8 (2.0) |
| リンパ節症 | 1 (0.2) | 0 | 1 (0.3) |
| リンパ組織過形成 | 0 | 1 (0.2) | 0 |
| リンパ球減少症 | 15 (2.9) | 17 (3.2) | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 血液およびリンパ系障害 (Cont.) | | | |
| 大赤血球症 | 0 | 0 | 1 (0.3) |
| 好中球減少症 | 11 (2.1) | 26 (4.9) | 16 (4.1) |
| 好中球増加症 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 正色素性貧血 | 0 | 1 (0.2) | 0 |
| 正色素性正球性貧血 | 0 | 0 | 2 (0.5) |
| 血小板減少症 | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| 血小板増加症 | 0 | 2 (0.4) | 0 |
| 心臓障害 | 1 (0.2) | 3 (0.6) | 3 (0.8) |
| 心房細動 | 0 | 0 | 1 (0.3) |
| 冠動脈疾患 | 0 | 0 | 1 (0.3) |
| 動悸 | 1 (0.2) | 0 | 0 |
| 洞性徐脈 | 0 | 1 (0.2) | 0 |
| 頻脈 | 0 | 1 (0.2) | 0 |
| 発作性頻脈 | 0 | 1 (0.2) | 0 |
| 心室性期外収縮 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 先天性、家族性および遺伝性障害 | 1 (0.2) | 0 | 0 |
| 陰嚢水瘤 | 1 (0.2) | 0 | 0 |
| 耳および迷路障害 | 1 (0.2) | 0 | 2 (0.5) |
| 耳鳴 | 0 | 0 | 1 (0.3) |
| 回転性めまい | 0 | 0 | 1 (0.3) |
| 頭位性回転性めまい | 1 (0.2) | 0 | 0 |
| 内分泌障害 | 1 (0.2) | 0 | 0 |
| アンドロゲン欠乏症 | 1 (0.2) | 0 | 0 |
| 眼障害 | 5 (1.0) | 3 (0.6) | 1 (0.3) |
| 眼瞼痙攣 | 1 (0.2) | 0 | 0 |
| ドライアイ | 0 | 1 (0.2) | 0 |
| 眼痛 | 1 (0.2) | 0 | 0 |
| 虹彩毛様体炎 | 0 | 1 (0.2) | 0 |
| 瞼板腺炎 | 1 (0.2) | 0 | 1 (0.3) |
| 眼部不快感 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 眼障害 (Cont.) | | | |
| 霧視 | 1 (0.2) | 0 | 0 |
| 視力障害 | 1 (0.2) | 0 | 0 |
| 胃腸障害 | 55 (10.5) | 55 (10.5) | 38 (9.6) |
| 腹部不快感 | 1 (0.2) | 2 (0.4) | 0 |
| 腹部膨満 | 0 | 2 (0.4) | 0 |
| 腹痛 | 3 (0.6) | 0 | 0 |
| 上腹部痛 | 5 (1.0) | 8 (1.5) | 3 (0.8) |
| 口角口唇炎 | 1 (0.2) | 1 (0.2) | 0 |
| アフタ性潰瘍 | 2 (0.4) | 1 (0.2) | 1 (0.3) |
| 根尖肉芽腫 | 0 | 1 (0.2) | 0 |
| 大腸炎 | 1 (0.2) | 0 | 0 |
| 便秘 | 3 (0.6) | 3 (0.6) | 4 (1.0) |
| 下痢 | 8 (1.5) | 10 (1.9) | 6 (1.5) |
| 口内乾燥 | 0 | 1 (0.2) | 1 (0.3) |
| 十二指腸潰瘍 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 消化不良 | 2 (0.4) | 2 (0.4) | 0 |
| 小腸炎 | 0 | 1 (0.2) | 1 (0.3) |
| 腸炎 | 0 | 1 (0.2) | 0 |
| びらん性十二指腸炎 | 1 (0.2) | 0 | 0 |
| 変色便 | 1 (0.2) | 0 | 0 |
| 鼓腸 | 1 (0.2) | 2 (0.4) | 0 |
| 胃炎 | 2 (0.4) | 3 (0.6) | 1 (0.3) |
| びらん性胃炎 | 2 (0.4) | 0 | 0 |
| 胃十二指腸出血 | 1 (0.2) | 0 | 0 |
| 胃十二指腸潰瘍 | 0 | 1 (0.2) | 0 |
| 胃食道逆流性疾患 | 1 (0.2) | 0 | 0 |
| 痔核 | 1 (0.2) | 0 | 0 |
| 腸管ポリープ | 0 | 0 | 1 (0.3) |
| 口腔内白斑症 | 0 | 0 | 1 (0.3) |
| 口腔内潰瘍形成 | 2 (0.4) | 1 (0.2) | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 胃腸障害 (Cont.) | | | |
| 悪心 | 8 (1.5) | 8 (1.5) | 10 (2.5) |
| 食道潰瘍 | 0 | 1 (0.2) | 0 |
| 口腔障害 | 0 | 1 (0.2) | 0 |
| 口腔粘膜水疱形成 | 0 | 1 (0.2) | 0 |
| 膵炎 | 1 (0.2) | 0 | 0 |
| 歯周の炎症 | 1 (0.2) | 0 | 0 |
| レッチング | 1 (0.2) | 0 | 0 |
| 口内炎 | 2 (0.4) | 1 (0.2) | 1 (0.3) |
| 舌障害 | 0 | 0 | 1 (0.3) |
| 舌潰瘍 | 1 (0.2) | 1 (0.2) | 0 |
| 歯の障害 | 1 (0.2) | 0 | 0 |
| 歯痛 | 1 (0.2) | 0 | 0 |
| 嘔吐 | 1 (0.2) | 2 (0.4) | 5 (1.3) |
| 一般・全身障害および投与部位の状態 | 12 (2.3) | 22 (4.2) | 48 (12.2) |
| 医薬品副作用 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | |
| 無力症 | 1 (0.2) | 3 (0.6) | 0 |
| 悪寒 | 2 (0.4) | 0 | 0 |
| 疲労 | 4 (0.8) | 3 (0.6) | 2 (0.5) |
| 炎症 | 0 | 1 (0.2) | 0 |
| インフルエンザ様疾患 | 0 | 2 (0.4) | 0 |
| 注射部位内出血 | 0 | 0 | 1 (0.3) |
| 注射部位湿疹 | 0 | 0 | 3 (0.8) |
| 注射部位紅斑 | 0 | 0 | 5 (1.3) |
| 注射部位過敏反応 | 0 | 0 | 1 (0.3) |
| 注射部位硬結 | 0 | 0 | 1 (0.3) |
| 注射部位疼痛 | 0 | 1 (0.2) | 4 (1.0) |
| 注射部位そう痒感 | 0 | 0 | 2 (0.5) |
| 注射部位反応 | 0 | 1 (0.2) | 20 (5.1) |
| 注射部位蕁麻疹 | 0 | 0 | 3 (0.8) |
| 倦怠感 | 2 (0.4) | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 一般・全身障害および投与部位の状態 (Cont.) | | | |
| 疼痛 | 0 | 1 (0.2) | 2 (0.5) |
| 末梢腫脹 | 1 (0.2) | 1 (0.2) | 0 |
| 発熱 | 2 (0.4) | 8 (1.5) | 2 (0.5) |
| 腫脹 | 0 | 1 (0.2) | 0 |
| 肝胆道系障害 | 16 (3.1) | 16 (3.0) | 8 (2.0) |
| 胆石症 | 0 | 0 | 1 (0.3) |
| 肝機能異常 | 9 (1.7) | 10 (1.9) | 2 (0.5) |
| 肝腫瘤 | 0 | 1 (0.2) | 0 |
| 脂肪肝 | 1 (0.2) | 2 (0.4) | 0 |
| 肝炎 | 1 (0.2) | 0 | 0 |
| 肝毒性 | 1 (0.2) | 1 (0.2) | 0 |
| 高ビリルビン血症 | 2 (0.4) | 1 (0.2) | 0 |
| 高トランスアミナーゼ血症 | 0 | 0 | 1 (0.3) |
| 肝障害 | 0 | 1 (0.2) | 2 (0.5) |
| 肝損傷 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 肝胆道系障害 (Cont.) | | | |
| 非アルコール性脂肪性肝炎 | 1 (0.2) | 0 | 0 |
| 門脈血栓症 | 0 | 0 | 1 (0.3) |
| 脂肪性肝炎 | 1 (0.2) | 0 | 0 |
| 免疫系障害 | 0 | 2 (0.4) | 3 (0.8) |
| 食物アレルギー | 0 | 1 (0.2) | 0 |
| 過敏症 | 0 | 1 (0.2) | 3 (0.8) |
| 感染症および寄生虫症 | 247 (47.1) | 326 (62.0) | 186 (47.1) |
| 腹部膿瘍 | 0 | 1 (0.2) | 0 |
| 四肢膿瘍 | 0 | 3 (0.6) | 1 (0.3) |
| 急性副鼻腔炎 | 1 (0.2) | 0 | 1 (0.3) |
| 歯槽骨炎 | 0 | 0 | 1 (0.3) |
| 虫垂炎 | 0 | 1 (0.2) | 0 |
| 異型肺炎 | 0 | 1 (0.2) | 0 |
| 菌血症 | 0 | 1 (0.2) | 0 |
| 細菌感染 | 1 (0.2) | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 体部白癬 | 1 (0.2) | 0 | 0 |
| 骨髄炎 | 0 | 0 | 1 (0.3) |
| 気管支炎 | 9 (1.7) | 18 (3.4) | 5 (1.3) |
| 細菌性気管支炎 | 1 (0.2) | 1 (0.2) | 0 |
| 蜂巣炎 | 2 (0.4) | 1 (0.2) | 7 (1.8) |
| 慢性扁桃炎 | 0 | 0 | 1 (0.3) |
| 結膜炎 | 2 (0.4) | 0 | 2 (0.5) |
| 膀胱炎 | 2 (0.4) | 2 (0.4) | 4 (1.0) |
| サイトメガロウイルス感染 | 0 | 1 (0.2) | 0 |
| 毛嚢虫症 | 1 (0.2) | 0 | 0 |
| 憩室炎 | 0 | 0 | 1 (0.3) |
| 耳感染 | 3 (0.6) | 0 | 1 (0.3) |
| 丹毒 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 大腸菌性尿路感染 | 2 (0.4) | 1 (0.2) | 0 |
| 眼感染 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 毛包炎 | 6 (1.1) | 5 (1.0) | 1 (0.3) |
| 真菌感染 | 1 (0.2) | 0 | 0 |
| 皮膚真菌感染 | 2 (0.4) | 5 (1.0) | 3 (0.8) |
| せつ | 1 (0.2) | 0 | 0 |
| 胃腸炎 | 7 (1.3) | 7 (1.3) | 2 (0.5) |
| ウイルス性胃腸炎 | 0 | 3 (0.6) | 0 |
| 消化管感染 | 1 (0.2) | 0 | 0 |
| 陰部ヘルペス | 3 (0.6) | 1 (0.2) | 1 (0.3) |
| 歯肉炎 | 1 (0.2) | 3 (0.6) | 0 |
| 鼠径部膿瘍 | 0 | 1 (0.2) | 0 |
| H1N1インフルエンザ | 1 (0.2) | 0 | 0 |
| B型肝炎再活性化 | 1 (0.2) | 0 | 0 |
| 単純ヘルペス | 3 (0.6) | 11 (2.1) | 1 (0.3) |
| ヘルペスウイルス感染 | 1 (0.2) | 0 | 0 |
| 帯状疱疹 | 15 (2.9) | 27 (5.1) | 2 (0.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 麦粒腫 | 1 (0.2) | 0 | 0 |
| 伝染性単核症 | 0 | 1 (0.2) | 0 |
| インフルエンザ | 10 (1.9) | 9 (1.7) | 2 (0.5) |
| クレブシエラ感染 | 1 (0.2) | 0 | 0 |
| 喉頭炎 | 0 | 2 (0.4) | 1 (0.3) |
| 潜伏結核 | 2 (0.4) | 0 | 2 (0.5) |
| 下気道感染 | 3 (0.6) | 3 (0.6) | 3 (0.8) |
| 肺感染 | 0 | 2 (0.4) | 0 |
| リンパ管炎 | 0 | 1 (0.2) | 0 |
| 爪感染 | 0 | 4 (0.8) | 0 |
| 鼻ヘルペス | 0 | 0 | 2 (0.5) |
| 上咽頭炎 | 17 (3.2) | 17 (3.2) | 31 (7.9) |
| 爪真菌症 | 0 | 1 (0.2) | 1 (0.3) |
| 口腔カンジダ症 | 2 (0.4) | 4 (0.8) | 1 (0.3) |
| 口腔真菌感染 | 0 | 1 (0.2) | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 口腔ヘルペス | 8 (1.5) | 37 (7.0) | 11 (2.8) |
| 中咽頭カンジダ症 | 0 | 1 (0.2) | 0 |
| 外耳炎 | 0 | 1 (0.2) | 0 |
| 中耳炎 | 0 | 1 (0.2) | 2 (0.5) |
| 急性中耳炎 | 0 | 3 (0.6) | 1 (0.3) |
| 爪囲炎 | 2 (0.4) | 3 (0.6) | 1 (0.3) |
| 歯周炎 | 2 (0.4) | 1 (0.2) | 0 |
| 咽頭炎 | 5 (1.0) | 3 (0.6) | 2 (0.5) |
| レンサ球菌性咽頭炎 | 1 (0.2) | 0 | 1 (0.3) |
| ニューモシスチス・イロベチイ肺炎 | 0 | 1 (0.2) | 0 |
| 肺炎 | 3 (0.6) | 3 (0.6) | 3 (0.8) |
| レンサ球菌性肺炎 | 0 | 1 (0.2) | 0 |
| 歯髄炎 | 1 (0.2) | 0 | 0 |
| 化膿性分泌物 | 0 | 1 (0.2) | 0 |
| 腎盂腎炎 | 0 | 1 (0.2) | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 膿疱性皮疹 | 0 | 4 (0.8) | 0 |
| 気道感染 | 11 (2.1) | 8 (1.5) | 3 (0.8) |
| ウイルス性気道感染 | 0 | 1 (0.2) | 0 |
| 鼻炎 | 0 | 4 (0.8) | 2 (0.5) |
| サルモネラ症 | 0 | 0 | 1 (0.3) |
| 卵管炎 | 0 | 1 (0.2) | 0 |
| 敗血症 | 2 (0.4) | 0 | 0 |
| 副鼻腔炎 | 4 (0.8) | 11 (2.1) | 6 (1.5) |
| 皮膚感染 | 2 (0.4) | 0 | 0 |
| 軟部組織感染 | 0 | 0 | 2 (0.5) |
| ブドウ球菌性菌血症 | 0 | 1 (0.2) | 0 |
| ブドウ球菌感染 | 1 (0.2) | 0 | 1 (0.3) |
| ブドウ球菌性敗血症 | 0 | 1 (0.2) | 0 |
| ブドウ球菌皮膚感染 | 1 (0.2) | 0 | 0 |
| 皮下組織膿瘍 | 0 | 1 (0.2) | 0 |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| 白癬感染 | 1 (0.2) | 0 | 1 (0.3) |
| 手白癬 | 0 | 1 (0.2) | 0 |
| 足部白癬 | 2 (0.4) | 1 (0.2) | 0 |
| 癜風 | 1 (0.2) | 0 | 0 |
| 扁桃炎 | 3 (0.6) | 4 (0.8) | 2 (0.5) |
| 細菌性扁桃炎 | 2 (0.4) | 1 (0.2) | 0 |
| 歯膿瘍 | 3 (0.6) | 0 | 0 |
| 歯感染 | 1 (0.2) | 1 (0.2) | 0 |
| 気管炎 | 0 | 3 (0.6) | 0 |
| 気管気管支炎 | 1 (0.2) | 0 | 0 |
| トリコモナス症 | 0 | 0 | 1 (0.3) |
| 上気道感染 | 54 (10.3) | 52 (9.9) | 45 (11.4) |
| 尿路感染 | 20 (3.8) | 21 (4.0) | 11 (2.8) |
| 尿路性敗血症 | 0 | 1 (0.2) | 0 |
| 腟感染 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 感染症および寄生虫症 (Cont.) | | | |
| ウイルス感染 | 0 | 1 (0.2) | 1 (0.3) |
| ウイルス性咽頭炎 | 0 | 1 (0.2) | 0 |
| ウイルス性副鼻腔炎 | 0 | 1 (0.2) | 0 |
| ウイルス性気管炎 | 1 (0.2) | 0 | 0 |
| ウイルス性上気道感染 | 4 (0.8) | 1 (0.2) | 4 (1.0) |
| 外陰部炎 | 1 (0.2) | 0 | 0 |
| 外陰部腟カンジダ症 | 3 (0.6) | 2 (0.4) | 1 (0.3) |
| 外陰腟真菌感染 | 2 (0.4) | 6 (1.1) | 1 (0.3) |
| 創傷感染 | 0 | 0 | 1 (0.3) |
| 傷害、中毒および処置合併症 | 1 (0.2) | 5 (1.0) | 3 (0.8) |
| 偶発的過量投与 | 0 | 0 | 1 (0.3) |
| 節足動物咬傷 | 0 | 1 (0.2) | 0 |
| 挫傷 | 0 | 1 (0.2) | 1 (0.3) |
| 大腿骨骨折 | 0 | 1 (0.2) | 0 |
| 仙骨骨折 | 0 | 1 (0.2) | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 傷害、中毒および処置合併症 (Cont.) | | | |
| 注射に伴う反応 | 0 | 0 | 1 (0.3) |
| 処置による疼痛 | 0 | 1 (0.2) | 0 |
| 皮膚擦過傷 | 1 (0.2) | 0 | 0 |
| 臨床検査 | 173 (33.0) | 224 (42.6) | 135 (34.2) |
| アラニンアミノトランスフェラーゼ増加 | 41 (7.8) | 33 (6.3) | 32 (8.1) |
| αヒドロキシ酪酸脱水素酵素増加 | 0 | 1 (0.2) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 28 (5.3) | 24 (4.6) | 22 (5.6) |
| 血中アルカリホスファターゼ増加 | 1 (0.2) | 0 | 0 |
| 血中ビリルビン増加 | 1 (0.2) | 0 | 4 (1.0) |
| 血中コレステロール増加 | 4 (0.8) | 4 (0.8) | 0 |
| 血中クレアチンホスホキナーゼ増加 | 57 (10.9) | 86 (16.3) | 28 (7.1) |
| 血中クレアチニン増加 | 5 (1.0) | 4 (0.8) | 2 (0.5) |
| 血中ブドウ糖異常 | 1 (0.2) | 0 | 0 |
| 血中ブドウ糖増加 | 1 (0.2) | 0 | 2 (0.5) |
| 血中乳酸脱水素酵素増加 | 0 | 1 (0.2) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| 血中リン減少 | 1 (0.2) | 0 | 0 |
| 血中カリウム増加 | 0 | 5 (1.0) | 1 (0.3) |
| 血圧上昇 | 2 (0.4) | 2 (0.4) | 4 (1.0) |
| 血中甲状腺刺激ホルモン減少 | 1 (0.2) | 0 | 0 |
| 血中トリグリセリド減少 | 0 | 0 | 1 (0.3) |
| 血中トリグリセリド増加 | 1 (0.2) | 1 (0.2) | 0 |
| 血中尿素増加 | 0 | 1 (0.2) | 0 |
| 血中尿酸増加 | 0 | 3 (0.6) | 0 |
| ヘモグロビン減少 | 1 (0.2) | 3 (0.6) | 0 |
| 肝酵素上昇 | 2 (0.4) | 2 (0.4) | 6 (1.5) |
| 高比重リポ蛋白増加 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| 未熟顆粒球数増加 | 1 (0.2) | 0 | 0 |
| 肝機能検査値上昇 | 4 (0.8) | 2 (0.4) | 1 (0.3) |
| 低比重リポ蛋白減少 | 0 | 0 | 1 (0.3) |
| 低比重リポ蛋白増加 | 3 (0.6) | 2 (0.4) | 0 |

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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| リンパ球数減少 | 2 (0.4) | 4 (0.8) | 0 |
| 平均赤血球容積増加 | 2 (0.4) | 4 (0.8) | 1 (0.3) |
| 筋酵素上昇 | 1 (0.2) | 0 | 0 |
| 骨髄球存在 | 0 | 1 (0.2) | 0 |
| 好中球数減少 | 2 (0.4) | 7 (1.3) | 4 (1.0) |
| 血小板数増加 | 1 (0.2) | 2 (0.4) | 1 (0.3) |
| 総蛋白増加 | 1 (0.2) | 0 | 0 |
| 尿中蛋白陽性 | 0 | 0 | 1 (0.3) |
| 赤血球数減少 | 0 | 4 (0.8) | 1 (0.3) |
| 血沈亢進 | 1 (0.2) | 0 | 0 |
| トランスアミナーゼ上昇 | 2 (0.4) | 7 (1.3) | 8 (2.0) |
| 尿検査異常 | 0 | 1 (0.2) | 0 |
| 尿中白血球エステラーゼ陽性 | 0 | 0 | 2 (0.5) |
| 超低比重リポ蛋白増加 | 2 (0.4) | 4 (0.8) | 1 (0.3) |
| 体重減少 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 臨床検査 (Cont.) | | | |
| 体重増加 | 1 (0.2) | 2 (0.4) | 2 (0.5) |
| 白血球数減少 | 1 (0.2) | 13 (2.5) | 6 (1.5) |
| 尿中白血球陽性 | 0 | 0 | 1 (0.3) |
| 代謝および栄養障害 | 13 (2.5) | 26 (4.9) | 18 (4.6) |
| 炭水化物不耐症 | 0 | 0 | 1 (0.3) |
| 糖尿病 | 0 | 0 | 1 (0.3) |
| コントロール不良の糖尿病 | 0 | 0 | 1 (0.3) |
| 脂質異常症 | 2 (0.4) | 5 (1.0) | 3 (0.8) |
| 耐糖能障害 | 0 | 0 | 1 (0.3) |
| 高カルシウム血症 | 0 | 1 (0.2) | 0 |
| 高コレステロール血症 | 2 (0.4) | 7 (1.3) | 1 (0.3) |
| 高血糖 | 1 (0.2) | 3 (0.6) | 3 (0.8) |
| 高脂血症 | 1 (0.2) | 6 (1.1) | 1 (0.3) |
| 高トリグリセリド血症 | 0 | 0 | 3 (0.8) |
| 高尿酸血症 | 4 (0.8) | 3 (0.6) | 2 (0.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 代謝および栄養障害 (Cont.) | | | |
| 低血糖 | 1 (0.2) | 0 | 0 |
| 低カリウム血症 | 1 (0.2) | 0 | 1 (0.3) |
| 低リン酸血症 | 1 (0.2) | 0 | 0 |
| ビタミンD欠乏 | 0 | 1 (0.2) | 0 |
| 筋骨格系および結合組織障害 | 13 (2.5) | 11 (2.1) | 8 (2.0) |
| 背部痛 | 0 | 0 | 2 (0.5) |
| 軟骨疾患 | 0 | 1 (0.2) | 0 |
| 側腹部痛 | 0 | 1 (0.2) | 0 |
| 関節雑音 | 0 | 1 (0.2) | 0 |
| 関節硬直 | 1 (0.2) | 0 | 0 |
| 筋痙縮 | 2 (0.4) | 1 (0.2) | 1 (0.3) |
| 筋力低下 | 1 (0.2) | 1 (0.2) | 0 |
| 筋骨格系胸痛 | 0 | 3 (0.6) | 0 |
| 筋肉痛 | 2 (0.4) | 1 (0.2) | 0 |
| 頚部痛 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 筋骨格系および結合組織障害 (Cont.) | | | |
| 四肢痛 | 1 (0.2) | 0 | 0 |
| 乾癬性関節症 | 5 (1.0) | 2 (0.4) | 4 (1.0) |
| 脊椎痛 | 1 (0.2) | 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) | 4 (0.8) | 10 (1.9) | 2 (0.5) |
| 肛門性器疣贅 | 0 | 1 (0.2) | 0 |
| 基底細胞癌 | 0 | 1 (0.2) | 1 (0.3) |
| ボーエン病 | 0 | 1 (0.2) | 0 |
| 遠隔転移を伴う肺癌 | 1 (0.2) | 0 | 0 |
| メラノサイト性母斑 | 0 | 1 (0.2) | 0 |
| 遠隔転移を伴う膵癌 | 0 | 0 | 1 (0.3) |
| 皮膚乳頭腫 | 2 (0.4) | 4 (0.8) | 0 |
| 扁平上皮癌 | 0 | 1 (0.2) | 0 |
| 皮膚有棘細胞癌 | 1 (0.2) | 1 (0.2) | 0 |
| 神経系障害 | 19 (3.6) | 27 (5.1) | 15 (3.8) |
| 手根管症候群 | 0 | 1 (0.2) | 0 |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 浮動性めまい | 3 (0.6) | 2 (0.4) | 1 (0.3) |
| 体位性めまい | 0 | 0 | 1 (0.3) |
| 頭痛 | 10 (1.9) | 11 (2.1) | 8 (2.0) |
| 肝性脳症 | 0 | 0 | 1 (0.3) |
| ラクナ脳卒中 | 1 (0.2) | 0 | 0 |
| 嗜眠 | 1 (0.2) | 1 (0.2) | 0 |
| 記憶障害 | 0 | 2 (0.4) | 0 |
| 片頭痛 | 0 | 1 (0.2) | 0 |
| 神経痛 | 0 | 1 (0.2) | 0 |
| 錯感覚 | 1 (0.2) | 1 (0.2) | 0 |
| 末梢性感覚ニューロパチー | 0 | 2 (0.4) | 0 |
| 睡眠の質低下 | 0 | 0 | 1 (0.3) |
| ヘルペス後神経痛 | 1 (0.2) | 2 (0.4) | 0 |
| 感覚障害 | 0 | 2 (0.4) | 0 |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 神経系障害 (Cont.) | | | |
| 傾眠 | 0 | 1 (0.2) | 2 (0.5) |
| 緊張性頭痛 | 1 (0.2) | 0 | 0 |
| 三叉神経痛 | 1 (0.2) | 0 | 0 |
| 精神障害 | 5 (1.0) | 5 (1.0) | 5 (1.3) |
| 不安 | 0 | 2 (0.4) | 0 |
| 抑うつ気分 | 0 | 0 | 3 (0.8) |
| うつ病 | 1 (0.2) | 0 | 0 |
| 不眠症 | 3 (0.6) | 3 (0.6) | 2 (0.5) |
| 睡眠障害 | 1 (0.2) | 0 | 0 |
| 腎および尿路障害 | 6 (1.1) | 13 (2.5) | 11 (2.8) |
| 尿路結石 | 0 | 1 (0.2) | 0 |
| 慢性腎臓病 | 0 | 1 (0.2) | 0 |
| 糖尿病性腎症 | 0 | 1 (0.2) | 0 |
| 排尿困難 | 0 | 2 (0.4) | 1 (0.3) |
| 糖尿 | 0 | 0 | 1 (0.3) |

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Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 腎および尿路障害 (Cont.) | | | |
| 血尿 | 1 (0.2) | 4 (0.8) | 3 (0.8) |
| 緊張性膀胱 | 1 (0.2) | 0 | 0 |
| 白血球尿 | 2 (0.4) | 1 (0.2) | 0 |
| 尿意切迫 | 1 (0.2) | 0 | 0 |
| 頻尿 | 0 | 1 (0.2) | 0 |
| 多尿 | 0 | 0 | 1 (0.3) |
| 蛋白尿 | 1 (0.2) | 2 (0.4) | 4 (1.0) |
| 尿路の炎症 | 0 | 0 | 1 (0.3) |
| 生殖系および乳房障害 | 7 (1.3) | 2 (0.4) | 1 (0.3) |
| 無月経 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 乳房嚢胞 | 1 (0.2) | 0 | 0 |
| 前立腺結石 | 1 (0.2) | 0 | 0 |
| 線維嚢胞性乳腺疾患 | 0 | 1 (0.2) | 0 |
| 月経過多 | 1 (0.2) | 0 | 0 |
| 不規則月経 | 2 (0.4) | 0 | 0 |

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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA<br>15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA<br>30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 生殖系および乳房障害 (Cont.) | | | |
| 前立腺炎 | 1 (0.2) | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 17 (3.2) | 30 (5.7) | 23 (5.8) |
| 喘息 | 0 | 0 | 1 (0.3) |
| 咳嗽 | 2 (0.4) | 14 (2.7) | 2 (0.5) |
| 発声障害 | 0 | 1 (0.2) | 0 |
| 呼吸困難 | 1 (0.2) | 0 | 1 (0.3) |
| 労作性呼吸困難 | 1 (0.2) | 0 | 0 |
| 鼻出血 | 1 (0.2) | 0 | 1 (0.3) |
| 肺浸潤 | 0 | 0 | 1 (0.3) |
| 鼻閉 | 0 | 0 | 2 (0.5) |
| 鼻部不快感 | 1 (0.2) | 0 | 0 |
| 鼻の炎症 | 0 | 1 (0.2) | 0 |
| 鼻潰瘍 | 0 | 1 (0.2) | 0 |
| 口腔咽頭不快感 | 0 | 0 | 1 (0.3) |
| 口腔咽頭痛 | 2 (0.4) | 3 (0.6) | 8 (2.0) |

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Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 (Cont.) | | | |
| 咽頭の炎症 | 0 | 1 (0.2) | 1 (0.3) |
| 胸膜炎 | 1 (0.2) | 0 | 0 |
| 肺臓炎 | 0 | 0 | 1 (0.3) |
| 自然気胸 | 0 | 1 (0.2) | 0 |
| 肺塞栓症 | 2 (0.4) | 2 (0.4) | 0 |
| 肺線維症 | 0 | 1 (0.2) | 0 |
| 肺高血圧症 | 1 (0.2) | 0 | 0 |
| 呼吸窮迫 | 1 (0.2) | 0 | 0 |
| アレルギー性鼻炎 | 1 (0.2) | 0 | 0 |
| 鼻漏 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| 咽喉刺激感 | 0 | 3 (0.6) | 0 |
| 扁桃の炎症 | 0 | 0 | 1 (0.3) |
| 上気道の炎症 | 1 (0.2) | 1 (0.2) | 1 (0.3) |
| 皮膚および皮下組織障害 | 33 (6.3) | 32 (6.1) | 41 (10.4) |
| ざ瘡 | 1 (0.2) | 3 (0.6) | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
Subjects in UPA 15 mg QD/30mg QD group include those who started UPA 15 mg QD/30mg QD at the beginning of the study and those who switched to UPA 15 mg/30mg QD at Week 24.
E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| | UPA | | |
|---|---|---|---|
| | 15 mg QD (N = 617) (PYs = 524.1) | 30 mg QD (N = 612) (PYs = 526.0) | ADA 40 mg EOW (N = 429) (PYs = 394.5) |
| System Organ Class<br>MedDRA 22.0 Preferred Term | Events<br>(E/100 PYs) | Events<br>(E/100 PYs) | Events<br>(E/100 PYs) |
| 皮膚および皮下組織障害 (Cont.) | | | |
| 光線性口唇炎 | 0 | 1 (0.2) | 0 |
| 脱毛症 | 2 (0.4) | 1 (0.2) | 6 (1.5) |
| 水疱 | 2 (0.4) | 3 (0.6) | 0 |
| 肝斑 | 0 | 1 (0.2) | 0 |
| 皮膚嚢腫 | 1 (0.2) | 0 | 0 |
| 皮膚炎 | 2 (0.4) | 1 (0.2) | 2 (0.5) |
| ざ瘡様皮膚炎 | 0 | 1 (0.2) | 0 |
| アレルギー性皮膚炎 | 0 | 1 (0.2) | 2 (0.5) |
| アトピー性皮膚炎 | 1 (0.2) | 0 | 0 |
| 皮膚乾燥 | 0 | 1 (0.2) | 0 |
| 異汗性湿疹 | 0 | 1 (0.2) | 0 |
| 湿疹 | 1 (0.2) | 0 | 1 (0.3) |
| 紅斑 | 0 | 5 (1.0) | 1 (0.3) |
| 環状紅斑 | 0 | 0 | 1 (0.3) |
| 毛髪成長異常 | 1 (0.2) | 0 | 0 |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

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| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 多汗症 | 2 (0.4) | 0 | 0 |
| 嵌入爪 | 0 | 0 | 2 (0.5) |
| 間擦疹 | 1 (0.2) | 0 | 0 |
| 爪郭の炎症 | 0 | 1 (0.2) | 0 |
| 爪成長異常 | 1 (0.2) | 0 | 0 |
| 爪破損 | 1 (0.2) | 0 | 0 |
| 丘疹 | 0 | 1 (0.2) | 1 (0.3) |
| 光線過敏性反応 | 0 | 0 | 1 (0.3) |
| そう痒症 | 0 | 1 (0.2) | 6 (1.5) |
| 全身性そう痒症 | 1 (0.2) | 0 | 1 (0.3) |
| 乾癬 | 5 (1.0) | 2 (0.4) | 7 (1.8) |
| 膿疱性乾癬 | 0 | 1 (0.2) | 0 |
| 発疹 | 1 (0.2) | 4 (0.8) | 3 (0.8) |
| 毛孔性皮疹 | 1 (0.2) | 0 | 1 (0.3) |
| 全身性皮疹 | 1 (0.2) | 0 | 2 (0.5) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

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by Primary MedDRA System Organ Class and Preferred Term - Long Term
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|---|---|---|---|
| 皮膚および皮下組織障害 (Cont.) | | | |
| 斑状皮疹 | 2 (0.4) | 1 (0.2) | 0 |
| 斑状丘疹状皮疹 | 1 (0.2) | 0 | 1 (0.3) |
| 皮膚剥脱 | 0 | 1 (0.2) | 0 |
| 皮膚刺激 | 1 (0.2) | 1 (0.2) | 0 |
| 皮膚病変 | 3 (0.6) | 0 | 0 |
| 顔面腫脹 | 1 (0.2) | 0 | 0 |
| 蕁麻疹 | 0 | 0 | 3 (0.8) |
| 血管障害 | 10 (1.9) | 5 (1.0) | 9 (2.3) |
| 深部静脈血栓症 | 2 (0.4) | 0 | 0 |
| 血腫 | 0 | 0 | 1 (0.3) |
| ほてり | 3 (0.6) | 0 | 0 |
| 高血圧 | 4 (0.8) | 4 (0.8) | 3 (0.8) |
| 高血圧クリーゼ | 1 (0.2) | 0 | 0 |
| リンパ浮腫 | 0 | 0 | 1 (0.3) |
| レイノー現象 | 0 | 0 | 1 (0.3) |

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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

TABLE 14.3__1.6.2

Treatment-Emergent Adverse Events with Reasonably Possibly of Being Related to Study Drug per 100 Patient Years
by Primary MedDRA System Organ Class and Preferred Term - Long Term
(Safety Analysis Set)

| System Organ Class<br>MedDRA 22.0 Preferred Term | UPA 15 mg QD<br>(N = 617)<br>(PYs = 524.1)<br>Events<br>(E/100 PYs) | UPA 30 mg QD<br>(N = 612)<br>(PYs = 526.0)<br>Events<br>(E/100 PYs) | ADA 40 mg EOW<br>(N = 429)<br>(PYs = 394.5)<br>Events<br>(E/100 PYs) |
|---|---|---|---|
| 血管障害 (Cont.) | | | |
| 血栓性静脈炎 | 0 | 0 | 1 (0.3) |
| 表在性血栓性静脈炎 | 0 | 1 (0.2) | 1 (0.3) |
| 血管炎 | 0 | 0 | 1 (0.3) |

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of study drug and up to 30 days after the last dose of UPA and up to 70 days for adalimumab, if subject discontinued prematurely from the study.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.
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E/100 PYs = Events per 100 patient-years.

Program Source Code: [redacted]

被験者番号 [redacted] (Investigator [redacted])

**Reason for Narrative**

| Adverse Event Preferred Term(s) | Serious Adverse Event | Adverse Event Leading to Discontinuation of Study Drug | Death | Event of Interest |
|---|---|---|---|---|
| 変形性関節症 | X | | | |
| 肺塞栓症 | X | X | | X |

| Treatment Group | Age at Study Start | Sex | Race |
|---|---|---|---|
| UPA 30 mg QD | 6[redacted] | FEMALE | WHITE |

| Medical History | Onset Year |
|---|---|
| OTHER: PLAQUE PSORIASIS | 19[redacted] |
| OTHER: APPENDECTOMY | 19 |
| OTHER: HEADACHES | 19 |
| CANCER: BASAL CELL CARCINOMA | 20 |
| OTHER: OBESITY | 20 |
| HYPERTENSION | 20 |
| SLEEP APNEA | 20 |
| OTHER: HYPERLIPIDEMIA | 20 |
| OTHER: INSOMNIA | 20 |
| PSORIATIC ARTHRITIS | 20 |
| OTHER: MULTIPLE LEFT ARM FRACTURES | 20 |
| DRUG ALLERGIES/REACTIONS: METHOTREXATE ALLERGY | 20 |
| OTHER: BLADDER INFECTIONS | 20 |
| OTHER: BENIGN THYROID NODULE | 20 |
| DEGENERATIVE DISC DISEASE: CERVICAL, THORACIC, AND LUMBAR | 20 |
| OSTEOARTHRITIS | 20 |
| OTHER: BILATERAL HEEL SPURS | 20 |
| OTHER: SHORTNESS OF BREATH | 20[redacted] |

| Prior Procedures | Procedure Year |
|---|---|
| SURGERY: CHOLECYSTECTOMY | 19[redacted] |
| SURGERY: HYSTERECTOMY | 19 |
| SURGERY: GASTRIC BANDING | 20 |
| SURGERY: REMOVAL OF GASTRIC BAND | 20 |
| SURGERY: REMOVAL OF LEFT THYROID NODULE | 20[redacted] |

| Tobacco Use | Status | Number/Day | Number of Years | Year Stopped |
|---|---|---|---|---|
| CHEWING TOBACCO | NEVER | | | |
| CIGARETTES | NEVER | | | |
| CIGARS | NEVER | | | |
| E-CIGARETTES | NEVER | | | |
| PIPES | NEVER | | | |

| Alcohol Use | Status | Number/Day |
|---|---|---|
| ALCOHOL | CURRENT | Less than 2 DRINKS |

**Study Drug Administration**

| Study Drug | Dose/Units | Route | Frequency | First Dose Date/Day | Last Dose Date/Day | Duration (Days) |
|---|---|---|---|---|---|---|
| ABT-494 | 30 MG | ORAL | QD | [redacted] / 1 | [redacted] / 164 | 164 |
| ABT-494 | 30 MG | ORAL | QD | [redacted] / 165 | [redacted] / 394 | 230 |
| ABT-494 | 30 MG | ORAL | QD | [redacted] / 395 | [redacted] / 712 | 318 |

**Previous Therapy - Prior to baseline/enrollment**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day |
|---|---|---|---|
| IBUPROFEN | 200 mg | BID | Y-M: 20[redacted] |
| AMLODIPINE | 5 mg | QD | Y-M: 20[redacted] |
| ATORVASTATIN | 20 mg | QD | Y-M: 20[redacted] |
| DYAZIDE | 1 OTHER: TABLET | QD | Y-M: 20[redacted] |
| HYDROXYZINE | 25 mg | QD | Y-M: 20[redacted] |
| LISINOPRIL | 20 mg | QD | Y-M: 20[redacted] |
| METHOTREXATE | 10 mg | EVERY WEEK | Y-M: 20[redacted] |
| CENTRUM | 1 OTHER: TABLET | QD | Y-M: 20[redacted] / -87 |

**Other Medications - Medications taken within 30 days prior to each narrative event until AE stopped or end of study**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day | Stop Year-Month / RX Day |
|---|---|---|---|---|
| IBUPROFEN | 200 mg | BID | Y-M: 20[redacted] | Y-M: 20[redacted] / 505 |
| AMLODIPINE | 5 mg | QD | Y-M: 20[redacted] | NOT REPORTED |
| DYAZIDE | 1 OTHER: TABLET | QD | Y-M: 20[redacted] | NOT REPORTED |
| LISINOPRIL | 20 mg | QD | Y-M: 20[redacted] | NOT REPORTED |
| ATORVASTATIN | 20 mg | QD | Y-M: 20[redacted] | Y-M: 20[redacted] / 493 |
| HYDROXYZINE | 25 mg | QD | Y-M: 20[redacted] | Y-M: 20[redacted] / 497 |
| CENTRUM | 1 OTHER: TABLET | QD | Y-M: 20[redacted] / 87 | -NOT REPORTED |
| MUPIROCIN | 2 % | BID | Y-M: 20[redacted] / 217 | Y-M: 20[redacted] / 228 |
| VALACICLOVIR | 1000 mg | TID | Y-M: 20[redacted] / 224 | Y-M: 20[redacted] / 232 |
| LIDOCAINE | 2 mL | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 352 | Y-M: 20[redacted] / 352 |
| ROPIVACAINE | 2 mL | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 352 | Y-M: 20[redacted] / 352 |
| TRIAMCINOLONE | 80 mg | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 352 | Y-M: 20[redacted] / 352 |

| | | | | |
|---|---|---|---|---|
| ISOSORBIDE MONONITRATE | 10 mg | BID | Y-M: 20[redacted] / 377 | Y-M: 20[redacted] / 493 |
| VALACICLOVIR | 1000 g | TID | Y-M: 20[redacted] / 384 | Y-M: 20[redacted] / 390 |
| VALACICLOVIR | 1000 g | QD | Y-M: 20[redacted] / 391 | Y-M: 20[redacted] / 687 |
| ANESTHETICS, GENERAL | UNKNOWN OTHER: UNKNOWN | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 457 | Y-M: 20[redacted] / 457 |
| CEFAZOLIN | UNKNOWN OTHER: UNKNOWN | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 457 | Y-M: 20[redacted] / 457 |
| MACROGOL 3350 | 1 OTHER: TABLET | PRN | Y-M: 20[redacted] / 458 | Y-M: 20[redacted] / 465 |
| VICODIN | 7.5/325 mg | PRN | Y-M: 20[redacted] / 458 | Y-M: 20[redacted] / 485 |
| ACETYLSALICYLIC ACID | 81 mg | BID | Y-M: 20[redacted] / 458 | Y-M: 20[redacted] / 486 |
| DOCUSATE | 1 OTHER: TABLET | PRN | Y-M: 20[redacted] / 466 | NOT REPORTED |
| NAPROXEN | 500 mg | QD | Y-M: 20[redacted] / 569 | NOT REPORTED |
| FUROSEMIDE | 40 mg | QD | Y-M: 20[redacted] / 685 | NOT REPORTED |
| ACICLOVIR | 800 mg | QD | Y-M: 20[redacted] / 687 | NOT REPORTED |
| LEVOTHYROXINE | 0.05 mg | QD | Y-M: 20[redacted] / 687 | NOT REPORTED |
| HEPARIN | 8300 IU | OTHER: ONCE | Y-M: 20[redacted] / 713 | Y-M: 20[redacted] / 713 |
| IOPAMIDOL | 79 OTHER: CC | OTHER: SINGLE DOSE | Y-M: 20[redacted] / 713 | Y-M: 20[redacted] / 713 |
| HEPARIN | 3800 IU | OTHER: ONCE | Y-M: 20[redacted] / 714 | Y-M: 20[redacted] / 714 |
| APIXABAN | 5 mg | BID | Y-M: 20[redacted] / 715 | NOT REPORTED |
| APIXABAN | 10 mg | BID | Y-M: 20[redacted] / 715 | Y-M: 20[redacted] / 721 |

**Event #1: Serious Adverse Event**

**Event Description** WORSENING OF OSTEOARTHRITIS RIGHT HIP

**Preferred term** 変形性関節症

**AE Onset Date / Rx Day** [redacted]20[redacted] / 157

**Age at AE Onset** 6[redacted]

**Laboratory Testing**

NOT REPORTED

**Microbiology**

NOT REPORTED

**SAE Supplemental Procedure**

[redacted]20[redacted] (RX DAY 457): REBOTICALLY ASSISTED AND CT-GUIDED PATIENT SPECIFIC CEMENTLESS RIGHT TOTAL HIP ARTHROPLASTY.: PATIENT AT HOME AND CURRENTLY RECEIVING PHYSICAL THERAPY AT HER HOME.

**AE Stopped Rx Day** 458

| | |
|---|---|
| **Duration of AE** | 302 DAYS |
| **Severity** | Severe |
| **Relation to Study Drug by Investigator** | No Reasonable Possibility |
| **Investigator Alternative Etiology** | SEVERE OSTEOARTHRITIS AND SHE HAS FAILED SEVERAL ATTEMPTS AT CONSERVATIVE TREATMENT. |
| **Discontinued Study Drug Due to the Event** | NO |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

**Event #3: Serious Adverse Event, AE Leading to Discontinuation of Study Drug, Event of Interest - Adjudicated Cardiovascular Events**

| | |
|---|---|
| **Event Description** | PULMONARY EMBOLISM BILATERAL |
| **Preferred term** | 肺塞栓症 |
| **AE Onset Date / Rx Day** | [redacted]20[redacted] / 713 (1 DAY AFTER LAST TREATMENT) |
| **Age at AE Onset** | 6[redacted] |

**Laboratory Testing**

[redacted]20[redacted] (RX DAY 713): Chloride: 108 [98 - 107] MMOL/L; Erythrocytes: 3.5 [3.8 - 5.8] 10^12/L; Hematocrit: 0.34 [0.35 - 0.47] FRACTION OF 1; Hemoglobin: 116 [117 - 161] G/L; NPTST167-D-DIMER: 748 [NOT REPORTED - NOT REPORTED] UNIT NOT REPORTED; NPTST351-NTPROBNP: 59 [NOT REPORTED - NOT REPORTED] PG/ML; NPTST477-TROPONIN-I: .012 [NOT REPORTED - 0.034] ng/mL; Prothrombin Intl. Normalized Ratio: 1 [0.9 - 1.2] RATIO; [redacted]20[redacted] (RX DAY 714): Erythrocytes: 3.4 [3.8 - 5.8] 10^12/L; Hematocrit: 0.33 [0.35 - 0.47] FRACTION OF 1; Hemoglobin: 111 [117 - 161] G/L; NPTST071-BASELINE LA PTT: 157.8 [33.2 - 40.6] SEC; NPTST194-FACTOR 8: 216 [50 - 150] %; NPTST393-PROTEIN C FUNC: 145 [70 - 130] %; NPTST458-THROMBIN TIME MHC: 120 [14.1 - 17] SEC; [redacted]20[redacted] (RX DAY 715): Erythrocytes: 3.7 [3.8 - 5.8] 10^12/L

**Microbiology**

NOT REPORTED

**SAE Supplemental Procedure**

[redacted]20[redacted](RX DAY 713): CTA CHEST WITH AND WITHOUT CONTRAST: MULTIPLE BILATERAL PULMONARY EMBOLI, MORE PROMINENT IN THE RIGHT LUNG. 6MM RIGHT UPPER LOBE PULMONARY NODULE.; ECG: NORMAL SINUS RHYTHM, NONSPECIFIC ST ABNORMALITY, ABNORMAL ECG; [redacted]20[redacted] (RX DAY 714): CT ABDOMEN AND PELVIS WITHOUT INFUSION: NO ACUTE ABNORMALITIES, SMALL HIATAL HERNIA, VENOUS COMPRESSION DEFORMITY, SCATTERED DIVERTICULA IN THE LEFT COLON; ECHOCARDIOGRAM: LEFT VENTRICULAR HYPERTROPHY, MITRAL VALVE MILD REGURGITATION.; LOWER EXTREMITY VENOUS DOPPLER: NO EVIDENCE OF OBSTRUCTIVE THROMBUS IN THE VISUALIZED LOWER EXTREMITY DEEP VEINS RIGHT OR LEFT.

| | |
|---|---|
| **AE Stopped Rx Day** | 715 (3 DAYS AFTER LAST TREATMENT) |
| **Duration of AE** | 3 DAYS |
| **Severity** | Severe |
| **Relation to Study Drug by Investigator** | Reasonable Possibility |
| **Investigator Alternative Etiology** | NOT REPORTED |
| **Discontinued Study Drug Due to the Event** | YES |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION, OTHER MEDICALLY IMPORTANT SERIOUS EVENT, LIFE THREATENING |

Generated: [redacted]
Program Source Code: [redacted]

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 6[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，右股関節の変形性関節症の悪化の事象を発現した。

**Event 1 の臨床経過：**

関連する病歴は，局面型乾癬，睡眠時無呼吸，乾癬性関節炎，多発性左腕骨折，両側性踵骨棘，頚椎，胸椎及び腰椎の椎間板変性疾患，変形性関節症，息切れ及び非喫煙者であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。本事象発現前において，盲検化された皮下注製剤が投与されたのは 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月，被験者は右股関節の変形性関節症の悪化を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，右股関節の変形性関節症の悪化は消失した。

右股関節痛の悪化が数ヵ月続いていた。これは急速に悪化し，持続していた。右股関節痛は，両側臀部に及ぶ中等度から重度の刺すような鋭い疼痛であった。被験者は保存的治療を数回試したが，改善には至らなかった。被験者は人工股関節全置換術を受けることにした。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は入院した。被験者は，引っかかり感，可動域減少，椅子からの立ち上がりが困難，靴下や靴を履くのが困難，摩擦感，ひきずり足歩行，関節の固まり，こわばり感及び脱力といった随伴症状を訴えた。20[redacted] 年 [redacted] 月 [redacted] 日，被験者はロボット支援 CT ガイド下セメントレス右人工股関節置換術を受けた。手術所見は，重度の右大腿骨頭及び右寛骨臼表面の変形であった。被験者は手術に十分耐えた。被験者は，術後とその後 24 時間，アスピリンと抗生物質を予防的に投与された。間欠的空気圧迫装置の使用，大腿部までの長さの TED ソックスの使用，静脈血栓塞栓症予防のための早期モビライゼーション及び許容範囲内のウェイトベアリングが開始された。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院し，理学療法を継続することとなった。

投与された薬剤は，リドカイン，kenalog，naprosyn，norco 及びロピバカインであった。

**The patient's past medications include:**

METHOTREXATE for PSORIATIC ARTHRITIS (20[redacted] - 20[redacted])

Causality for UPADACITINIB (Blinded)

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1) Osteoarthritis aggravated (10031162) (Osteoarthritis (10031161) ) [v.22.0] [10031162]

**Causality as per reporter (Drug/Vaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** rechallenge was done, reaction did not recur

AlternativeEtiology for UPADACITINIB (Blinded)

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Event of WORSENING OF OSTEOARTHRITIS RIGHT HIP

**- Investigator:** SEVERE OSTEOARTHRITIS AND SHE HAS FAILED SEVERAL ATTEMPTS AT CONSERVATIVE TREATMENT

**- AbbVie:** risk factors include pre-existing osteoarthritis and advanced age.

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 6[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，両側肺塞栓症の事象を発現した。

**Event 3 の臨床経過：**

関連する病歴は，局面型乾癬，肥満，高血圧，睡眠時無呼吸，高脂血症，乾癬性関節炎，変形性関節症，息切れ，非喫煙者及び飲酒者（1 日 2 杯未満）であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。報告によれば，本事象発現前において，盲検化された皮下注製剤の最終投与は 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は両側肺塞栓症を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，両側肺塞栓症は消失した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は，特に 3 週間に及ぶ歩行時の息切れ（SOB）／呼吸困難（非重篤）の増加により，外来を受診した。これらの症状は徐々に悪化した。時折，胸部不快感があった。被験者によれば，下肢の痛みや腫れ，咳はないとのことであった。D ダイマー増加が認められ，被験者は救急治療室（ER）を受診するよう指示された。被験者は ER を受診した。CT 血管造影で両側肺塞栓症（PE）が明らかとなり，そのまま入院した。PE は右肺上葉でより顕著であり，右肺上葉小結節（非重篤）も認められた。被験者によれば，ここ最近の手術歴及び旅行歴はなく，運動不能な状態でもなかった。また被験者によれば，PE 及び深部静脈血栓症（DVT）の病歴はなく，血液凝固障害の家族歴もなかった。ヘパリンのボーラス投与及び点滴が開始された。20[redacted] 年 [redacted] 月 [redacted] 日，肺診察時に被験者の睡眠時無呼吸と CPAP 開始の必要性について説明が行われた。診察時において，被験者には，デスクワークをはじめ，比較的体を動かすことの少ない生活であること以外には，明確な増悪因子が存在しないことがわかった。そのため，抗凝固療法期間を少なくとも最長で 3 年に延長することを検討する必要があった。腹腔内に大きな疾患が存在する可能性を排除するため，両側静脈ドップラー超音波検査および腹部 CT スキャンが行われた。入院中，ヘパリン点滴は経口抗凝固薬エリキュース 10 mg 1 日 2 回に切り替えられた。被験者は室内気下で問題なく歩き回っており，酸素飽和度は 90%超で維持されていた。被験者によれば，さらなる SOB／呼吸困難はなかった。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院し，医師による経過観察を受けることとなった。

本事象により治験薬の投与が完全に中止された。

投与された薬剤は，エリキュース及びヘパリンであった。

**The patient's past medications include:**

MOTRIN foPSORIATIC ARTHRITIS (20[redacted] - [redacted] [redacted] 20[redacted])

METHOTREXATE for PSORIATIC ARTHRITIS (20[redacted] - 20[redacted])

Causality for UPADACITINIB (Blinded)

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1) Pulmonary embolism (10037377) (Pulmonary embolism (10037377) ) [v.22.1] [10037377]

**Causality as per reporter (Drug/Vaccine):** Reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** No rechallenge was done, recurrence is not applicable

Alternative Etiology for UPADACITINIB (Blinded)

---

Event of PULMONARY EMBOLISM BILATERAL

**- Investigator:** Not applicable

**- AbbVie:** Risk factors include pre-existing psoriasis, obesity and advanced age.

Relevant Laboratory & Other Diagnostic Tests

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[redacted] **20[redacted] BASELINE LA PTT:** 157.8 SEC (normal 33.2 to 40.6)

[redacted] **20[redacted] BMI:** 41.8 kg/m2

[redacted] **20[redacted] CHEST X-RAY:** screening: normal

[redacted] **20[redacted] CHLORIDE:** 108 MEQ/L (normal 98 to 107)

[redacted] **20[redacted] CT ABDOMEN:** No acute abnormalities, Small hiatal hernia, venous compression deformity, scattered diverticula in the left colon (non-serious)

[redacted] **20[redacted] CT ANGIOGRAM CHEST:** Multiple bilateral pulmonary emboli, more prominent in the right lung. 6mm right upper lobe pulmonary nodule (non-serious)

[redacted] **20[redacted] D-DIMER:** 748 no unit

[redacted] **20[redacted] ECG:** Normal sinus rhythm, nonspecific ST abnormality, abnormal ECG

[redacted] **20[redacted] ECHOCARDIOGRAM:** Left ventricular hypertrophy, Mitral valve mild regurgitation

[redacted] **20[redacted] FACTOR 8 TEST:** 216 % (normal 50 to 150)

[redacted] **20[redacted] HEMATOCRIT:** 33.8 % (normal 35.0 to 47.0)

[redacted] **20[redacted] HEMATOCRIT:** 32.7 % (normal 35.0 to 47.0)

[redacted] **20[redacted] HEMOGLOBIN:** 11.6 G/DL (normal 11.7 to 16.1)

[redacted] **20[redacted] INTERNATIONAL NORMALIZED RATIO:** 1.0 ratio (normal 0.9 to 1.2)

[redacted] **20[redacted] LOWER EXTREMITY VENOUS DOPPLER:** No evidence of obstructive thrombus in the visualized lower extremity deep veins right or left

[redacted] **20[redacted] NTPRO BNP:** 59 PG/ML

[redacted] **20[redacted] OXYGEN SATURATION:** >90%

[redacted] **20[redacted] PROTEIN C FUNCTION:** 145 % (normal 70 to 130)

[redacted] **20[redacted] RED BLOOD CELLS:** 3.54 M/mcl (normal 3.80 to 5.80)

[redacted] **20[redacted] RED BLOOD CELLS:** 3.44 M/mcl (normal 3.80 to 5.80)

[redacted] **20[redacted] THROMBIN TIME MHC:** > 120.0 seconds

[redacted] **20[redacted] TROPONIN I:** .012 NG/ML (normal 0.000 to 0.034)

被験者番号 [redacted] (Investigator [redacted])

**Reason for Narrative**

| Adverse Event Preferred Term(s) | Serious Adverse Event | Adverse Event Leading to Discontinuation of Study Drug | Death | Event of Interest |
|---|---|---|---|---|
| 脱髄 | X | | | |

| Treatment Group | Age at Study Start | Sex | Race |
|---|---|---|---|
| UPA 30 mg QD | 3[redacted] | FEMALE | WHITE |

| Medical History | Onset Year |
|---|---|
| CHOLECYSTITIS | 20[redacted] |
| OTHER: HEADACHES | 20[redacted] |
| OBESITY | 20[redacted] |
| OTHER: PLAQUE PSORIASIS | 20[redacted] |
| PSORIATIC ARTHRITIS | 20[redacted] |
| OTHER: DEMYELINATING DISEASE | 20[redacted] |

| Prior Procedures | Procedure Year |
|---|---|
| Not reported. | |

| Tobacco Use | Status | Number/Day | Number of Years | Year Stopped |
|---|---|---|---|---|
| CHEWING TOBACCO | NEVER | | | |
| CIGARETTES | NEVER | | | |
| CIGARS | NEVER | | | |
| E-CIGARETTES | NEVER | | | |
| PIPES | NEVER | | | |

| Alcohol Use | Status | Number/Day |
|---|---|---|
| ALCOHOL | NEVER | |

**Study Drug Administration**

| Study Drug | Dose/Units | Route | Frequency | First Dose Date/Day | Last Dose Date/Day | Duration (Days) |
|---|---|---|---|---|---|---|
| ABT-494 | 30 MG | ORAL | QD | [redacted]20[redacted] / 1 | [redacted]20[redacted] / 36 | 36 |

**Previous Therapy - Prior to baseline/enrollment**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day |
|---|---|---|---|
| METHOTREXATE | 15 mg | QD | Y-M: 20[redacted] |
| CYANOCOBALAMIN | 1 OTHER: TAB | QD | Y-M: 20[redacted] |
| IBUPROFEN | 800 mg | QD | Y-M: 20[redacted] |
| PYRIDOXINE | 1 OTHER: TAB | QD | Y-M: 20[redacted] |
| TRAMADOL | 50 mg | QD | Y-M: 20[redacted] |
| PREDNISONE | 10 mg | QD | Y-M: 20[redacted] / -46 |

**Other Medications - Medications taken within 30 days prior to each narrative event until AE stopped or end of study**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day | Stop Year-Month / RX Day |
|---|---|---|---|---|
| CYANOCOBALAMIN | 1 OTHER: TAB | QD | Y-M: 20[redacted] | ONGOING |
| IBUPROFEN | 800 mg | QD | Y-M: 20[redacted] | ONGOING |
| PYRIDOXINE | 1 OTHER: TAB | QD | Y-M: 20[redacted] | ONGOING |
| TRAMADOL | 50 mg | QD | Y-M: 20[redacted] | ONGOING |
| PREDNISONE | 10 mg | QD | Y-M: 20[redacted] / -46 | ONGOING |
| PANTOPRAZOLE | 40 mg | QD | Y-M: 20[redacted] / 16 | ONGOING |
| DIPHENHYDRAMINE | 25 mg | OTHER: ONCE | Y-M: 20[redacted] / 16 | Y-M: 20[redacted] / 16 |
| HYDROMORPHONE | 0.5 mg | TID | Y-M: 20[redacted] / 16 | Y-M: 20[redacted] / 16 |
| METHYLPREDNISOLONE | 250 mg | TID | Y-M: 20[redacted] / 16 | Y-M: 20[redacted] / 16 |
| METOCLOPRAMIDE | 10 mg | OTHER: ONCE | Y-M: 20[redacted] / 16 | Y-M: 20[redacted] / 16 |
| PREDNISONE | 50 mg | QD | Y-M: 20[redacted] / 16 | Y-M: 20[redacted] / 27 |

**Event #1: Serious Adverse Event**

**Event Description** DEMYELINATING DISEASE FLARE

**Preferred term** 脱髄

**AE Onset Date / Rx Day** [redacted]20[redacted] / 16

**Age at AE Onset** 3[redacted]

**Laboratory Testing**

NOT REPORTED

**Microbiology**

[redacted]20[redacted] (RX DAY 17): CEREBROSPINAL FLUID NPTST307-LUMBAR PUNCTURE: Negative

**SAE Supplemental Procedure**

[redacted]20[redacted] (RX DAY 16): MRI BRAIN W/ +W/O CONTRAST: 1. REDEMONSTRATED NUMEROUS SUPRATENTORIAL WHITE MATTER LESIONS, NONSPECIFIC BUT SIGNIFICANTLY GREATER THAN EXPECTED FOR AGE. THE MAJORITY OF LESIONS APPEAR SIMILAR TO THE PRIOR STUDY, ALTHOUGH A FEW LESIONS APPEAR SLIGHTLY INCREASED IN CONSPICUITY AND A FEW LESIONS APPEAR SLIGHTLY DECREASED IN CONSPICUITY. FINDINGS PRESUMABLY RELATE TO THE PATIENT'S HISTORY OF DEMYELINATING DISEASE. NO ENHANICINGLESION IS IDENTIFIED TO SUGGEST ACTIVE DEMYELINATION 2 NO ACUTE INFARCTION OR HEMORRAGE; [redacted]20[redacted] (RX DAY 17): FL LUMBAR PUNCTURE: RESULTS NO OLIGOCLONAL BANDS CSF PROTEIN LEVEL WAS NORMAL; MRI SPINE CERVICAL W/ + W/O CONTRAST: NO MRI FEATURES OF DEMYELINATING DISEASE EARLY DEGENERATIVE SPONDYLOSIS. NO SIGNIFICANT CANAL STENOSIS NO FORAMINAL NARROWING

**AE Stopped Rx Day** 20

**Duration of AE** 5 DAYS

**Severity** Moderate

**Relation to Study Drug by Investigator** No Reasonable Possibility

| | |
|---|---|
| **Investigator Alternative Etiology** | [redacted] 20[redacted] SHE HAD WORKUP FOR WEAKNESS |
| **Discontinued Study Drug Due to the Event** | NO |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

Generated: [redacted]
Program Source Code [redacted]

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 3[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，脱髄性疾患の再燃の事象を発現した。

**Event 1 の臨床経過：**

関連する病歴は，肥満，局面型乾癬，乾癬性関節炎，脱髄性疾患，非喫煙者，禁酒及び多発性硬化症疑いの病歴であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。本事象発現前において，盲検化された皮下注製剤の最終投与は 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は脱髄性疾患の再燃を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，脱髄性疾患の再燃は消失した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は救急科を受診し，「あちこちの」痛み，頭痛，脱力，歩行困難，発話困難，手指関節痛（大抵は午前中に出現し，1 日中持続）などを訴えた。被験者は，過去数ヵ月間にわたって進行性の脱力及び歩行困難があったと述べた。また被験者は，物を落としたり，日常生活動作を行うことができずに欠勤したりしたことを報告した。身体的診察で MCP 関節腫脹及び両膝・両肘・腹部の多発性局面型乾癬が認められた。その後，被験者は精査及び管理のため入院した。神経学的診察が完了した。20[redacted] 年 [redacted] 月 [redacted] 日，神経学医は脱髄性症候群と多発性硬化症（MS）の鑑別が必要であると暫定的に判断した。脊椎穿刺，転倒の評価及び頚椎 MRI の実施が推奨されるとともに，ソルメドロール（メチルプレドニゾロン）250 mg TID 2 日間の投与が開始された。腰椎穿刺でオリゴクローナルバンドは存在しないことが確認された。理学療法が追加で指示された。20[redacted] 年 [redacted] 月 [redacted] 日，神経学医の印象では，結合組織障害で見られることがある脱髄性症候群の可能性が高く，MS に典型的な所見ではなかった（CSF 検査も陰性）。入院中，被験者の症状は改善した。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院し，神経学医による

経過観察を受けることとなった。

被験者は本治験を中止した。

投与された薬剤は，オンダンセトロン，ヒドロモルフォン，ヒドロモルフォン-アセトアミノフェン，プロクロルペラジン，ソル・メドロール及び dilaudid であった。

Causality for UPADACITINIB (Blinded)

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1) Demyelination (10012305) (Demyelination (10012305) ) [v.22.1] [10012305]

**Causality as per reporter (DruVaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** rechallenge was done, reaction did not recur

Alternative Etiology for UPADACITINIB (Blinded)

---

Event of DEMYELINATING DISEASE FLARE

**- Investigator:** [redacted] 20[redacted]: The patient had a work-up for weakness.

**- AbbVie:** Reported event is more likely related to pre-existing Demyelinating disease associated with abnormal MRI finding ([redacted] 20[redacted])

Relevant Laboratory & Other Diagnostic Tests

---

[redacted] **20[redacted] BLOOD PRESSURE:** 142/80mmHg

[redacted] **20[redacted] CREATININE:** 0.5 no unit

[redacted] **20[redacted] EKG:** Normal sinus rhythm. 74bpm. Nonspecific T waves. No ST elevation or depression. QTc 435ms.

[redacted] **20[redacted] FL LUMBAR PUNCTURE:** Results no oligoclonal bands CSF protein level was normal.

[redacted] **20[redacted] GLUCOSE:** 126 no unit

[redacted] **20[redacted] HGB:** 12.4 no unit

**20[redacted] LUMBAR PUNCTURE:** Positive for oligoclonal bands.

[redacted] **20[redacted] MRI BRAIN:** Numerous supratentorial white matter hyperintensities which was presumed to be related to demyelinating disease. No acute infarction or hemorrhage.

[redacted] **20[redacted] MRI BRAIN W/ +W/O CONTRAST:** 1. Redemonstrated numerous supratentorial white matter lesions, nonspecific but significantly greater than expected for age. The majority of lesions appear similar to the prior study, although a few lesions appear slightly increased in conspicuity and a few lesions appear slightly decreased in conspicuity. Findings presumably relate to the patient's history of demyelinating disease. No enhancing lesion is identified to suggest active demyelination. 2. No acute infarction or hemorrhage.

[redacted] **20[redacted] MRI LUMBAR SPINE:** Degenerative joint disease and moderate bulging disk.

[redacted] **20[redacted] MRI SPINE CERVICAL W/ + W/O CONTRAST:** No MRI features of demyelinating disease; early degenerative spondylosis. No significant canal stenosis no foraminal narrowing.

[redacted] **20[redacted] PLT:** 277 no unit

[redacted] **20[redacted] POTASSIUM:** 3.5 no unit

[redacted] **20[redacted] SODIUM:** 138 no unit

[redacted] **20[redacted] SPO2:** 99 %

[redacted] **20[redacted] TSH:** 2.38 no unit

[redacted] **20[redacted] WBC:** 9.2 no unit

被験者番号 [redacted] (Investigator [redacted])

**Reason for Narrative**

| Adverse Event Preferred Term(s) | Serious Adverse Event | Adverse Event Leading to Discontinuation of Study Drug | Death | Event of Interest |
|---|---|---|---|---|
| 上部消化管出血 | X | | | |
| 憩室炎 | X | | | X |

| Treatment Group | Age at Study Start | Sex | Race |
|---|---|---|---|
| UPA 15 mg QD | 6[redacted] | FEMALE | WHITE |

| Medical History | Onset Year |
|---|---|
| OTHER: CYST ON VOCAL CORDS | 19[redacted] |
| HYPERTENSION | 19 |
| OTHER: POST MENOPAUSAL | 19 |
| GOUT: HISTORY OF GOUT-INACTIVE | 20 |
| COGNITIVE OR PSYCHIATRIC DISORDER: INSOMNIA | 20 |
| DIABETES MELLITUS: TYPE II | 20 |
| OTHER: DIABETIC NEUROPATHY | 20 |
| ANEMIA: LACK OF HEALTHY RED BLOOD CELLS | 20 |
| GASTROINTESTINAL BLEED: BLEEDING IN THE INTESTINE | 20 |
| MYOCARDIAL INFARCTION | 20 |
| OTHER: HERNIATED DISKS LOWER BACK | 20 |
| CONGESTIVE HEART FAILURE | 20 |
| MYOCARDIAL INFARCTION | 20 |
| COGNITIVE OR PSYCHIATRIC DISORDER: ANXIETY | 20 |
| HYPOTHYROIDISM | 20 |
| OTHER: PLAQUE PSORIASIS | 20 |
| PSORIATIC ARTHRITIS | 20 |
| OTHER: CKE-STAGE 3 | 20 |
| OTHER: HYPERCHOLESTEROLEMIA | 20 |

| Prior Procedures | Procedure Year |
|---|---|
| SURGERY: TRACHEOTOMY | 19[redacted] |
| SURGERY: C-SECTION | 19 |
| SURGERY: TUBAL LIGATION | 19 |
| SURGERY: LEFT HIP REPLACED | 20 |
| SURGERY: RT HIP REPLACED | 20 |
| SURGERY: LFT KNEE REPLACED | 20 |

| Tobacco Use | Status | Number/Day | Number of Years | Year Stopped |
|---|---|---|---|---|
| CHEWING TOBACCO | NEVER | | | |
| CIGARETTES | NEVER | | | |
| CIGARS | NEVER | | | |

| | |
|---|---|
| E-CIGARETTES | NEVER |
| PIPES | NEVER |

| Alcohol Use | Status | Number/Day |
|---|---|---|
| ALCOHOL | NEVER | |

**Study Drug Administration**

| Study Drug | Dose/Units | Route | Frequency | First Dose Date/Day | Last Dose Date/Day | Duration (Days) |
|---|---|---|---|---|---|---|
| ABT-494 | 15 MG | ORAL | QD | [redacted]20[redacted] / 1 | [redacted]20[redacted] / 171 | 171 |
| ABT-494 | 15 MG | ORAL | QD | [redacted]20[redacted] / 172 | [redacted]20[redacted] / 221 | 50 |

**Previous Therapy - Prior to baseline/enrollment**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day |
|---|---|---|---|
| GABAPENTIN | 600 mg | TID | Y-M: 20[redacted] |
| ALLOPURINOL | 100 mg | QD | Y-M: 20[redacted] |
| HEPATITIS B IMMUNIZATION | NOT REPORTED | NOT REPORTED | Y-M: 20[redacted] |
| TRAZODONE | 150 mg | QD | Y-M: 20[redacted] |
| FUROSEMIDE | 40 mg | QD | Y-M: 20[redacted] |
| INSULIN ASPART | 40 OTHER: UNITS | BID | Y-M: 20[redacted] |
| RISTFOR | 50/1000 mg | BID | Y-M: 20[redacted] |
| ATORVASTATIN | 10 mg | QD | Y-M: 20[redacted] |
| IBUPROFEN | 600 mg | TID | Y-M: 20[redacted] / -352 |
| LEVOTHYROXINE | .025 mg | QD | Y-M: 20[redacted] / -352 |
| NAPROXEN | 500 mg | BID | Y-M: 20[redacted] / -352 |
| CITALOPRAM | 20 mg | QD | Y-M: 20[redacted] / -168 |
| FOLIC ACID | 1 mg | QD | Y-M: 20[redacted] / -168 |
| METHOTREXATE | 7.5 mg | EVERY WEEK | Y-M: 20[redacted] / -168 |

**Other Medications - Medications taken within 30 days prior to each narrative event until AE stopped or end of study**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day | Stop Year-Month / RX Day |
|---|---|---|---|---|
| GABAPENTIN | 600 mg | TID | Y-M: 20[redacted] | ONGOING |
| TRAZODONE | 150 mg | QD | Y-M: 20[redacted] | ONGOING |
| FUROSEMIDE | 40 mg | QD | Y-M: 20[redacted] | ONGOING |
| INSULIN ASPART | 40 OTHER: UNITS | BID | Y-M: 20[redacted] | ONGOING |
| RISTFOR | 50/1000 mg | BID | Y-M: 20[redacted] | ONGOING |
| ATORVASTATIN | 10 mg | QD | Y-M: 20[redacted] | ONGOING |
| LEVOTHYROXINE | .025 mg | QD | Y-M: 20[redacted] / -352 | ONGOING |
| IBUPROFEN | 600 mg | TID | Y-M: 20[redacted] / -352 | Y-M: 20[redacted] / 181 |
| NAPROXEN | 500 mg | BID | Y-M: 20[redacted] / -352 | Y-M: 20[redacted] / 181 |
| CITALOPRAM | 20 mg | QD | Y-M: 20[redacted] / -168 | ONGOING |

| | | | | |
|---|---|---|---|---|
| FOLIC ACID | 1 mg | QD | Y-M: 20[redacted] / - 168 | ONGOING |
| METHOTREXATE | 7.5 mg | EVERY WEEK | Y-M: 20[redacted] / - 168 | ONGOING |
| NITROFURANTOIN | 100 mg | BID | Y-M: 20[redacted] / 144 | Y-M: 20[redacted] / 171 |
| BISMUTH | 17.6 mg | PRN | Y-M: 20[redacted] / 168 | ONGOING |
| LOPERAMIDE | 2 mg | PRN | Y-M: 20[redacted] / 168 | ONGOING |
| BLOOD AND RELATED PRODUCTS | 2 OTHER: UNITS | OTHER: ONCE | Y-M: 20[redacted] / 177 | Y-M: 20[redacted] / 177 |
| ONDANSETRON | 4 mg | OTHER: ONCE | Y-M: 20[redacted] / 177 | Y-M: 20[redacted] / 177 |
| PANTOPRAZOLE | 80 mg | OTHER: ONCE | Y-M: 20[redacted] / 177 | Y-M: 20[redacted] / 177 |
| PIPERACILLIN W/TAZOBACTAM | 100 mL | OTHER: ONCE | Y-M: 20[redacted] / 177 | Y-M: 20[redacted] / 177 |
| SODIUM CHLORIDE | 500 mL | OTHER: ONCE | Y-M: 20[redacted] / 177 | Y-M: 20[redacted] / 177 |
| PANTOPRAZOLE | 40 mg | QD | Y-M: 20[redacted] / 179 | ONGOING |
| SUCRALFATE | 1 g | QID | Y-M: 20[redacted] / 179 | ONGOING |
| TRAMADOL | 50 mg | QID | Y-M: 20[redacted] / 181 | ONGOING |
| CIPROFLOXACIN | 400 mg | OTHER: ONCE | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| METRONIDAZOLE | 500 mg | OTHER: ONCE | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| ONDANSETRON | UNKNOWN OTHER: UNKNOWN | OTHER: UNKNOWN | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| PANADEINE CO | 30/300 mg | PRN | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| RED BLOOD CELLS | 1 OTHER: UNIT | OTHER: ONCE | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| SODIUM CHLORIDE | UNKNOWN OTHER: UNKNOWN | OTHER: UKNOWN | Y-M: 20[redacted] / 238 | Y-M: 20[redacted] / 238 |
| PLATELETS | 1 OTHER: UNIT | OTHER: ONCE | Y-M: 20[redacted] / 244 | Y-M: 20[redacted] / 244 |
| RED BLOOD CELLS | 2 OTHER: UNITS | OTHER: ONCE | Y-M: 20[redacted] / 244 | Y-M: 20[redacted] / 244 |

**Event #1: Serious Adverse Event**

| | |
|---|---|
| **Event Description** | UPPER GI BLEED |
| **Preferred term** | 上部消化管出血 |
| **AE Onset Date / Rx Day** | [redacted]20[redacted] / 177 |
| **Age at AE Onset** | 6[redacted] |

**Laboratory Testing**

[redacted]20[redacted] (RX DAY 177): Albumin: 31 [36 - 51] G/L; Blood Urea Nitrogen: 16.8 [2.1 - 8.6] MMOL/L; Creatinine: 133 [44 - 88] UMOL/L; Erythrocytes: 2.4 [3.9 - 5] 10^12/L; Hematocrit: 0.24 [0.35 - 0.45] FRACTION OF 1; Hemoglobin: 77 [120 - 155] G/L; Leukocytes: 13.4 [4.8 - 10.8] 10^9/L; NPTST006-A/G RATIO: 1 [1.5 - 2.5] RATIO; NPTST091-BNP: 155

[0 - 100] PG/ML; NPTST200-FECAL OCCULT BLOOD: POSITIVE [0 - 0] POSITIVE OR NEGATIVE, NO UNITS; NPTST297-LACTIC ACID: 3.1 [0 - 2] MMOL/L; NPTST317-MCHC: 32.4 [33.4 - 35.5] G/DL; NPTST318-MCV: 100.4 [82.5 - 98] FL; NPTST399-PROTIME: 12.7 [9.5 - 12.5] SEC; NPTST414-RDW: 16.7 [11.8 - 15.6] %; NPTST472-TROPONIN I: 0.05 [0 - 0.04] NG/ML; Neutrophils: 10.3 [1.7 - 7] 10^9/L; Protein: 62 [64 - 84] G/L; [redacted]20[redacted] (RX DAY 178): Blood Urea Nitrogen: 14.3 [2.1 - 8.6] MMOL/L; Calcium: 2.05 [2.15 - 2.59] MMOL/L; Chloride: 112 [98 - 110] MMOL/L; Creatinine: 141 [44 - 88] UMOL/L; Hematocrit: 0.26 [0.35 - 0.45] FRACTION OF 1; Hemoglobin: 83 [120 - 155] G/L; [redacted]20[redacted] (RX DAY 179): Blood Urea Nitrogen: 13.2 [2.1 - 8.6] MMOL/L; Calcium: 1.95 [2.15 - 2.59] MMOL/L; Creatinine: 150 [44 - 88] UMOL/L; Erythrocytes: 2.5 [3.9 - 5] 10^12/L; Hematocrit: 0.25 [0.35 - 0.45] FRACTION OF 1; Hemoglobin: 83 [120 - 155] G/L; Leukocytes: 10.9 [4.8 - 10.8] 10^9/L; NPTST414-RDW: 17.6 [11.8 - 15.6] %; [redacted]20[redacted] (RX DAY 180): Erythrocytes: 2.5 [3.9 - 5] 10^12/L; Hematocrit: 0.24 [0.35 - 0.45] FRACTION OF 1; Hemoglobin: 79 [120 - 155] G/L; NPTST317-MCHC: 32.8 [33.4 - 35.5] G/DL; NPTST414-RDW: 17.3 [11.8 - 15.6] %

**Microbiology**

[redacted]20[redacted] (RX DAY 179): OTHER STOMACH BX NPTST366-PATHOLOGY EXAM: Not applicable-ACTIVE EROSIVE GASTRITIS; NO HELICOBACTERPYLORI ORGANISMS IDENTIFIED

**SAE Supplemental Procedure**

[redacted]20[redacted] (RX DAY 177): CT ABDOMEN PELVIS WITHOUT ORAL OR IV CONTRAST: NO EVIDENCE OF ACUTE INTRA-ABDOMINAL PROCESS; DIVERTICULOSIS WITHOUT EVIDENCE OF DIVERTICULITIS; SUBCUTANEOUS STRANDING ALONG THE ANTERIOR ABDOMINAL WALL GREATEST ON THE RIGHT WHICH MAY BE RELATED TOSCARRING OR EDEMA; POSSIBILITY OF CELLULITIS IS NOT EXCLUDED.; EKG: SINUS TACHYCARDIA; X-RAY CHEST 1 VIEW: THE LUNGS ARE HYPEREXPANDED; PULMONARY VASCULARITY IS PROMINENT; THERE IS AN ENLARGED CARDIOMEDIASTINAL SILHOUETTE; OSSEOUS STRUCTURES ARE WITHIN EXPECTED LIMITS FOR PATIENT'S AGE. CARDIOMEGALY WITHPROMINENCE OF PULMONARY VASCULARITY; PLEASE CORRELATE FOR EARLY CHF.; [redacted]20[redacted] (RX DAY 178): ESOPHAGOGASTRODUODENOSCOPY WITH BIOPSY: MEDIUM HIATAL HERNIA; EROSIVE GASTRITIS - ONE 5 MM ULCER WITH A CLEAN BASE NOTED IN THE ANTRUM.

| | |
|---|---|
| **AE Stopped Rx Day** | 178 |
| **Duration of AE** | 2 DAYS |
| **Severity** | Severe |
| **Relation to Study Drug by Investigator** | No Reasonable Possibility |
| **Investigator Alternative Etiology** | BLEEDING ULCERS |
| **Discontinued Study Drug Due to the Event** | NO |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

**Event #3: Serious Adverse Event, Event of Interest - Serious Infections**

| | |
|---|---|
| **Event Description** | DIVERTICULITIS |
| **Preferred term** | 憩室炎 |
| **AE Onset Date / Rx Day** | [redacted]20[redacted] / 238 (17 DAYS AFTER LAST TREATMENT) |
| **Age at AE Onset** | 6[redacted] |

**Laboratory Testing**

[redacted]20[redacted] (RX DAY 238): Hemoglobin: 70 [120 - 155] G/L; NPTST355-OCCULT BLOOD X 1: NEG [NOT REPORTED - NOT REPORTED] UNKNOWN; NPTST358-OVA PARASITE SCREEN: NO OVA, CYST, OR PAR [NOT REPORTED - NOT REPORTED] UNKOWN; NPTST432-SHIGA-LIKE TOXIN ANTIGEN, EIA: NEGATIVE [NOT REPORTED - NOT REPORTED] UNKNOWN; Platelets: 68 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 239): Hemoglobin: 78 [120 - 155] G/L; Hemoglobin: 78 [120 - 155] G/L; NPTST156-CULTURE: NEGATIVE [NOT REPORTED - NOT REPORTED] UNKNOWN; Platelets: 55 [150 - 450] 10^9/L; Platelets: 62 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 240): Hemoglobin: 70 [120 - 155] G/L; Hemoglobin: 75 [120 - 155] G/L; Platelets: 40 [150 - 450] 10^9/L; Platelets: 23 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 241): Hemoglobin: 76 [120 - 155] G/L; Platelets: 25 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 242): Hemoglobin: 78 [120 - 155] G/L; Platelets: 27 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 243): Hemoglobin: 71 [120 - 155] G/L; Platelets: 21 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 244): Hemoglobin: 76 [120 - 155] G/L; Hemoglobin: 78 [120 - 155] G/L; Platelets: 19 [150 - 450] 10^9/L; Platelets: 18 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 245): NPTST355-OCCULT BLOOD X 1: POSITIVE [NOT REPORTED - NOT REPORTED] UNKNOWN; [redacted]20[redacted] (RX DAY 246): Hemoglobin: 94 [120 - 155] G/L; NPTST365-PATHOLOGY: ABNORMAL [NOT REPORTED - NOT REPORTED] UNKNOWN; Platelets: 40 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 247): Hemoglobin: 87 [120 - 155] G/L; Platelets: 58 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 248): Hemoglobin:

288 [120 - 155] G/L; Platelets: 99 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 249): Hemoglobin: 96 [120 - 155] G/L; Hemoglobin: 94 [120 - 155] G/L; Platelets: 207 [150 - 450] 10^9/L; Platelets: 164 [150 - 450] 10^9/L; [redacted]20[redacted] (RX DAY 250): Hemoglobin: 90 [120 - 155] G/L; Platelets: 241 [150 - 450] 10^9/L

**Microbiology**

NOT REPORTED

**SAE Supplemental Procedure**

[redacted]20[redacted] (RX DAY 238): CT ABDOMEN PELVIS WITHOUT ORAL OR IV CONTRAST: SIGMOID DIVERTICULOSIS WITH EARLY OR MILD CHANGES OF DIVERTICULITIS. NO MASS, FREE FLUID OR ADENOPATHY.; EKG: ACCELERATED JUNCTIONAL RHYTHM, LOW VOLTAGE, EXTREMITY AND PRECORDIAL LEADS, PROBABLE ANTEROSEPTAL INFARCT; X-RAY CHEST 1 VIEW: NO ACUTE RADIOGRAPHIC ABNORMALITIES. NO CHANGE BORDERLINE HEART SIZE COMPARED WITH PRIOR STUDY.; [redacted]20[redacted] (RX DAY 239): BX DUODENAL MASS: CHANGES C/W ACTIVE EROSIVE PEPTIC DUODENOPATHY.; ESOPHAGOGASTRODUODENSCOPY/EGD/EUS: EUS:EXERTION THE PANCREAS FROM THE BODY OF THE STOMACH REVEALED THE 4.8 MM HYPOECHOIC LESION WITH A HYPERECHOIC CENTER IN THE GENU OF THE PANCEAS. MY INTENTION WAS TO FNA THIS HOWEVER PATIENT COULD NOT TOLERATE ANESTHESIA ANY FURTHER AS SUCH THE PROCEDURE HAD TO BE ABORTED. PLEASE NOTE THAT I WAS ALSO UNABLE TO EXAMINE THE HEAD OF THE PANCREAS AND AMPULLA DUE TO THE FACT THE PATIENT COULD NOT TOLERATE THE ANESTHESIA. EGD:OROPHARYNX: LIMITED EXAM OF THE POSTERIOR PHARYNX, VOCAL CORDS AND UES APPEARED NORMAL. GE JUNCTION: NORMAL. ESPHAGUS: NORMAL. STOMACH: GASTRITIS. BIOPSIED.ONE 4 MM ULCER.; STOMACH BX: MILD CHRONIC INACTIVE GASTRITIS. NO HELICOBACTER PYLORI ORGANISMS IDENTIFIED; [redacted]20[redacted] (RX DAY 240): PERIPHERAL SMEAR: PANCYTOPENIA WITH SEVERE MACROCYTIC ANEMIA, SLIGHT NEUTROPHILIC LEFT SHIFT, AND THROMBOCYTOPENIA; [redacted]20[redacted] (RX DAY 246): BONE MARROW ASPIRATION: CHANGES C/W MYELODYSPLASTIC SYNDROME WITH MULTIDINEAGE DYSPLASIA & 3-4% BLASTS. HYPERCELLULAR BONE MARROW (50%) WITH ERYTHROID HYPERPLASIA

| | |
|---|---|
| **AE Stopped Rx Day** | 253 (32 DAYS AFTER LAST TREATMENT) |
| **Duration of AE** | 16 DAYS |
| **Severity** | Severe |
| **Relation to Study Drug by Investigator** | No Reasonable Possibility |
| **Investigator Alternative Etiology** | DIVERTICULOSIS |
| **Discontinued Study Drug Due to the Event** | NO |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

Generated: [redacted]
Program Source Code: [redacted]

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 6[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，上部消化管出血の事象を発現した。

**Event 1 の臨床経過：**

関連する病歴は，2 型糖尿病，局面型乾癬，非喫煙者及び非飲酒者であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。本事象発現前において，盲検化された皮下注製剤の最終投与は 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は上部消化管出血を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，上部消化管出血は消失した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は胃腸出血，トロポニン増加，急性失血性貧血，裂孔ヘルニア，消化性潰瘍疾患及びびらん性胃炎で入院した。被験者は悪心，嘔吐及び下痢の症状を呈していた。被験者は改善し，20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院した。

被験者が使用していたナプロキセン及びイブプロフェンが本事象の危険因子であると考えられた。

投与された薬剤は，塩化ナトリウム 0.9%，zofran，スクラルファート，ピペラシリン・タゾバクタム合剤及び pantoprazole であった。

Causality for ABT-494 (Blinded)

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1) Upper gastrointestinal bleeding (10071910) (Upper gastrointestinal haemorrhage (10046274) ) [v.22.0] [10071910]

**Causality as per reporter (Drug/Vaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** rechallenge was done, reaction did not recur

Alternative Etiology for ABT-494 (Blinded)

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Event of UPPER GI BLEED

**- Investigator:** BLEEDING ULCERS

**- AbbVie:** RISK FACTORS INCLUDE SUBJECT'S LONG TERM USE OF NAPROXEN and methotrexate.

Relevant Laboratory & Other Diagnostic Tests

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[redacted] **20[redacted] A/G RATIO:** 1.0 ratio (normal 1.5 to 2.5)

[redacted] **20[redacted] ALBUMIN:** 3.1 G/DL (normal 3.6 to 5.1)

[redacted] **20[redacted] BNP:** 155 PG/ML (normal 0 to 100)

[redacted] **20[redacted] BUN:** 47 mg/dL (normal 6.0 to 24)

[redacted] **20[redacted] BUN:** 40 mg/dL

[redacted] **20[redacted] BUN:** 37.0 mg/dL

[redacted] **20[redacted] CREATININE:** 1.5 mg/dL (normal 0.5 to 1.0)

[redacted] **20[redacted] CREATININE:** 1.7 mg/dL (normal 0.5 to 1.0)

[redacted] **20[redacted] CT ABDOMEN AND PELVIS:** NO EVIDENCE OF ACUTE INTRA-ABDOMINAL PROCESS; DIVERTICULOSIS WITHOUT EVIDENCE OF DIVERTICULITIS; SUBCUTANEOUS STRANDING ALONG THE ANTERIOR ABDOMINAL WALL GREATEST ON THE RIGHT WHICH MAY BE RELATED TO SCARRING OR EDEMA; POSSIBILITY OF CELLULITIS IS NOT EXCLUDED.

[redacted] **20[redacted] CT ABDOMEN AND PELVIS:** NO EVIDENCE OF ACUTE INTRA-ABDOMINAL PROCESS; DIVERTICULOSIS WITHOUT EVIDENCE OF DIVERTICULITIS; SUBCUTANEOUS STRANDING ALONG THE ANTERIOR ABDOMINAL WALL GREATEST ON THE RIGHT WHICH MAY BE RELATED TO SCARRING OR EDEMA; POSSIBILITY OF CELLULITIS IS NOT EXCLUDED.

[redacted] **20[redacted] EGD WITH BIOPSY:** MEDIUM HIATAL HERNIA; EROSIVE GASTRITIS - ONE 5 MM ULCER WITH A CLEAN BASE NOTED IN THE ANTRUM.

[redacted] **20[redacted] EGD WITH BIOPSY:** MEDIUM HIATAL HERNIA; EROSIVE GASTRITIS - ONE 5 MM ULCER WITH A CLEAN BASE NOTED IN THE ANTRUM.

[redacted] **20[redacted] EKG:** SINUS TACHYCARDIA

[redacted] **20[redacted] FECAL OCCULT BLOOD:** Positive

[redacted] **20[redacted] HEMATOCRIT:** 23.7 % (normal 34.9 to 44.5)

[redacted] **20[redacted] HEMATOCRIT:** 25.8 % (normal 34.9 to 44.5)

[redacted] **20[redacted] HEMATOCRIT:** 24.6 % (normal 34.9 to 44.5)

[redacted] **20[redacted] HEMATOCRIT:** 24.1 % (normal 34.9 to 44.5)

[redacted] **20[redacted] HEMOGLOBIN:** 7.7 G/DL (normal 12 to 15.5)

[redacted] **20**[redacted] **HEMOGLOBIN:** 8.3 G/DL (normal 12 to 15.5)

[redacted] **20**[redacted] **HEMOGLOBIN:** 8.3 G/DL (normal 12 to 15.5)

[redacted] **20**[redacted] **HEMOGLOBIN:** 7.9 G/DL (normal 12 to 15.5)

[redacted] **20**[redacted] **LACTIC ACID:** 3.1 MMOL/L (normal 0 to 2)

[redacted] **20**[redacted] **MCHC:** 32.8 G/DL (normal 33.4 to 35.5)

[redacted] **20**[redacted] **NEUTROPHILS ABS:** 10.3 X10**3/MCL (normal 1.7 to 7.0)

[redacted] **20**[redacted] **PATHOLOGY:** Stomach biopsy: active erosive gastritis, no helicobacter pylori organisms identified

[redacted] **20**[redacted] **PROTIME:** 12.7 SEC (normal 9.5 to 12.5)

[redacted] **20**[redacted] **RBC:** 2.36 X10**6/MCL (normal 3.9 to 5.03)

[redacted] **20**[redacted] **RBC:** 2.52 X10**6/MCL (normal 3.9 to 5.03)

[redacted] **20**[redacted] **RBC:** 2.47 X10**6/MCL (normal 3.9 to 5.03)

[redacted] **20**[redacted] **RDW:** 17.3 % (normal 11.8 to 15.6)

[redacted] **20**[redacted] **TOTAL PROTEIN:** 6.2 G/DL (normal 6.4 to 8.4)

[redacted] **20**[redacted] **TROPONIN I:** 0.05 NG/ML (normal 0 to 0.04)

[redacted] **20**[redacted] **WBC:** 13.4 X10**3/MCL (normal 4.8 to 10.8)

[redacted] **20**[redacted] **WBC:** 10.9 X10**3/MCL (normal 4.8 to 10.8)

[redacted] **20**[redacted] **X-RAY CHEST:** THE LUNGS ARE HYPEREXPANDED; PULMONARY VASCULARITY IS PROMINENT; THERE IS AN ENLARGED CARDIOMEDIASTINAL SILHOUETTE; OSSEOUS STRUCTURES ARE WITHIN EXPECTED LIMITS FOR PATIENT'S AGE. CARDIOMEGALY WITH PROMINENCE OF PULMONARY VASCULARITY; PLEASE CORRELATE FOR EARLY CHF.
**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 6[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，憩室炎の事象を発現した。

**Event 3 の臨床経過：**

関連する病歴は，高血圧，2 型糖尿病，糖尿病性ニューロパチー，胃腸出血，甲状腺機能低下症，局面型乾癬，乾癬性関節炎，CKE-STAGE 3，非喫煙者，非飲酒者及び貧血であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。本事象発現前において，盲検化された皮下注製剤の最終投与は 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は憩室炎を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，憩室炎は消失した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は重篤な事象である上部消化管出血を発現した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は救急科を受診し，疲労，直腸出血及び吐血を訴えた。被験者はその後入院した。RBC 輸血及び血小板アフェレーシス輸血が行われた。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院した。

治験責任医師によると，過去の上部消化管出血が危険因子であると考えられた。

投与された薬剤は，メトロニダゾール，シプロフロキサシン，塩化ナトリウム，zofran，ピペラシリン・タゾバクタム合剤，pantoprazole 及びアセトアミノフェン・コデイン合剤であった。

**The patient's past medications include:**

IBUPROFEN for PSORIATIC ARTHRITIS ([redacted] 20[redacted] - [redacted] 20[redacted])

NAPROXEN for PSORIATIC ARTHRITIS ([redacted] 20[redacted] - [redacted] 20[redacted])

CIPRO for URINARY TRACT INFECTION ([redacted] 20[redacted] - [redacted] 20[redacted])

NITROFURANTOIN for URINARY TRACT INFECTION ([redacted] 20[redacted] - [redacted] 20[redacted])

Causality for ABT-494 (Blinded)

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1) Diverticulitis (10013538) (Diverticulitis (10013538) ) [v.21.1] [10013538]

**Causality as per reporter (Drug/Vaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Not Applicable

Alternative Etiology for ABT-494 (Blinded)

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Event of DIVERTICULITIS

**- Investigator:** Diverticulosis

**- AbbVie:** EVENT IS MORE LIKELY RELATED TO SUBJECT'S AGE AND MORBID OBESITY .

Relevant Laboratory & Other Diagnostic Tests

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[redacted] **BIOPSY:** Positive SMALL INTESTINE 'DUODENAL MASS' ENDOSCOPIC BIOPSY: CHANGES C/W ACTIVE EROSIVE PEPTIC DUODENOPATHY. STOMACH, ANTRUM AND BODY, ENDOSCOPIC BIOPSIES: MILD CHRONIC INACTIVE GASTRITIS, NO H.PYLORI ORGANISMS IDENTIFIED

[redacted] **BIOPSY STOMACH:** MILD CHRONIC INACTIVE GASTRITIS. NO HELICOBACTER PYLORI ORGANISMS IDENTIFIED

[redacted] **BONE MARROW ASPIRATION:** CHANGES CONSISTENT WITH MYELODYSPLASTIC SYNDROME WITH MULTIDINEAGE DYSPLASIA & 3-4% BLASTS. HYPERCELLULAR BONE MARROW (50%) WITH ERYTHROID HYPERPLASIA (abnormal)

[redacted] **CHEST X-RAY:** Mild cardiomegaly

[redacted] **CT ABDOMEN PELVIS WITHOUT ORAL OR IV CONTRAST:** SIGMOID DIVERTICULOSIS WITH EARLY OR MILD CHANGES OF DIVERTICULITIS. NO MASS, FREE FLUID OR ADENOPATHY

[redacted] **DUODENAL MASS BIOPSY:** CHANGES CONSISTENT WITH ACTIVE EROSIVE PEPTIC DUODENOPATHY.

[redacted] **EKG:** ACCELERATED JUNCTIONAL RHYTHM, LOW VOLTAGE, EXTREMITY AND PRECORDIAL LEADS, PROBABLE ANTEROSEPTAL INFARCT

[redacted] **ESOPHAGOGASTRODUODENOSCOPY:** EUS: EXERTION THE PANCREAS FROM THE BODY OF THE STOMACH REVEALED THE 4.8 MM HYPOECHOIC LESION WITH A HYPERECHOIC CENTER IN THE GENU OF THE PANCEAS. MY INTENTION WAS TO FNA THIS, HOWEVER, PATIENT COULD NOT TOLERATE ANESTHESIA ANY FURTHER AS SUCH THE PROCEDURE HAD TO BE ABORTED. PLEASE NOTE THAT I WAS ALSO UNABLE TO EXAMINE THE HEAD OF THE PANCREAS AND AMPULLA DUE TO THE FACT THE PATIENT COULD NOT TOLERATE THE ANESTHESIA. EGD:OROPHARYNX: LIMITED EXAM OF THE POSTERIOR PHARYNX, VOCAL CORDS AND UES APPEARED NORMAL. GE JUNCTION: NORMAL. ESPHAGUS: NORMAL. STOMACH: GASTRITIS. BIOPSIED.ONE 4 MM ULCER.

[redacted] 20[redacted] **HEMOGLOBIN:** 7.0 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.8 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.0 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.5 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.6 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.8 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.1 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.6 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 7.8 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 8.7 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 28.8 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 9.4 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **HEMOGLOBIN:** 9.0 G/DL (normal 12.0 to 15.50)

[redacted] 20[redacted] **NOSE CULTURE:** Negative

[redacted] 20[redacted] **OCCULT BLOOD:** Negative

[redacted] 20[redacted] **OCCULT BLOOD:** Positive

[redacted] 20[redacted] **PERIPHERAL SMEAR:** PANCYTOPENIA WITH SEVERE MACROCYTIC ANEMIA, SLIGHT NEUTROPHILIC LEFT SHIFT, AND THROMBOCYTOPENIA

[redacted] 20[redacted] **PLATELET COUNT:** 60 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 62 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 40 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 24 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 21 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 25 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 27 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 19 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 18 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 40 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 58 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 99 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 164 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 207 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **PLATELET COUNT:** 241 10^3/uL (normal 150 to 450)

[redacted] 20[redacted] **SHIGA-LIKE TOXIN ANTIGEN, EIA FROM STOOL SAMPLE:** Negative

[redacted] 20[redacted] **X-RAY CHEST 1 VIEW:** NO ACUTE RADIOGRAPHIC ABNORMALITIES. NO CHANGE BORDERLINE HEART SIZE COMPARED WITH PRIOR STUDY

被験者番号 [redacted] (Investigator [redacted])

**Reason for Narrative**

| Adverse Event Preferred Term(s) | Serious Adverse Event | Adverse Event Leading to Discontinuation of Study Drug | Death | Event of Interest |
|---|---|---|---|---|
| 頚部脊柱管狭窄症 | X | | | |

| Treatment Group | Age at Study Start | Sex | Race |
|---|---|---|---|
| Placebo to UPA 15 mg QD | 5[redacted] | MALE | WHITE |

| Medical History | Onset Year |
|---|---|
| OTHER: C4 C5 FUSION | 20[redacted] |
| OTHER: CERVICAL SPONDYLOSIS WITH MYELOPATHY | 20 |
| OTHER: VASOVAGAL SYNCOPE | 20 |
| OBESITY | 20 |
| OTHER: PERIPHERAL VASCULAR DISEASE BILATERAL FEET | 20 |
| OTHER: THYROTOXICOSIS | 20 |
| OTHER: DYSPEPSIA | 20 |
| DEPRESSION | 20 |
| OTHER: ANXIETY | 20 |
| OTHER: INSOMNIA | 20 |
| OTHER: ELEVATION OF LDH LEVELS | 20 |
| OTHER: NONSPECIFIC MILD ELEVATION OF TRANSAMINASE | 20 |
| OTHER: PLAQUE PSORIASIS | 20 |
| HYPERTENSION | 20 |
| OTHER: IRRITABLE BOWEL SYNDROME | 20 |
| OTHER: EXERCISE INDUCED ASTHMA | 20 |
| OTHER: LEFT HIP REPLACEMENT | 20 |
| PSORIATIC ARTHRITIS | 20 |

| Prior Procedures | Procedure Year |
|---|---|
| SURGERY: LEFT ULNAR TRANSPOSITION SURGERY | 20[redacted] |

| Tobacco Use | Status | Number/Day | Number of Years | Year Stopped |
|---|---|---|---|---|
| CHEWING TOBACCO | NEVER | | | |
| CIGARETTES | NEVER | | | |
| CIGARS | NEVER | | | |
| E-CIGARETTES | NEVER | | | |
| PIPES | NEVER | | | |

| Alcohol Use | Status | Number/Day |
|---|---|---|
| ALCOHOL | NEVER | |

**Study Drug Administration**

| Study Drug | Dose/Units | Route | Frequency | First Dose Date/Day | Last Dose Date/Day | Duration (Days) |
|---|---|---|---|---|---|---|
| PLACEBO | | ORAL | QD | [redacted] / 1 | [redacted] / 168 | 168 |
| ABT-494 | 15 MG | ORAL | QD | [redacted] / 169 | [redacted] / 390 | 222 |
| ABT-494 | 15 MG | ORAL | QD | [redacted] / 391 | | |

**Previous Therapy - Prior to baseline/enrollment**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day |
|---|---|---|---|
| OMEPRAZOLE | 40 mg | QD | Y-M: 20[redacted] |
| ESCITALOPRAM | 10 mg | QD | Y-M: 20[redacted] |
| VENLAFAXINE | 75 mg | QD | Y-M: 20[redacted] |
| BUSPIRONE | 20 mg | QD | Y-M: 20[redacted] |
| METHYLPREDNISOLONE | 40 mg | OTHER: ONCE | Y-M: 20[redacted] |
| LOSARTAN | 100 mg | QD | Y-M: 20[redacted] |
| ACETYLSALICYLIC ACID | 81 mg | QD | Y-M: 20[redacted] / -216 |
| SALBUTAMOL | 90 OTHER: MCG | PRN | Y-M: 20[redacted] / -216 |
| PREDNISONE | 20 mg | QD | Y-M: 20[redacted] / -210 |
| CELECOXIB | 200 mg | BID | Y-M: 20[redacted] / -169 |
| ESOMEPRAZOLE | 40 mg | QD | Y-M: 20[redacted] / -169 |
| LORAZEPAM | 0.5 mg | QD | Y-M: 20[redacted] / -169 |
| VALPROIC ACID | 250 mg | QD | Y-M: 20[redacted] / -169 |
| VENLAFAXINE | 75 mg | QD | Y-M: 20[redacted] / -169 |
| FOLIC ACID | 1 OTHER: TABLET | QD | Y-M: 20[redacted] / -160 |
| METHOTREXATE | 15 mg | EVERY WEEK | Y-M: 20[redacted] / -160 |
| METHOTREXATE | 20 mg | EVERY WEEK | Y-M: 20[redacted] / -132 |

**Other Medications - Medications taken within 30 days prior to each narrative event until AE stopped or end of study**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day | Stop Year-Month / RX Day |
|---|---|---|---|---|
| ESCITALOPRAM | 10 mg | QD | Y-M: 20[redacted] | NOT REPORTED |
| BUSPIRONE | 20 mg | QD | Y-M: 20[redacted] | NOT REPORTED |
| LOSARTAN | 100 mg | QD | Y-M: 20[redacted] | NOT REPORTED |
| ACETYLSALICYLIC ACID | 81 mg | QD | Y-M: 20[redacted] / -216 | NOT REPORTED |
| SALBUTAMOL | 90 OTHER: MCG | PRN | Y-M: 20[redacted] / -216 | NOT REPORTED |
| CELECOXIB | 200 mg | BID | Y-M: 20[redacted] / -169 | NOT REPORTED |
| ESOMEPRAZOLE | 40 mg | QD | Y-M: 20[redacted] / -169 | NOT REPORTED |
| LORAZEPAM | 0.5 mg | QD | Y-M: 20[redacted] / -169 | NOT REPORTED |
| VALPROIC ACID | 250 mg | QD | Y-M: 20[redacted] / -169 | NOT REPORTED |
| VENLAFAXINE | 75 mg | QD | Y-M: 20[redacted] / -169 | NOT REPORTED |
| FOLIC ACID | 1 OTHER: TABLET | QD | Y-M: 20[redacted] / -160 | NOT REPORTED |
| METHOTREXATE | 7.5 mg | EVERY WEEK | Y-M: 20[redacted] / 260 | NOT REPORTED |
| BUPIVACAINE | 0.25 % | OTHER: ONCE | Y-M: 20[redacted] / 318 | Y-M: 20[redacted] / 318 |
| EPINEPHRINE | 30 mL | OTHER: ONCE | Y-M: 20[redacted] / 318 | Y-M: 20[redacted] / 318 |

**Event #1: Serious Adverse Event**

| | |
|---|---|
| **Event Description** | CERVICAL STENOSIS |
| **Preferred term** | 頚部脊柱管狭窄症 |
| **AE Onset Date / Rx Day** | [redacted]20[redacted] / 318 |
| **Age at AE Onset** | [redacted] |

**Laboratory Testing**
NOT REPORTED

**Microbiology**
NOT REPORTED

**SAE Supplemental Procedure**
[redacted]20[redacted] (RX DAY 318): C3, C4, C5, C6, C7 POSTERIOR LAMINECTOMIES: EXTUBATED, AWAKE, AND STABLE TO THE RECOVERY ROOM IN GOOD CONDITION

| | |
|---|---|
| **AE Stopped Rx Day** | 321 |
| **Duration of AE** | 4 DAYS |
| **Severity** | Mild |
| **Relation to Study Drug by Investigator** | No Reasonable Possibility |
| **Investigator Alternative Etiology** | UNKNOWN |
| **Discontinued Study Drug Due to the Event** | NO |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

Generated: [redacted]
Program Source Code: [redacted]

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 5[redacted] 歳男性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，頚椎狭窄の事象を発現した。

**Event 1 の臨床経過：**

関連する病歴は，C4 及び C5 の融合，頚椎症性脊髄症，肥満，甲状腺中毒症，左尺骨転位術，局面型乾癬，左人工股関節置換術，乾癬性関節炎，非喫煙者及び非飲酒者であった。

本治験において，被験者は，盲検性維持のため，盲検化された経口製剤の連日投与と盲検化された皮下注製剤の 2 週ごとの投与を受ける予定である。本事象発現前において，盲検化された皮下注製剤の最終投与は 20[redacted] 年 [redacted] 月 [redacted] 日であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は頚椎狭窄を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，頚椎狭窄は消失した。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は，頚椎狭窄に続発した神経根障害に伴う薬剤抵抗性頚部痛のため入院した。同日，被験者は，頚椎狭窄治療並びに頚椎・神経根除圧のための C3，C4，C5，C6

及び C7 の後方椎弓切除術を受けた。治療の一環として理学療法が行われた。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院した。

Causality for UPADACITINIB (Blinded)

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1) Spinal stenosis cervical (10041593) (Cervical spinal stenosis (10008313) ) [v.22.1] [10041593]

**Causality as per reporter (Drug/Vaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** rechallenge was done, reaction did not recur

Alternative Etiology for UPADACITINIB (Blinded)

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Event of CERVICAL STENOSIS

**- Investigator:** Unknown

**- AbbVie:** Event more likely related to pre-existing cervical spondylosis with myelopathy and prior C4-C5 fusion [redacted] 20[redacted].

被験者番号 [redacted] (Investigator [redacted])

**Reason for Narrative**

| Adverse Event Preferred Term(s) | Serious Adverse Event | Adverse Event Leading to Discontinuation of Study Drug | Death | Event of Interest |
|---|---|---|---|---|
| 胸痛 | X | X | | X |

| Treatment Group | Age at Study Start | Sex | Race |
|---|---|---|---|
| Placebo to UPA 30 mg QD | 7[redacted] | FEMALE | WHITE |

| Medical History | Onset Year |
|---|---|
| OTHER: ARTHRITIS | 20[redacted] |
| HYPERTENSION | 20 |
| HYPOTHYROIDISM | 20 |
| OBESITY | 20 |
| OTHER: DIABETIC NEUROPATHY | 20 |
| OTHER: HYPERCHOLESTEREMIA | 20 |
| OTHER: PLAQUE PSORIASIS | 20 |
| DEPRESSION | 20 |
| PSORIATIC ARTHRITIS | 20 |
| DIABETES MELLITUS | 20 |
| OTHER: ALLERGIC TO MORPHINE SULFATE | 20 |
| OTHER: ATRIAL FIBRILLATION | 20 |
| OTHER: CORONARY ARTERY DISEASE | 20 |
| MYOCARDIAL INFARCTION | 20 |

| Prior Procedures | Procedure Year |
|---|---|
| SURGERY: HYSTERECTOMY | 19[redacted] |
| SURGERY: STENT RCA | 20 |

| Tobacco Use | Status | Number/Day | Number of Years | Year Stopped |
|---|---|---|---|---|
| CHEWING TOBACCO | NEVER | | | |
| CIGARETTES | FORMER | 1 PACK | 5 | 20[redacted] |
| CIGARS | NEVER | | | |
| E-CIGARETTES | NEVER | | | |
| PIPES | NEVER | | | |

| Alcohol Use | Status | Number/Day |
|---|---|---|
| ALCOHOL | NEVER | |

**Study Drug Administration**

| Study Drug | Dose/Units | Route | Frequency | First Dose Date/Day | Last Dose Date/Day | Duration (Days) |
|---|---|---|---|---|---|---|
| PLACEBO | | ORAL | QD | [redacted]20[redacted] / 1 | [redacted]20[redacted] / 112 | 112 |

**Previous Therapy - Prior to baseline/enrollment**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day |
|---|---|---|---|
| ATORVASTATIN | 80 mg | QD | Y-M: 20[redacted] |
| FOLIC ACID | 1 mg | QD | Y-M: 20[redacted] |
| GABAPENTIN | 900 mg | BID | Y-M: 20[redacted] |
| IRON | 325 mg | QD | Y-M: 20[redacted] |
| LEVOTHYROXINE | 75 OTHER: MCG | QD | Y-M: 20[redacted] |
| LISINOPRIL | 20 mg | BID | Y-M: 20[redacted] |
| METFORMIN | 850 mg | BID | Y-M: 20[redacted] |
| METHOTREXATE | 15 mg | EVERY WEEK | Y-M: 20[redacted] |
| METOPROLOL | 50 mg | QD | Y-M: 20[redacted] |
| APIXABAN | 5 mg | BID | Y-M: 20[redacted] / -240 |
| CLOPIDOGREL | 75 mg | QD | Y-M: 20[redacted] / -240 |

**Other Medications - Medications taken within 30 days prior to each narrative event until AE stopped or end of study**

| Medication Name (WHO Drug) | Dose/Units | Frequency | Start Year-Month / RX Day | Stop Year-Month / RX Day |
|---|---|---|---|---|
| ATORVASTATIN | 80 mg | QD | Y-M: 20[redacted] | ONGOING |
| FOLIC ACID | 1 mg | QD | Y-M: 20[redacted] | ONGOING |
| GABAPENTIN | 900 mg | BID | Y-M: 20[redacted] | ONGOING |
| IRON | 325 mg | QD | Y-M: 20[redacted] | ONGOING |
| LEVOTHYROXINE | 75 OTHER: MCG | QD | Y-M: 20[redacted] | ONGOING |
| LISINOPRIL | 20 mg | BID | Y-M: 20[redacted] | ONGOING |
| METFORMIN | 850 mg | BID | Y-M: 20[redacted] | ONGOING |
| METHOTREXATE | 15 mg | EVERY WEEK | Y-M: 20[redacted] | ONGOING |
| METOPROLOL | 50 mg | QD | Y-M: 20[redacted] | ONGOING |
| APIXABAN | 5 mg | BID | Y-M: 20[redacted] / -240 | ONGOING |
| CLOPIDOGREL | 75 mg | QD | Y-M: 20[redacted] / -240 | ONGOING |
| GLYCERYL TRINITRATE | 0.4 mg | PRN | Y-M: 20[redacted] / 112 | Y-M: 20[redacted] / 112 |

**Event #1: Serious Adverse Event, AE Leading to Discontinuation of Study Drug, Event of Interest - Adjudicated Cardiovascular Events**

| | |
|---|---|
| **Event Description** | CHEST PAIN |
| **Preferred term** | 胸痛 |
| **AE Onset Date / Rx Day** | [redacted]20[redacted] / 112 |
| **Age at AE Onset** | [redacted] |

**Laboratory Testing**

[redacted]20[redacted] (RX DAY 112): Hematocrit: 0.42 [0.33 - 0.44] FRACTION OF 1; Hemoglobin: 139 [110 - 148] G/L; NPTST480-TRP: 0.17 [0 - 0.05] NG/ML; [redacted]20[redacted] (RX DAY 113): NPTST480-TRP: 0.25 [0 - 0.05] NG/ML; NPTST480-TRP: 0.23 [0 - 0.05] NG/ML

**Microbiology**
NOT REPORTED
**SAE Supplemental Procedure**
[redacted]20[redacted] (RX DAY 112): CHEST X RAY: NO ACUTE PULMONARY DISEASE. BORDERLINE CARDIOMEGALY.; ELECTROCARDIOGRAM: A FIB WITH RAPID VENTRICULAR RESPONSE, LEFT AXIS DEVIATION, LBBB.; [redacted]20[redacted] (RX DAY 113): ECHOCARDIOGRAM: NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION. MODERATE ANNULAR CALCIFICATION. MILD THICKENING OF BOTH LEAFLET OF MITRAL VALVE WITH MILDLY REDUCED MOBILITY. MILDLY INCREASED LEFT ATRIAL SIZE. MODERATE CONCENTRIC LEFT VENTRICULAR HYPERTROPHY. AORTIC SCLEROSIS WITHOUT HEMODYNAMICALLY SIGNIFICANT STENOSIS AND NO SIGNIFICANT INSUFFICIENCY.; ELECTROCARDIOGRAM: NORMAL SINUS RHYTHM, LEFT AXIS DEVIATION, LEFT VENTRICULAR HYPERTROPHY WITH QRS WIDENING AND REPOLARIZATION ABNORMALITY.; INSTANTANEOUS FRACTIONAL FLOW RESERVE OF THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY.: THE RIGHT CORONARY ARTERY IS A LARGE SIZE VESSEL, DOMINANT. IN THE PROXIMAL SEGMENT, THE STENTS ARE PATENT. DISTALLY, THERE IS NO SIGNIFICANT DISEASE. IT BIFUCRATES INTO A POSTERIOR DESCENDING ARTERYAND POSTEROLATERAL VESSEL WITH NO SIGNIFICANT DISEASE.; INSTANTANEOUS FRACTIONAL FLOW RESERVE OF THE RAMUS INTERMEDIUS: NORMALIZED THE WIRE BEFORE INSERTING THE GUIDE. ENGAGED THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY. IFR WAS 0.95, INDICATING NONSIGNIFICANT STENOSIS. DID THE SAME THING FOR THE RAMUS INTERMEDIUS. IFR WAS 1.34, ALSO INDICATING NONSIGNIFICANT STENOSIS.; LEFT HEART CATHETERIZATION: THE LEFT MAIN: THE PATIENT HAS ACTUALLY NO LEFT MAIN. THE CIRCUMFLEX ARTERY, THE RAMUS INTERMEDIUS, AND THE LAD COME FROM SEPRATE OSTIA. ALL ARISE FROM THE LEFT CORONARY CUSP.; LEFT VENTRICULOGRAM: LEFT VENTRICULAR PRESSURE SYSTOLIC WAS 166, DIASTOLIC 9, END DIASTOLIC 17. AORTIC PRESSURE IS 158 OVER DIASTOLIC OF 49 WITH MEAN OF 92. NO GRADIENT ACROSS THE AORTIC VALVE. THERE WAS FAINT OPACIFICATION OF THE LEFT VENTRICLE. WE COULD NOT COMMENT ON THE LEFT VENTRICULAR FUNCTION.; SELECTIVE CORONARY ANGIOGRAPHY: THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY APPEARED TO BE SUSPICIOUS. HOWEVER, THERE MAY BE 40% DISEASE IN SOME VIEWS. MILD AND DISTALLY, THERE IS NO SIGNIFICANT DISEASE. THE FIRST DIAGONAL HASNO SIGNIFICANT DISEASE.

| | |
|---|---|
| **AE Stopped Rx Day** | 114 (2 DAYS AFTER LAST TREATMENT) |
| **Duration of AE** | 3 DAYS |
| **Severity** | Severe |
| **Relation to Study Drug by Investigator** | No Reasonable Possibility |
| **Investigator Alternative Etiology** | HISTORY OF MYOCARDIAL INFARCTION, ATRIAL FIBRILLATION AND CAROTID ARTERIAL DISEASE. |
| **Discontinued Study Drug Due to the Event** | YES |
| **SAE Criteria** | REQUIRES OR PROLONGS HOSPITALIZATION |

Generated: [redacted]
Program Source Code: [redacted]

**Investigator No.:** [redacted]

**Subject Number:** [redacted]

**Protocol Number:** M15-572

治験責任医師からの報告。本被験者は米国の 7[redacted] 歳女性であり，ABT-494（ウパダシチニブ）の治験で盲検化された治験薬が投与され，胸痛の事象を発現した。

**Event 1 の臨床経過：**

関連する病歴は，関節炎，糖尿病性ニューロパチー，高コレステロール血症，高血圧，甲状腺機能低下症，肥満，局面型乾癬，うつ病，乾癬性関節炎，糖尿病，心房細動，頚動脈疾患，心筋梗塞，元喫煙者（1 日 1 箱を 5 年間），非飲酒者，冠動脈疾患，ステント留置後状態及び高脂血症であった。

20[redacted] 年 [redacted] 月 [redacted] 日，被験者は胸痛を発現した。20[redacted] 年 [redacted] 月 [redacted] 日，胸痛は消失した。

**退院時サマリーより：**20[redacted] 年 [redacted] 月 [redacted] 日，被験者は胸痛が 1 日続いたため救急治療室を受診した。被験者はニトログリセリンを投与されたが軽減は見られなかった。12 誘導心電図検査で RVR を伴う心房細動が認められ，心拍数は 118 回/分であった。被験者は ED にてカルディゼムを投与された。ED にて，血圧が 96/55，心拍数が 170 回/分，呼吸数が 16 回/分，体温が 97°F，パルスオキシメトリが 98%であった。心エコー検査では，駆出率が 55%～60%で，中等度の同心円状左室肥大が認められた。臨床検査の結果，CBC 及び BMP は正常で，ヘモグロビン A1C が 8.5，トロポニンが 0.027，再検査時のトロポニンが 0.169，0.245 であった。胸部 X 線検査で大動脈アテローム硬化症が認められたが，急性心肺疾患は認められなかった。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は入院し，心臓専門医による診察を受けた。胸痛は，ニトログリセリン投与下である程度軽減したものの持続した。20[redacted] 年 [redacted] 月 [redacted] 日，左心カテーテル検査が行われた。この検査で，RCA に留置されたステントの開存，鈍角枝の完全閉塞（側枝の状態は良好），左下行前動脈口及び中間枝口の著明ではない狭窄が認められた。被験者は，エリキュース及びプラビックスを継続し，アスピリンを中止するよう指示された。20[redacted] 年 [redacted] 月 [redacted] 日，被験者は退院した。

投与された薬剤は，restoril，アミオダロン，prolonix，ノルバスク，プラビックス，アミオダロン及びニトログリセリンであった。

Causality for ABT-494 (Blinded)

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1) Chest pain (10008479) (Chest pain (10008479) ) [v.22.0] [10008479]

**Causality as per reporter (Drug/Vaccine):** No reasonable possibility

**Causality as per Mfr. (Drug/Vaccine):** No reasonable possibility

**Dechallenge:** Yes

**Rechallenge:** No rechallenge was done, recurrence is not applicable

Alternative Etiology for ABT-494 (Blinded)

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Event of CHEST PAIN

**- Investigator:** History of myocardial infarction, atrial fibrillation and carotid artery disease.

**- AbbVie:** Risk factors include pre-existing history of myocardial infarction, diabetes mellitus, hypertension, and hypercholesterolemia.

Relevant Laboratory & Other Diagnostic Tests

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[redacted] **20[redacted] ALBUMIN:** 30 No units

[redacted] **20[redacted] ALK PHOS:** 135 No units

[redacted] **20[redacted] ALKALINE PHOSPHASTASE:** 135 No units

[redacted] **20[redacted] ALT:** 27 No units

**Unknown date BLOOD PRESSURE:** 96/55 bpm

**Unknown date BODY TEMPERATURE:** 97.0 F

[redacted] **20[redacted] BUN:** 23 No units

[redacted] **20[redacted] CALCIUM:** 8.8 No units

[redacted] **20[redacted] CARBON DIOXIDE:** 27 No units

**Unknown date CBC:** Normal

[redacted] **20[redacted] CHEST X-RAY:** NO ACUTE PULMONARY DISEASE. BORDERLINE CARDIOMEGALY.

[redacted] **20[redacted] CHLORIDE:** 106 No units

[redacted] **20[redacted] CREATININE:** 0.86 No units

[redacted] **20[redacted] ECHOCARDIOGRAM:** NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION. MODERATE ANNULAR CALCIFICATION. MILD THICKENING OF BOTH LEAFLET OF MITRAL VALVE WITH MILDLY REDUCED MOBILITY. MILDLY INCREASED LEFT ATRIAL SIZE. MODERATE CONCENTRIC LEFT VENTRICULAR HYPERTROPHY. AORTIC SCLEROSIS WITHOUT HEMODYNAMICALLY SIGNIFICANT STENOSIS AND NO SIGNIFICANT INSUFFICIENCY.

**Unknown date ECHOCARDIOGRAM:** Ejection fraction of 55% to 60%, moderate concentric left ventricular hypertrophy.

[redacted] 20[redacted] **EKG:** Atrial fibrillation with RVR with a rate of 118 beats per minute.

[redacted] 20[redacted] **ELECTROCARDIOGRAM:** A FIB WITH RAPID VENTRICULAR RESPONSE, LEFT AXIS DEVIATION, LBBB.

[redacted] 20[redacted] **ELECTROCARDIOGRAM:** NORMAL SINUS RHYTHM, LEFT AXIS DEVIATION, LEFT VENTRICULAR HYPERTROPHY WITH QRS WIDENING AND REPOLARIZATION ABNORMALITY.

[redacted] 20[redacted] **GLUCOSE:** 294 No units

[redacted] 20[redacted] **GLUCOSE:** 297 No units (normal 70 to 110)

[redacted] 20[redacted] **GLUCOSE:** 282 no units (normal 70 to 110)

[redacted] 20[redacted] **GLUCOSE:** 240 No units (normal 70 to 110)

**Unknown date HEART RATE:** 170 per min

**Unknown date HEMOGLOBIN A1C:** 8.5 No units

[redacted] 20[redacted] **INSTANTANEOUS FRACTIONAL FLOW RESERVE OF THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY:** THE RIGHT CORONARY ARTERY IS A LARGE SIZE VESSEL, DOMINANT. IN THE PROXIMAL SEGMENT, THE STENTS ARE PATENT. DISTALLY, THERE IS NO SIGNIFICANT DISEASE. IT BIFUCRATES INTO A POSTERIOR DESCENDING ARTERY AND POSTEROLATERAL VESSEL WITH NO SIGNIFICANT DISEASE.

[redacted] 20[redacted] **INSTANTANEOUS FRACTIONAL FLOW RESERVE OF THE RAMUS INTERMEDIUS:** NORMALIZED THE WIRE BEFORE INSERTING THE GUIDE. ENGAGED THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY. IFR WAS 0.95, INDICATING NONSIGNIFICANT STENOSIS. DID THE SAME THING FOR THE RAMUS INTERMEDIUS. IFR WAS 1.34, ALSO INDICATING NONSIGNIFICANT STENOSIS.

[redacted] 20[redacted] **LEFT VENTRICULOGRAM:** LEFT VENTRICULAR PRESSURE SYSTOLIC WAS 166, DIASTOLIC 9, END DIASTOLIC 17. AORTIC PRESSURE IS 158 OVER DIASTOLIC OF 49 WITH MEAN OF 92. NO GRADIENT ACROSS THE AORTIC VALVE. THERE WAS FAINT OPACIFICATION OF THE LEFT VENTRICLE. WE COULD NOT COMMENT ON THE LEFT VENTRICULAR FUNCTION.

[redacted] 20[redacted] **NEUT #:** 7.6 No units (normal 1.8 to 6.3)

[redacted] 20[redacted] **NEUTROPHILS:** 7.6 No units

[redacted] 20[redacted] **POTASSIUM:** 3.8 No units

[redacted] 20[redacted] **RBC:** 5.03 No units

[redacted] 20[redacted] **SELECTIVE CORONARY ANGIOGRAPHY:** THE OSTIUM OF THE LEFT ANTERIOR DESCENDING ARTERY APPEARED TO BE SUSPICIOUS. HOWEVER, THERE MAY BE 40% DISEASE IN SOME VIEWS. MILD AND DISTALLY, THERE IS NO SIGNIFICANT DISEASE. THE FIRST DIAGONAL HAS NO SIGNIFICANT DISEASE.

[redacted] 20[redacted] **SERUM TOTAL PROTEIN:** 6.4 No units

[redacted] **20[redacted] SODIUM:** 142 No units

[redacted] **20[redacted] TOTAL BILIRUBIN:** 0.5 No units

[redacted] **20[redacted] TROPONIN:** 0.169 NG/ML (normal 0 to 0.045)

[redacted] **20[redacted] TROPONIN:** 0.245 NG/ML (normal 0 to 0.045)

[redacted] **20[redacted] TROPONIN:** 0.234 NG/ML (normal 0 to 0.045)

**Unknown date TROPONINS:** 0.027 NG/ML (normal 0 to 0.045)

[redacted] **20[redacted] WBC:** 9.7 No units