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4.2　国際共同第 III 相試験（1305-0014 試験［評価資料：CTD 5.3.5.1-02-01］）

4.2.1　計画

4.2.1.1　治験名

A double blind, randomised, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Idiopathic Pulmonary Fibrosis (IPF)

4.2.1.2　治験実施施設

北米，南米，欧州，アフリカ，アジア，中東及びオセアニアの 36 カ国，332 施設

4.2.1.3　公表文献

なし（2025 年 4 月時点）

4.2.1.4　治験フェーズ

第 III 相

4.2.1.5　目的

本治験の目的は，特発性肺線維症（IPF）患者を対象に，BI 1015550（ネランドミラスト［以下，本薬］）9 mg 又は 18 mg を 1 日 2 回投与したときの有効性及び安全性をプラセボと比較評価することであった。

4.2.1.6　方法

本治験は，本薬の有効性，安全性及び薬物動態の評価を目的とした多施設共同，ランダム化，二重盲検，プラセボ対照，プロスペクティブ，国際共同第 III 相試験で，IPF 患者を対象としたピボタル試験であり，本薬 9 mg，本薬 18 mg 又はプラセボを 1 日 2 回，52 週間以上投与した。ベースライン時の抗線維化薬（AF）（ニンテダニブ又はピルフェニドン）使用の有無（非 AF 層，AF 層）を層別因子として，被験者を本薬 9 mg 1 日 2 回経口投与（本薬 9 mg 群），本薬 18 mg 1 日 2 回経口投与（本薬 18 mg 群），又はプラセボ 1 日 2 回経口投与（プラセボ群）に 1:1:1 の比でランダムに割り付けた。本治験は，52 週間以上の投与期（ランダム割付けから 52 週時までの Part A，及びそれ以降の Part B［ランダム化盲検投与を 52 週以降も継続］で構成）及び 7 日間の追跡調査期で構成された。最後にランダム割付けされた被験者が 52 週時の評価を完了した時点で，初回データベースロック（DBL1）（20[redacted] 年[redacted] 月[redacted] 日）に基づき主要解析を実施した。すべての被験者が治験薬投与終了（EOT）Visit 及び治験終了（EOS）Visit（該当する場合に実施）を完了した後，最終データベースロック（DBL2）（20[redacted] 年[redacted] 月[redacted] 日）後に最終解析を実施した。

4.2.1.7　被験者数

計画時：組入れ 963 名

解析時：スクリーニング 1720 名（DBL2 後，1719 名に修正），組入れ 1177 名

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ランダム化被験者数，投与被験者数及び主要評価項目の解析対象被験者数：

	ランダム化	投与	解析 [1]
本薬 9 mg 群	392 名	392 名	392 名
本薬 18 mg 群	392 名	392 名	392 名
プラセボ群	393 名	393 名	393 名

1 最大の解析対象集団（FAS）

4.2.1.8　診断

治験対象集団は，米国胸部医学会/欧州呼吸器学会/日本呼吸器学会/ラテンアメリカ胸部医学会（ATS/ERS/JRS/ALAT）による 2022 年改訂の診断ガイドライン［CTD 5.4-40_P22-03204］に基づき IPF と診断され，高分解能コンピュータ断層撮影（HRCT）で通常型間質性肺炎（UIP）又は probable UIP のパターンが IPF の臨床診断と合致している患者とした。

4.2.1.9　主な組入れ基準

40 歳以上で IPF と診断された患者を組み入れた。Visit 1 での努力肺活量（FVC）の予測値に対する割合（%FVC）が 45%以上，ヘモグロビン（Hb）で補正した一酸化炭素肺拡散能（DLCO）の予測値に対する割合（%DLCO）（以下，「%DLCO（Hb 補正）」）が 25%以上であることとした。また，Visit 1 前の 12 週間以上にわたりニンテダニブ又はピルフェニドンによる安定した治療を受けている，若しくは Visit 1 前の 8 週間以上にわたりニンテダニブ又はピルフェニドンによる治療を受けていない患者を組み入れた。

4.2.1.10　治験薬

BI 被験薬　本薬 C1 製剤：9 mg 及び 18 mg フィルムコート錠
用量：9 mg 1 日 2 回又は 18 mg 1 日 2 回
投与方法：経口投与

対照薬　プラセボ：フィルムコート錠（本薬 9 mg 錠及び 18 mg 錠にマッチさせた錠剤）
用量：マッチさせたプラセボを 1 日 2 回
投与方法：経口投与

4.2.1.11　投与期間

Part A：52 週間

Part B：52 週時以降

Part A を含めた最大総投与期間は DBL1 で 20.8 カ月，治験終了時（DBL2）に 22.9 カ月であった。

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4.2.1.12　有効性/臨床薬理に関する評価基準

本治験の主要評価項目は，52 週時の FVC（mL）のベースラインからの絶対変化量であった。重要な副次評価項目は複合評価項目であり，治験薬の初回投与日から，IPF の初回急性増悪，呼吸器疾患による初回入院又は死亡のいずれかが最初に発生するまでの期間と定義した。

その他の副次評価項目を以下に示す。

- 治験期間中の IPF の初回急性増悪又は死亡までの期間
- 治験期間中の呼吸器疾患による入院又は死亡までの期間
- 治験期間中の死亡までの期間
- 52 週時の%FVC のベースラインからの絶対変化量
- 治験期間中の%FVC のベースラインからの 10%超（絶対変化量）の低下又は死亡までの期間
- 52 週時の%DLCO（Hb 補正）のベースラインからの絶対変化量
- 治験期間中の%DLCO（Hb 補正）のベースラインからの 15%超（絶対変化量）の低下又は死亡までの期間
- 52 週時の Living with Pulmonary Fibrosis（L-PF）Symptoms 呼吸困難ドメインスコアのベースラインからの絶対変化量
- 52 週時の L-PF Symptoms 咳嗽ドメインスコアのベースラインからの絶対変化量
- 52 週時の L-PF Symptoms 疲労ドメインスコアのベースラインからの絶対変化量

その他の有効性評価項目には，FVC，DLCO，酸素飽和度（SpO_2）及び L-PF の評価に基づく評価項目，重要な副次複合臨床評価項目の個々の構成要素，非待機的入院，救援治療の使用，並びに L-PF 質問票に基づく酸素療法の使用が含まれた。

その他の評価項目として，本薬の定常状態での投与前の血漿中濃度（$C_{pre,ss}$）を評価した。

4.2.1.13　安全性に関する評価基準

安全性は，有害事象及び特に注目すべき有害事象（AESI），並びに特記すべき安全性に関する項目（非臨床試験でみられた毒性所見，他のホスホジエステラーゼ［PDE］4 阻害薬の重要な潜在的リスク又は特定されたリスク，本薬の作用機序に基づいて定義した）に基づき，記述的に評価した。AESI として，重度の薬物性肝障害（DILI）の可能性（以下，「Potential severe DILI」），血管炎（以下，「Vasculitis」），重度の感染症，重篤な感染症，日和見感染症又は結核菌感染（以下，「Severe, serious, opportunistic, or *Mycobacterium tuberculosis* infections」），重度のうつ病の新規発現（以下，「New onset of severe depression」），及び重度の不安の新規発現（以下，「New onset of severe anxiety」）を事前に規定した。特記すべき安全性に関する項目及び AESI の詳細な定義は，［CTD 2.7.4_1.1.2.2.5～6 項］を参照のこと。独立判定委員会は，すべての死亡例，主要心血管イベント（MACE）及び「Vasculitis」に関して盲検下で中央評価を行った。自殺傾向及び下痢について事前に規定された追加解析を実施した。さらに，身体所見，臨床検査及びバイタルサインにおける臨床的に問題となる所見又は変化について評価した。

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4.2.1.14　解析方法

中間事象に関する主要評価項目の主要なストラテジーでは，肺移植及び死亡を除くすべての中間事象は治療方針（treatment policy）ストラテジーに従った。主要解析は最大の解析対象集団（FAS）を対象として実施し，FAS には治験薬を 1 回以上投与したすべてのランダム割付けされた被験者を含めた。主要評価項目の主要解析は，混合効果反復測定モデル（MMRM）に基づく制限付き最尤法（REML）により，52 週時の FVC のベースラインからの変化量を投与群間で比較した。解析には，各 Visit 時における治療（カテゴリー変数），各 Visit 時におけるベースライン時の AF 投与（カテゴリー変数），及び各 Visit 時におけるベースライン時の FVC（連続変数）を固定効果として含めた。Visit は反復測定とし，被験者内誤差のモデリングには無構造の共分散構造を用いた。肺移植後のデータは除外した。52 週時以前に死亡し，肺移植を受けていなかった被験者の場合，死亡時又は死亡後の FVC のベースラインからの変化量は，各 Visit 時のすべての投与群でのすべての測定値（FVC のベースラインからの変化量）の 10 パーセンタイル値に基づき補完した。

主要評価項目と同様に，重要な副次評価項目の主要ストラテジーも治療方針ストラテジー（肺移植を除く）に従って取り扱い，52 週間以降のデータを含む DBL1 の全データを用いた。また，全治験期間のデータ（DBL2）を用いて重要な副次評価項目の補足解析を実施する計画とした。

重要な副次評価項目イベントが発生しなかった被験者は，いずれのイベントも認められないことが確認された最後の日を打ち切りとした。肺移植前にイベントが発生しなかった被験者は，肺移植を受けた時点で打ち切りとした。主要解析には，治療，ベースライン時の AF 投与，年齢（連続変数），ベースライン時の%FVC 及びベースライン時の%DLCO（Hb 補正）を共変量として含めた Cox 比例ハザードモデルを用いた。本薬群のプラセボ群に対するハザード比の検定には，Wald 検定を用いた。プラセボ群に対する本薬両投与群の主要評価項目及び重要な副次評価項目の検定には，反復検定手順としてグラフィカルアプローチを使用した。他の副次評価項目及びその他の評価項目はすべて探索的であり，多重性の調整は行わなかった。

4.2.2　結果

4.2.2.1　治験対象及び治験実施計画書の遵守状況

計 1720 名（DBL2 後，1719 名に修正）の被験者がスクリーニングされ，1177 名が 1:1:1 の比でランダム割付けされた。その内訳は，プラセボ群 393 名，本薬 9 mg 群 392 名，本薬 18 mg 群 392 名であった。ランダム割付けされた被験者の多くが欧州（37.6%）及びアジア（30.4%）からの被験者であり，次いで米国（16.7%）からの被験者であった。ランダム割付けされた被験者はすべて治験薬の投与を受けた。

ランダム割付けされ，治験薬の投与を受けた被験者の多くは男性であった（男性 : 83.0%，女性 : 17.0%）。ほぼすべてが白人（67.7%）又はアジア人（31.6%）であり，6 名（0.5%）が黒人又はアフリカ系アメリカ人，2 名（0.2%）がマルチレイシャルであった。大部分の被験者は高齢で，平均年齢は 70.2 歳（標準偏差［SD］：7.7）であった。ベースライン時に AF を使用していた被験者は 915 名（FAS の 77.7%）であった。AF 使用の平均期間は，ニンテダニブを使用していた被験者（535

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名［FAS の 45.5%］）で 28 カ月，ピルフェニドンを使用していた被験者（380 名［FAS の 32.3%］）で 33 カ月であった。ベースライン時に AF を使用していなかった被験者は 262 名（22.3%）であり，このうちの過半数（172 名［FAS の 14.6%］）は，全く AF 使用歴のない被験者であった。初回の IPF 診断からの期間の平均値は 3.5 年（SD：2.7）であり，被験者の約半数は初回診断から 3 年以上であった。

ベースラインの%FVC の平均値は 78.2%（SD：17.3），%DLCO の平均値は 50.9%（SD：16.3）であった。これらの特性は投与群間でおおむね同様であった。AF 層では，非 AF 層と比較して診断からの期間が長く，酸素療法の使用頻度が高く，%FVC 及び%DLCO が低かった。ベースライン時にニンテダニブ使用ありの集団とピルフェニドン使用ありの集団では，これらの特徴は同様であった。

本治験の主要解析は，ランダム割付けされた最後の被験者が 52 週時の評価を完了した後に実施された（DBL1 データ）。本治験の最終解析は，最後の被験者が治験を完了した後に実施された（DBL2 データ）。DBL1 で主要解析を実施するために治験依頼者は盲検解除されたが，治験担当医師及び被験者は DBL2 まで盲検化が維持された。主要評価項目は事前に規定されたとおり DBL1 で解析し，DBL2 での再解析は実施しなかった。

DBL1

計画した 52 週時までの投与期を完了した被験者は，治験薬の投与を受けた 1177 名中 962 名（81.7%）であった。また，主要評価項目のために計画された観察を完了した被験者は 1080 名（91.8%）であった。治験薬の投与を受けた 1177 名中 928 名（78.8%）は，DBL1 で治験薬投与を継続中であった。DBL1 までに治験薬の投与を中止した被験者（21.2%）の投与中止理由は有害事象（12.8%）が最も多く，次いで，その他（4.2%）及び被験者の意向による中止（3.8%）であった。DBL1 までの治験中に計画された観察を完了した被験者は 1138 名（96.7%）であった。その内訳は，DBL1 で治験を継続中の被験者が 1046 名（88.9%），DBL1 までに肺移植を受けた被験者が 17 名（1.4%），死亡した被験者が 75 名（6.4%）であった。被験者の内訳は投与群間で同様であったが，本薬 18 mg 群で，DBL1 までの治験薬の投与中止理由が有害事象であった被験者の割合が高く（プラセボ群 10.9%，本薬 9 mg 群 12.5%，本薬 18 mg 群 15.1%；以下同順），投与中止理由が被験者の意向であった被験者の割合が低く（4.8%，4.1%，2.6%），DBL1 までに死亡した被験者の割合が低かった（7.1%，6.6%，5.4%）。

ベースライン時の AF 使用の有無（非 AF 層，AF 層）による部分集団別に検討した結果，DBL1 までに治験薬の投与を中止した被験者の割合は，非 AF 層及び AF 層の両部分集団で，プラセボ群と本薬 9 mg 群で同程度（19.3%～21.8%）であったが，本薬 18 mg 群では部分集団間で異なる傾向がみられ，プラセボ群及び本薬 9 mg 群と比較して非 AF 層で低く（11.5%），AF 層で高かった（24.6%）。主な投与中止理由は有害事象であった。

さらに，ベースライン時の AF の種類（AF 使用なし，ニンテダニブ使用，ピルフェニドン使用）による部分集団別に検討した結果，ベースライン時にニンテダニブ使用ありの集団とピルフェニドン使用ありの集団との間で異なる傾向がみられた。DBL1 までに治験薬の投与を中止した被験

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者の割合は，ベースライン時にニンテダニブ使用ありの集団では，プラセボ群（19.7%）と比較して本薬 9 mg 群（25.0%）及び本薬 18 mg 群（29.8%）で高かったのに対し，ベースライン時にピルフェニドン使用ありの集団では，プラセボ群（21.1%）と比較して本薬 9 mg 群（16.7%）及び本薬 18 mg 群（17.3%）で低かった。

治験薬を 52 週間（12 カ月）以上投与された被験者の割合は，すべての投与群で 80%超であった。DBL1 までの投与期間の平均値は，すべての投与群で約 13 カ月（SD：4～5）であり，DBL1 までの投与期間が 15 カ月以上であった被験者の割合は約 36%であった。治験薬の投与期間は投与群間で同様であった。DBL1 までの観察期間の平均値は，すべての投与群で約 14.5 カ月（SD：2～3）であった。

DBL1 までに，治験実施計画書からの重要な逸脱がみられた被験者の割合（FAS の 9.5%）は投与群間で同程度であった。最もよくみられた治験実施計画書からの重要な逸脱は，ランダム割付け後最終投与までの間での強力な CYP3A4 阻害薬の併用であった（2.8%）。

DBL2

DBL2 後，スクリーニングされた被験者の合計は 1720 名から 1719 名に修正された。これは，1 名の被験者が再スクリーニングされ，異なる被験者番号でランダム割付けされたためである。

DBL2 までに 889 名（75.5%）が計画された投与を完了した。889 名の適格な被験者のうち，852 名（95.8%）が非盲検継続投与試験（1305-0031 試験）で本薬 18 mg 1 日 2 回投与を継続するか，又は本薬 18 mg 1 日 2 回投与に切り換えた。DBL2 では，治験薬の投与を中止した被験者（1177 名のうち 24.5%）の中止理由の傾向は，DBL1 と同様であった。投与中止理由は，有害事象（14.3%），次いで，その他（5.2%），及び被験者の意向による投与中止（4.5%）であった。1129 名の被験者（95.9%）が治験を完了した。このうち 1003 名の被験者（85.2%）が DBL2 までの治験中に計画された観察を完了し，22 名（1.9%）が肺移植を受け，104 名（8.8%）が死亡した。DBL1 までの結果と同様に，DBL2 での被験者の内訳は投与群間で同様であった。治験薬の投与中止理由は，すべての投与群で有害事象が最も多く，被験者の意向による中止又は死亡は本薬 18 mg 群で少なかった。また，AF 層/非 AF 層別及び AF の種類（ニンテダニブ又はピルフェニドン）別の内訳も DBL1 と同様であった。

DBL1 と DBL2 の間で，治験薬の投与期間の平均値は約 1.5 カ月増加し，すべての投与群で約 15 カ月（SD：約 5）に達し，約 73%の被験者が 15 カ月以上の投与を受けた。治験薬の曝露状況は投与群間で同様であった。DBL1 と DBL2 の間で，観察期間の平均値は約 2 カ月増加し，すべての投与群で約 16.5 カ月（SD：3～4）に達した。

DBL2 では，治験実施計画書からの重要な逸脱がみられた患者の割合（全体で 14.9%）は投与群間で同程度であり，最もよくみられた治験実施計画書からの重要な逸脱は強力な CYP3A4 阻害薬の併用（4.6%）であった。

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4.2.2.2　有効性/臨床薬理

有効性主要評価項目及び重要な副次評価項目

DBL1

本治験の主要評価項目は，52 週時の FVC（mL）のベースラインからの絶対変化量であった。52 週時の FVC（mL）のベースラインからの調整済み平均絶対変化量は，プラセボ群−183.5 mL（95%信頼区間［CI］：−210.9〜−156.1），本薬 9 mg 群−138.6 mL（95% CI：−165.6〜−111.6），本薬 18 mg 群−114.7 mL（95% CI：−141.8〜−87.5）であった（表 4.2.2.2: 1）。以下に示すとおり，本薬 9 mg 群及び本薬 18 mg 群とプラセボ群との投与群間差はいずれも統計学的に有意であった。52 週時の FVC（mL）のベースラインからの絶対変化量のプラセボ群との調整済み平均値の差は，本薬 9 mg 群では 44.9 mL（95% CI：6.4〜83.3，p=0.0222），本薬 18 mg 群では 68.8 mL（95% CI：30.3〜107.4，p=0.0005）であった。全体の第一種の過誤確率を 5%に保つためのグラフィカルアプローチによる検定手順に基づき，主要評価項目について，本薬の両用量でプラセボに対する優越性が示された。検定された最初の用量である本薬 18 mg 1 日 2 回投与では p=0.0005 であり，最初に割り当てられた α=0.04 を下回った。本薬 9 mg 1 日 2 回投与では p=0.0222 であり，更新された α=0.03 を下回った。

FVC のベースラインからの調整済み平均絶対変化量は，本薬 9 mg 群及び本薬 18 mg 群の両投与群でランダム割付け後早期の 2 週時からプラセボ群と比較して FVC 低下抑制が認められ，52 週時まで維持された。

感度分析及び補足解析のすべての結果が，主要評価項目の主要解析の結果と一貫していた。

主要評価項目に対する治療効果は，人口統計学的特性，ベースライン時の疾患特性及びベースライン時の AF の使用状況別の事前に規定した部分集団のほとんどで一貫していた。特に，本薬（9 mg 及び 18 mg の 1 日 2 回投与）の一貫した治療効果は，非 AF 層及び AF 層の両層で認められた。ただし，プラセボ群に対する本薬 9 mg 群の治療効果は，非 AF 層と比較して AF 層で数値的に小さかった。この結果は，ベースライン時にピルフェニドン使用ありの本薬 9 mg 群で治療効果がみられなかったことに起因していた（表 4.2.2.2: 1）。

ベースライン時にピルフェニドン使用ありの集団では，非 AF 層と比較して，本薬 9 mg 群における本薬（薬理学的活性のある R 体のエナンチオマー）の投与前血漿中濃度に 55%の低下がみられた。このことが，この部分集団で本薬 9 mg 群にみられた治療効果の欠如の要因となった可能性がある。本薬 18 mg 群における本薬（薬理学的活性のある R 体のエナンチオマー）の投与前血漿中濃度は，非 AF 層と比較してベースライン時にピルフェニドン使用ありの集団で 48%低下した（臨床薬理の結果は以下を参照のこと）。この薬物-薬物間相互作用がみられたことから，ベースライン時にピルフェニドン使用ありの集団を除外した事後解析を実施した（表 4.2.2.2: 2）。52 週時の FVC（mL）のベースラインからの絶対変化量のプラセボ群との調整済み平均値の差は，本薬 9 mg 群では 66.4 mL（95% CI：19.8〜112.9），本薬 18 mg 群では 71.6 mL（95% CI：24.4〜118.8）であった。ピルフェニドン使用ありの集団を除いた本薬 9 mg 群におけるプラセボ群に対する 66.4 mL（95% CI：19.8〜112.9）の治療効果は，ベースライン時にピルフェニドン使用ありの集団の本薬 18 mg 群での 63.4 mL（95% CI：−3.6〜130.3）の治療効果と同様であった（表 4.2.2.2: 1）。

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表 4.2.2.2: 1 全体集団（主要解析）及びベースライン時の AF 使用状況別の 52 週時の FVC（mL）のベースラインからの絶対変化量－FAS（DBL1）

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
All patients (primary analysis), N analysed	391		390		392	
Baseline (mean, SD)	2863.9	804.6	2837.2	781.4	2827.3	758.0
Week 52 change from baseline						
Adjusted mean	−183.5		−138.6		−114.7	
95% CI	−210.9	−156.1	−165.6	−111.6	−141.8	−87.5
Comparison vs. placebo						
Adjusted mean	-		44.9		68.8	
95% CI			6.4	83.3	30.3	107.4
p value			0.0222		0.0005	
Patients without background AF therapy[1], N analysed	87		86		87	
Baseline (mean, SD)	2833.3	885.7	2763.6	739.3	2761.5	778.4
Week 52 change from baseline						
Adjusted mean	−148.7		−70.2		−79.1	
95% CI	−206.8	−90.5	−127.5	−13.0	−136.6	−21.5
Comparison vs. placebo						
Adjusted mean	-		78.4		69.6	
95% CI			−3.2	160.0	−12.2	151.4
Patients with background AF therapy[1], N analysed	304		304		305	
Baseline (mean, SD)	2872.6	781.4	2858.5	793.1	2846.1	752.3
Week 52 change from baseline						
Adjusted mean	−193.7		−158.6		−124.9	
95% CI	−224.8	−162.7	−189.2	−127.92	−155.7	−94.1
Comparison vs. placebo						
Adjusted mean	-		35.2		68.8	
95% CI			−8.4	78.8	25.1	112.6
Patients with nintedanib background therapy[2], N analysed	172		184		178	
Baseline (mean, SD)	2971.3	802.5	2937.2	828.6	2863.3	805.1
Week 52 change from baseline						
Adjusted mean	−191.6		−130.7		−118.5	
95% CI	−232.6	−150.6	−169.9	−91.5	−159.3	−77.8
Comparison vs. placebo						
Adjusted mean	-		60.9		73.0	
95% CI			4.3	117.5	15.3	130.8
Patients with pirfenidone background therapy[2], N analysed	132		120		127	
Baseline (mean, SD)	2744.2	736.5	2737.9	722.2	2821.9	673.7
Week 52 change from baseline						
Adjusted mean	−197.0		−201.8		−133.7	
95% CI	−244.7	−149.4	−250.9	−152.8	−180.7	−86.6
Comparison vs. placebo						
Adjusted mean	-		−4.8		63.4	
95% CI			−73.2	63.5	−3.6	130.3

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bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
1 ベースライン時の AF 使用の有無（AF 層，非 AF 層）による部分集団と投与群との交互作用は p=0.3593（本薬 9 mg 群 vs. プラセボ群）及び p=0.9869（本薬 18 mg 群 vs. プラセボ群）
2 ベースライン時の AF の種類（ニンテダニブ使用，ピルフェニドン使用，AF 使用なし）による部分集団と投与群との交互作用は p=0.2250（本薬 9 mg 群 vs. プラセボ群）及び p=0.9772（本薬 18 mg 群 vs. プラセボ群）
引用元：CTD 5.3.5.1-02-01_1305-0014 試験_c43862255_Table 15.2.1.1: 1, Table 15.2.1.3.6: 1，Table 15.2.1.3.7: 1

表 4.2.2.2: 2　52 週時の FVC（mL）のベースラインからの絶対変化量－FAS（ベースライン時にピルフェニドン使用ありの集団を除外した事後解析）（DBL1）

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
All patients excluding those with pirfenidone background therapy, N analysed	259		270		265	
Baseline (mean, SD)	2925.1	832.1	2881.0	803.6	2829.9	796.4
Week 52 change from baseline						
Adjusted mean	−178.2		−111.8		−106.6	
95% CI	−211.6	−144.7	−144.1	−79.5	−139.8	−73.3
Comparison vs. placebo						
Adjusted mean	-		66.4		71.6	
95% CI			19.8	112.9	24.4,	118.8

bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
各 Visit 時における治療（カテゴリー変数）の効果，各 Visit 時におけるベースライン時の AF 投与（カテゴリー変数）の効果，及び各 Visit 時におけるベースライン時の FVC（mL）（連続変数）の効果を固定効果として含めた MMRM に基づく。
引用元：CTD 5.3.5.1-02-01_1305-0014 試験_c43862255_Appendix 16.1.13.1_Table 9.4.1.1

重要な副次的評価項目は，DBL1 までの治験期間中の IPF の初回急性増悪，呼吸器疾患による初回入院又は死亡のいずれかが最初に発生するまでの期間と定義した。重要な副次評価項目のイベントが発生した被験者は，プラセボ群 80 名（20.4%），本薬 9 mg 群 79 名（20.2%），本薬 18 mg 群 85 名（21.7%）であった。本薬のいずれの投与群でもプラセボ群との有意差は認められず，プラセボ群に対するハザード比は，本薬 9 mg 群では 1.03（95% CI：0.75～1.41，p=0.8568），本薬 18 mg 群では 1.17（95% CI：0.86～1.59，p=0.3102）であった。全体の第一種の過誤確率を 5%に保つためのグラフィカルアプローチによる検定手順に基づき，本薬の投与群で p 値が α=0.05 を上回った。重要な副次評価項目への寄与が最も大きかったイベントは，呼吸器疾患による入院であり，重要な副次評価項目の最初に発生したイベントのうちの約半数を占めた。

重要な副次評価項目のイベントが発生した被験者の割合は，非 AF 層のプラセボ群（27.6%）と比較して AF 層のプラセボ群（18.3%）で低かった。重要な副次評価項目のイベントが発生した被験者の割合は，非 AF 層では，プラセボ群（27.6%）と比較して本薬 9 mg 群（15.9%）及び本薬 18 mg 群（16.1%）で低かったのに対して，AF 層では，プラセボ群（18.3%）と比較して本薬 9 mg 群（21.4%）及び本薬 18 mg 群（23.3%）で数値的に高かった。

DBL2

DBL2 の結果で提示する p 値は探索的であり，多重性の調整は行わなかった。

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DBL2 までの追加の治験薬投与期間及び観察期間の増加に伴い，重要な副次評価項目のイベントが発生した被験者の割合は，すべての投与群で DBL2 までに増加し，プラセボ群での増加が最も大きかった。投与群間で重要な副次評価項目のイベントの発生リスクに差は認められなかった（図 4.2.2.2: 1）。

DBL1 から DBL2 までの間に，重要な副次評価項目に寄与するイベントが追加で 42 件発生した（DBL1 と比較して 17%増加）。本薬 9 mg 群（+11 件）及び本薬 18 mg 群（+8 件）と比較して，プラセボ群（+23 件）での追加の発生が多かった。DBL2 までの治験期間全体で，重要な副次評価項目のイベントが発生した被験者は，プラセボ群 103 名（26.2%），本薬 9 mg 群 90 名（23.0%），本薬 18 mg 群 93 名（23.7%）であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.92（95% CI：0.69～1.22），本薬 18 mg 群では 0.99（95% CI：0.75～1.31）であった。

非 AF 層での本薬の有益な傾向は DBL2 でも認められた。イベントが発生した被験者の割合は，プラセボ群（36.8%）と比較して，依然として本薬群で数値的に低かった（本薬 9 mg 群 17.0%，本薬 18 mg 群 21.8%）。プラセボ群に対するハザード比は本薬 9 mg 群で 0.47（95% CI：0.26～0.88），本薬 18 mg 群 0.62（95% CI：0.35～1.10）であった。AF 層では，イベントが発生した被験者の割合は，DBL1 では本薬群で高かったが，DBL2 では本薬 9 mg 群（24.7%）及び本薬 18 mg 群（24.3%）とプラセボ群（23.2%）で同程度であった。プラセボ群に対するハザード比は，本薬 9 mg 群で 1.12（95% CI：0.81～1.55），本薬 18 mg 群で 1.16（95% CI：0.83～1.60）であった。

他の副次評価項目

DBL1

DBL1 までの治験期間中に IPF の急性増悪が認められた又は死亡した被験者の割合は，プラセボ群 12.5%，本薬 9 mg 群 13.0%，本薬 18 mg 群 12.8%であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 1.12（95% CI：0.76～1.67），本薬 18 mg 群では 1.11（95% CI：0.75～1.65）であった。

DBL1 までの治験期間中に呼吸器疾患による入院が発生した又は死亡した被験者の割合は，プラセボ群 18.6%，本薬 9 mg 群 17.3%，本薬 18 mg 群 19.1%であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.98（95% CI：0.70～1.36），本薬 18 mg 群では 1.13（95% CI：0.82～1.56）であった。

DBL1 までの治験期間中に死亡した被験者は，プラセボ群 28 名（7.1%），本薬 9 mg 群 26 名（6.6%），本薬 18 mg 群 21 名（5.4%）であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 1.03（95% CI：0.60～1.76），本薬 18 mg 群では 0.81（95% CI：0.46～1.43）であった。

52 週時の%FVC のベースラインからの調整済み平均絶対変化量は，プラセボ群−4.9%（95% CI：−5.7～−4.2），本薬 9 mg 群−3.8%（95% CI：−4.5～−3.0），本薬 18 mg 群−3.2%（95% CI：−3.9～−2.5）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では 1.2%（95% CI：0.1～2.2），本薬 18 mg 群では 1.7%（95% CI：0.7～2.8）であった。

DBL1 までの治験期間中に%FVC のベースラインからの 10%超（絶対変化量）の低下が認められた又は死亡した被験者の割合は，プラセボ群 28.2%，本薬 9 mg 群 27.3%，本薬 18 mg 群 24.0%

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であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.96（95% CI：0.74～1.25），本薬 18 mg 群では 0.84（95% CI：0.64～1.10）であった。

52 週時の%DLCO（Hb 補正）のベースラインからの調整済み平均絶対変化量は，プラセボ群−6.1%（95% CI：−7.4～−4.9），本薬 9 mg 群−3.7%（95% CI：−4.9～−2.5），本薬 18 mg 群−4.5%（95% CI：−5.7～−3.3）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では 2.5%（95% CI：0.8～4.2），本薬 18 mg 群では 1.7%（95% CI：0～3.4）であった。

DBL1 までの治験期間中に%DLCO（Hb 補正）のベースラインからの 15%超（絶対変化量）の低下が発生した又は死亡した被験者の割合は，プラセボ群 16.8%，本薬 9 mg 群 15.1%，本薬 18 mg 群 15.1%であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.98（95% CI：0.69～1.41），本薬 18 mg 群では 0.88（95% CI：0.62～1.26）であった。

52 週時の L-PF Symptoms ドメインスコアのベースラインからの調整済み平均絶対変化量は，3 つの投与群間で同程度であった。

- L-PF Symptoms 呼吸困難ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 7.2（95% CI：5.7～8.8），本薬 9 mg 群 6.3（95% CI：4.7～7.8），本薬 18 mg 群 6.6（95% CI：5.1～8.2）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では−1.0（95% CI：−3.2～1.2），本薬 18 mg 群では−0.6（95% CI：−2.8～1.6）であった。
- L-PF Symptoms 咳嗽ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 4.5（95% CI：2.4～6.5），本薬 9 mg 群 4.4（95% CI：2.4～6.4），本薬 18 mg 群 3.9（95% CI：1.9～5.9）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では 0（95% CI：−2.9～2.8），本薬 18 mg 群では−0.6（95% CI：−3.4～2.3）であった。
- L-PF Symptoms 疲労ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 5.3（95% CI：3.6～7.1），本薬 9 mg 群 5.6（95% CI：3.9～7.3），本薬 18 mg 群 5.8（95% CI：4.1～7.5）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では 0.2（95% CI：−2.2～2.7），本薬 18 mg 群では 0.5（95% CI：−2.0～2.9）であった。

DBL2

DBL2 までのすべての time-to-event の副次評価項目において，プラセボ群に対するハザード比は DBL1 と比較して数値的に低かった（下記及び図 4.2.2.2: 1 を参照のこと）。

重要な副次評価項目のすべての構成要素において，DBL1 と DBL2 の間でのイベント数の最大増加はプラセボ群で認められ，本薬 18 mg 群で増加件数は最も少なかった。

DBL2 までの治験期間中に IPF の急性増悪が認められた又は死亡した被験者の割合は，プラセボ群 17.3%，本薬 9 mg 群 15.6%，本薬 18 mg 群 13.8%であった。プラセボ群に対するハザード比は DBL1 と比較して数値的に低く，本薬 9 mg 群では 0.97（95% CI：0.69～1.38），本薬 18 mg 群では 0.87（95% CI：0.61～1.24）であった。

DBL2 までの治験期間中に呼吸器疾患による入院又は死亡が発生した被験者の割合は，プラセボ群 23.9%，本薬 9 mg 群 20.2%，本薬 18 mg 群 21.4%であった。プラセボ群に対するハザード比

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は DBL1 と比較して数値的に低く，本薬 9 mg 群では 0.89（95% CI：0.66～1.20），本薬 18 mg 群では 0.97（95% CI：0.73～1.31）であった。

DBL2 までの治験期間中に死亡した被験者は，プラセボ群 42 名（10.7%），本薬 9 mg 群 36 名（9.2%），本薬 18 mg 群 26 名（6.6%）であった。プラセボ群に対するハザード比は DBL1 と比較して数値的に低く，本薬 9 mg 群では 0.95（95% CI : 0.61～1.49），本薬 18 mg 群では 0.66（95% CI : 0.41～1.08）であり，特に本薬 18 mg 群でリスクが 34%減少した。

DBL2 までの治験期間中に%FVC のベースラインからの 10%超（絶対変化量）の低下が認められた又は死亡した被験者の割合は，プラセボ群 38.9%，本薬 9 mg 群 33.7%，本薬 18 mg 群 29.6%であった。プラセボ群に対するハザード比は DBL1 と比較して数値的に低く，本薬 9 mg 群では 0.85（95% CI：0.67～1.07），本薬 18 mg 群では 0.75（95% CI：0.59～0.95）であった。

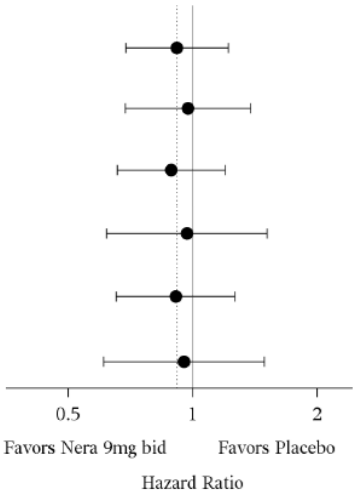
DBL2 までの治験期間中に%DLCO（Hb 補正）のベースラインからの 15%超（絶対変化量）の低下が発生した又は死亡した被験者の割合は，プラセボ群 22.9%，本薬 9 mg 群 20.9%，本薬 18 mg 群 19.9%であった。プラセボ群に対するハザード比は DBL1 と比較して数値的に低く，本薬 9 mg 群では 0.90（95% CI：0.67～1.22），本薬 18 mg 群では 0.84（95% CI：0.62～1.15）であった。

52 週時点でみられたプラセボ群と比較した本薬群での%DLCO（Hb 補正）のベースラインからの数値的減少は治験終了時点でも維持されていた。

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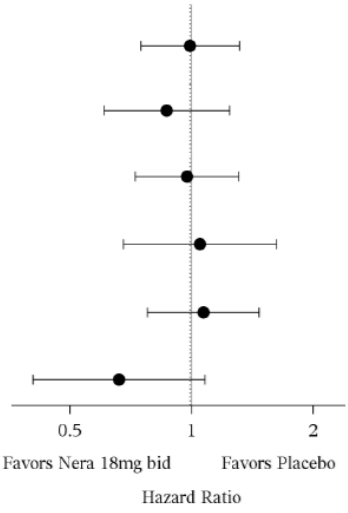
本薬 9 mg 群 vs. プラセボ群

	N with event / N analysed		Hazard ratio [95%-CI]	p-value
	Placebo	Nera 9mg bid		
Key secondary endpoint	103/393	90/392	0.92 [0.69, 1.22]	0.5443
Time to first acute IPF exacerbation or death	68/393	61/392	0.97 [0.69, 1.38]	0.8801
Time to first hospitalization for respiratory cause or death	94/393	79/392	0.89 [0.66, 1.20]	0.4339
Time to first acute IPF exacerbation	42/393	37/392	0.97 [0.62, 1.51]	0.8817
Time to first hospitalization for respiratory cause	76/393	66/392	0.91 [0.65, 1.26]	0.5692
Time to death	42/393	36/392	0.95 [0.61, 1.49]	0.8282



本薬 18 mg 群 vs. プラセボ群

	N with event / N analysed		Hazard ratio [95%-CI]	p-value
	Placebo	Nera 18mg bid		
Key secondary endpoint	103/393	93/392	0.99 [0.75, 1.31]	0.9512
Time to first acute IPF exacerbation or death	68/393	54/392	0.87 [0.61, 1.24]	0.4369
Time to first hospitalization for respiratory cause or death	94/393	84/392	0.97 [0.73, 1.31]	0.8596
Time to first acute IPF exacerbation	42/393	40/392	1.05 [0.68, 1.62]	0.8308
Time to first hospitalization for respiratory cause	76/393	75/392	1.07 [0.78, 1.47]	0.6889
Time to death	42/393	26/392	0.66 [0.41, 1.08]	0.0973



bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
名目上の p 値
引用元：CTD 5.3.5.1-02-01_1305-0014 試験_c43862255_Appendix 16.1.13.1_Figure 11.3.1.1.1

図 4.2.2.2: 1　重要な副次評価項目に含まれる各臨床イベントが最初に発生するまでの期間の Forest plot－FAS（DBL2）

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その他の有効性評価項目

DBL1

その他の有効性評価項目は，主要評価項目及び副評価項目と一貫した傾向を示した。ベースライン時に酸素療法を使用していなかった被験者のうち，DBL1 までの治験期間中に酸素療法を使用した被験者の割合は，プラセボ群では 19.5%（58/297 名），本薬 9 mg 群では 12.1%（38/315 名），本薬 18 mg 群では 16.0%（48/300 名）であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.63（95% CI：0.42～0.96），本薬 18 mg 群では 0.91（95% CI：0.62～1.33）であり，本薬群ではプラセボ群と比較して酸素療法の使用を開始するリスクが数値的に低かった。ベースライン時に酸素療法を使用していた被験者を対象とした，52 週時の睡眠時又は身体活動中の酸素流量のベースラインからの平均絶対変化量は，本薬群ではプラセボ群と比較して小さい傾向がみられた。非 AF 層では，救援治療として AF を開始した被験者の割合は，プラセボ群（10.3%［9/87 名］）と比較して，本薬 9 mg 群（3.4%［3/88 名］）及び本薬 18 mg 群（6.9%［6/87 名］）で数値的に低かった。SpO_2 のベースラインからの変化量については投与群間で意味のある差は認められなかった。

DBL2

その他の評価項目の DBL2 データは，DBL1 データと一貫していた。本薬の両投与群における FVC（mL）のベースラインからの調整済み平均絶対変化量は 52 週を超えて乖離し続けた。

ベースライン時に酸素療法を使用していなかった被験者のうち，DBL2 までの治験期間中に酸素療法を使用した被験者の割合は，プラセボ群では 22.6%（67/297 名），本薬 9 mg 群では 14.9%（47/315 名），本薬 18 mg 群では 18.7%（56/300 名）であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.67（95% CI：0.46～0.98），本薬 18 mg 群では 0.92（95% CI：0.64～1.32）であり，本薬群ではプラセボ群と比較して酸素療法の使用を開始するリスクが数値的に低かった。

DBL1 以降，非 AF 層で新たに AF 救援治療を開始した被験者は報告されなかった。

睡眠時又は身体活動中の酸素流量のベースラインからの平均絶対変化量は，DBL1 でプラセボ群と比較して本薬群で小さい傾向がみられたが，DBL2 でもその傾向が確認された。

臨床薬理の結果

本薬の薬理学的活性のある R 体のエナンチオマー（以下，R-BI 1015550）の定常状態における投与前血漿中濃度は，測定が行われた投与期間にわたって安定していた。R-BI 1015550 の定常状態での投与前血漿中濃度の投与期間全体を通じた幾何平均は，本薬 9 mg 群で 62.2 nmol/L，本薬 18 mg 群で 131 nmol/L であった。R-BI 1015550 の投与前血漿中濃度は，本薬 9 mg 群と本薬 18 mg 群で用量に比例した。

R-BI 1015550 の投与前血漿中濃度は，白人被験者と比較して，アジア人被験者では，本薬 9 mg 群で約 47%，本薬 18 mg 群で約 41%高かった。

R-BI 1015550 の投与前血漿中濃度は，ベースライン時に AF を使用していなかった被験者と比較して，ベースライン時にピルフェニドン使用していた被験者では，本薬 9 mg 群で 55%，本薬

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18 mg 群で 48%低下した。投与前血漿中濃度に基づく探索的部分集団解析により，年齢，性別，民族，制酸薬の使用は R-BI 1015550 の曝露量に影響しないことが示された。

4.2.2.3　　安全性

有害事象

DBL2 までの治験期間中の有害事象の概要を表 4.2.2.3: 1 に示す。重篤な有害事象及び死亡に至った有害事象の発現割合はプラセボ群と比較して本薬群で数値的に低く，死亡に至った有害事象の発現割合は本薬 18 mg 群で最も低かった。

表 4.2.2.3: 1　　DBL2 までの治験期間中の有害事象の概要－TS

Category of AEs	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	393	100.0	392	100.0	392	100.0
Patients with any AE	386	98.2	371	94.6	379	96.7
Severe AEs (CTCAE grade>2)	135	34.4	132	33.7	126	32.1
Investigator-defined drug-related AEs	150	38.2	179	45.7	208	53.1
AEs leading to permanent treatment discontinuation	51	13.0	53	13.5	63	16.1
Serious AEs	167	42.5	149	38.0	149	38.0
Resulted in death	26	6.6	21	5.4	11	2.8

AE：有害事象，bid：1 日 2 回（投与），CTCAE：有害事象共通用語規準，N：number，Nera：ネランドミラスト，TS：治験薬を 1 回以上投与したすべての被験者を含めた treated set
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 27.0
引用元：CTD 5.3.5.1-02-01_1305-0014 試験_c43862255_Appendix 16.1.13.1_Table 12.1.1.1.1

最もよくみられた有害事象は，MedDRA 器官別大分類（SOC）では「感染症および寄生虫症」（プラセボ群 64.6%，本薬 9 mg 群 64.8%，本薬 18 mg 群 63.8%；以下同順）であった。全体として，MedDRA 基本語（PT）で最もよくみられた有害事象は，下痢（18.3%，32.1%，42.4%）であり，次いで咳嗽（18.8%，18.4%，17.4%）及び COVID-19（14.5%，18.6%，14.5%）であった。

最もよくみられた重篤な有害事象は，SOC では「呼吸器、胸郭および縦隔障害」であった。PT では，最もよくみられた重篤な有害事象は状態悪化（8.1%, 6.1%, 7.1%）であり，次いで肺炎（5.6%，3.8%，3.8%），肺高血圧症（3.1%，2.3%，3.1%）及び特発性肺線維症（2.8%，3.1%，2.3%）であった。その他の各事象の発現割合は，呼吸不全を除き各投与群で 2%未満であった。治験薬投与下で死亡に至った有害事象の発現割合は，プラセボ群（6.6%）及び本薬 9 mg 群（5.4%）と比較して，本薬 18 mg 群（2.8%）で最も低かった。治験薬投与下で死亡に至った有害事象のうち，最もよくみられた PT は，状態悪化であった（1.8%，0.5%，1.3%）。

最もよくみられた投与中止に至った有害事象は，SOC では「胃腸障害」であった。PT で最もよくみられた投与中止に至った有害事象は下痢（0.5%，1.8%，6.1%）であり，本薬 18 mg 群で最も高かった。投与中止に至った無力症及び血管炎が各 4 名報告され，すべて本薬 18 mg 群であった。投与中止に至った有害事象のうち，下痢，無力症及び血管炎以外の各事象の発現割合は，投与群間でおおむね同程度であった。

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特記すべき安全性に関する項目及び AESI に基づく medical concept

本治験では，medical concept を表す特記すべき安全性に関する項目について解析した。特記すべき安全性に関する項目の定義の詳細は［CTD 2.7.4_2.1.1.8.1 項］を参照のこと。この medical concept には，治験実施計画書で AESI と定義した事象及び独立判定委員会により判定された結果も含む。

「Gastrointestinal symptoms」

特記すべき安全性に関する項目の「Gastrointestinal symptoms」の発現割合は，プラセボ群と比較して本薬群で高かった（プラセボ群 26.7%, 本薬 9 mg 群 41.3%, 本薬 18 mg 群 49.2%；以下同順）。これは，PT の下痢の発現割合がプラセボ群と比較して本薬群で高かったことに起因していた。特記すべき安全性に関する項目の「Gastrointestinal symptoms」のほかの PT の発現割合は 3 つの投与群間で同程度であった。下痢はほとんどが非重篤であり，重症度は軽度又は中等度であり，本薬投与継続中に回復した。投与中止に至った下痢のほとんどは本薬 18 mg 群で認められた。

「Weight decrease」

特記すべき安全性に関する項目の「Weight decrease」の発現割合は，プラセボ群と比較して本薬群で高かった（9.7%，11.2%，12.5%）。「Weight decrease」はほとんどが非重篤であり，投与を中止することなく，ほとんどが回復した。重篤な有害事象は 2 件であり，本薬 9 mg 群及び本薬 18 mg 群の各 1 名に各 1 件認められた。

体重の治験薬投与下の最終値はすべての投与群でベースラインから減少し，体重のベースラインから治験薬投与下の最終値までの絶対変化量の平均値は，プラセボ群−2.3 kg，本薬 9 mg 群−2.9 kg，本薬 18 mg 群−3.2 kg であった。DBL2 までの治験期間中の体重のベースラインからの最大相対変化率の平均値は，プラセボ群−4.9%（SD：5.1），本薬 9 mg 群−5.5%（SD：4.5）及び本薬 18 mg 群−6.2%（SD：4.9）であった。

その他の特記すべき安全性に関する項目

本薬の作用機序又は他の PDE4 阻害薬の重要な潜在的リスク若しくは特定されたリスク（心血管イベント，精神関連症状，「Vasculitis」，「Severe, serious, opportunistic, or *M. tuberculosis* infections」，「Malignancies」，並びに独立判定委員会により判定された「Vasculitis」及び MACE）あるいは「Potential severe DILI」に関連するその他の特記すべき安全性に関する項目については，投与群間で臨床的に問題となる差は認められなかった。同様に，AESI の発現割合も投与群間で大きな差はなかった。

部分集団における有害事象

DBL2 までの治験期間中の人口統計学的特性別及びベースライン特性別の部分集団における有害事象は，全体集団の有害事象プロファイルとおおむね一貫する傾向を示した。ベースライン時

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の AF の種類別の部分集団（ニンテダニブ使用，ピルフェニドン使用又は非 AF 層）の有害事象の解析から，試験全体でみられたように，プラセボ群と比較して本薬群での投与中止に至った有害事象の増加は，ベースライン時にニンテダニブ使用ありの集団（プラセボ群 13.9%，本薬 9 mg 群 18.5%，本薬 18 mg 群 23.0%；以下同順）によって引き起こされたことが示された。しかし，ベースライン時にピルフェニドン使用ありの集団（12.0%, 8.3%, 11.0%）又は非 AF 層（12.6%, 10.2%, 9.2%）では差は認められなかった。治験担当医師に因果関係ありと判断された有害事象の発現割合は，ベースライン時にニンテダニブ使用ありの集団及び非 AF 層の本薬群でプラセボ群と比較して増加したが，ベースライン時にピルフェニドン使用ありの集団では増加は認められなかった。

ベースライン時にニンテダニブ使用ありの集団では，特記すべき安全性に関する項目の「Weight decrease」の発現割合は本薬の用量増加に伴って増加したが，ベースライン時にピルフェニドン使用ありの集団又は非 AF 層では明らかな傾向は認められなかった。

ベースライン時の AF 使用の有無にかかわらず，特記すべき安全性に関する項目の「Gastrointestinal symptoms」の発現割合は本薬の用量増加に伴って増加したが，これは本薬群で下痢の発現割合が増加したことによるものであった。投与中止に至った下痢の大部分はベースライン時にニンテダニブ使用ありの本薬 18 mg 群で認められた。部分集団別に解析されたその他の特記すべき安全性に関する項目の有害事象は，全体集団とおおむね同様の傾向を示した。

臨床検査及びその他の観察項目

治験期間中の臨床検査項目又はバイタルサインについては，上記の体重減少を除いて，臨床的に意味のある経時的変化は認められず，投与群間で臨床的に意味のある差も認められなかった。治験期間中に肝酵素値の上昇がみられた被験者の割合は低く，投与群間で同程度であった。

4.2.2.4　結論

本治験では，ベースライン時に AF（ニンテダニブ又はピルフェニドン）投与を受けていた，又は受けていなかった IPF 患者を対象として，本薬 9 mg，本薬 18 mg 又はプラセボを 1 日 2 回，52 週間以上投与した。52 週時の FVC（mL）のベースラインからの低下の抑制について，本薬 9 mg 群及び本薬 18 mg 群とプラセボ群との投与群間差はいずれも統計学的に有意であり，本薬の両用量でプラセボに対する優越性が示された。本薬の治療効果は，AF 層及び非 AF 層の両層で認められた。しかし，ベースライン時にピルフェニドン使用ありの集団では，本薬 9 mg 群と本薬 18 mg 群の間で治療効果に差が認められた。ベースライン時にピルフェニドン使用ありの集団で本薬の投与前血漿中濃度の意味のある減少が認められ，本薬 9 mg 1 日 2 回投与の治療効果がこの部分集団で認められなかった可能性がある。ベースライン時にピルフェニドン使用ありの集団を除いた事後解析では，ベースラインからの FVC の変化量における治療効果は本薬 9 mg 群と本薬 18 mg 群で同程度であった。全体として，主要解析（DBL1）までに，重要な副次評価項目（治験期間中の IPF の初回急性増悪，呼吸器疾患による初回入院又は死亡のいずれかが最初に発生するまでの期間）について，本薬群とプラセボ群の間で統計学的に有意な差は認められなかった。しかし，

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本薬群では FVC 低下抑制だけでなく，52 週時の DLCO の変化量及び酸素療法の開始までの期間に関する有益な効果が認められた。

被験者の 4 分の 3 以上が AF 層であったにもかかわらず，プラセボ群では 52 週間にわたって FVC の低下が認められ，IPF に対してより有効な治療を求めるアンメットニーズがあることが強く示唆された。

AF 使用の有無にかかわらず，本薬の両用量とも許容可能な安全性及び忍容性プロファイルを示した。重度の有害事象及び重篤な有害事象（死亡に至った有害事象を含む）が認められた被験者の割合は投与群間で同程度であり，死亡に至った有害事象の発現割合は本薬 18 mg 群で最も低かった。ベースライン時にニンテダニブ使用ありの集団において，プラセボ群と比較して，本薬の用量増加に伴って投与中止に至った有害事象及び投与中断に至った有害事象の増加が認められたが，ベースライン時にピルフェニドン使用ありの集団又は非 AF 層では本薬の用量増加に伴う増加は認められなかった。下痢は本薬群で最もよくみられた有害事象かつ投与中止に至った有害事象であり，すべての投与群で最もよくみられた治験担当医師に因果関係ありと判断された有害事象であった。すべての投与群において，下痢の発現割合は，ベースライン時にピルフェニドン使用ありの集団又は非 AF 層と比較して，ベースライン時にニンテダニブ使用ありの集団で高かった。その他の有害事象の発現割合は投与群間でおおむね同程度であった。

概して，平均約 1.5 カ月の追加の投与期間と平均約 2 カ月の追加の観察期間を含む本治験の最終解析（DBL2）の結果により，主要解析（DBL1）の結果が裏付けられ，本薬 9 mg 群及び本薬 18 mg 群では 52 週間を超えて FVC の低下抑制が継続し，経時的な FVC 推移のプラセボ群との差が維持された。これは，重要な副次評価項目の傾向によりさらに裏付けられ，投与期間の延長に伴い，プラセボ群に対する本薬 9 mg 群及び本薬 18 mg 群のハザード比は DBL1 と比較して DBL2 で数値的に低かった。特に，本薬 18 mg 群の死亡リスクは DBL2 で数値的に 34%減少し，長期的な疾患修飾効果がさらに示された。DBL2 の安全性データに，DBL1 と比較して新たな安全性の懸念は認められず，良好な長期の安全性及び忍容性が確認された。

以上から，ベースライン時の AF 使用の有無にかかわらず，本薬 9 mg 1 日 2 回及び本薬 18 mg 1 日 2 回の投与はいずれも，FAS における FVC 低下の抑制に有効であり，本薬の安全性及び忍容性プロファイルは許容可能であった。しかし，ベースライン時にピルフェニドン使用ありの集団では，本薬 9 mg 1 日 2 回投与の有益な効果は認められず，これは，本薬曝露量の減少を引き起こす相互作用に起因している可能性が高い。

4.2.3　付録

本治験全体（DBL2）で認められたすべての有害事象及び治験担当医師に治験薬と因果関係ありと判断された有害事象を Table 99.2 に，重篤な有害事象の被験者一覧を Listing 12.5.2.1 に，死亡に至った有害事象の被験者一覧を Listing 12.5.2.8 に示す。

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	393	100.00	393	100.00	392	100.00	392	100.00	392	100.00	392	100.00
Total with adverse events	386	98.22	150	38.17	371	94.64	179	45.66	379	96.68	208	53.06
Infections and infestations(感染症および寄生虫症)	254	64.63	11	2.80	254	64.80	11	2.81	250	63.78	12	3.06
COVID-19(ＣＯＶＩＤ－１９)	57	14.50	1	0.25	73	18.62	0	0.00	57	14.54	1	0.26
Upper respiratory tract infection(上気道感染)	44	11.20	0	0.00	46	11.73	2	0.51	56	14.29	1	0.26
Nasopharyngitis(上咽頭炎)	50	12.72	3	0.76	44	11.22	1	0.26	45	11.48	2	0.51
Bronchitis(気管支炎)	39	9.92	0	0.00	31	7.91	1	0.26	35	8.93	0	0.00
Pneumonia(肺炎)	32	8.14	3	0.76	33	8.42	1	0.26	31	7.91	0	0.00
Respiratory tract infection(気道感染)	13	3.31	0	0.00	15	3.83	0	0.00	24	6.12	3	0.77
Influenza(インフルエンザ)	16	4.07	0	0.00	11	2.81	0	0.00	18	4.59	0	0.00
Urinary tract infection(尿路感染)	20	5.09	1	0.25	12	3.06	0	0.00	13	3.32	0	0.00
Sinusitis(副鼻腔炎)	11	2.80	0	0.00	14	3.57	0	0.00	13	3.32	0	0.00
Lower respiratory tract infection(下気道感染)	8	2.04	0	0.00	19	4.85	0	0.00	9	2.30	0	0.00
Rhinitis(鼻炎)	12	3.05	1	0.25	9	2.30	0	0.00	9	2.30	0	0.00
Herpes zoster(帯状疱疹)	9	2.29	1	0.25	5	1.28	0	0.00	9	2.30	1	0.26
Gastroenteritis(胃腸炎)	10	2.54	0	0.00	2	0.51	0	0.00	8	2.04	0	0.00
Latent tuberculosis(潜伏結核)	7	1.78	0	0.00	4	1.02	1	0.26	8	2.04	1	0.26
Cystitis(膀胱炎)	7	1.78	0	0.00	1	0.26	0	0.00	5	1.28	1	0.26
Conjunctivitis(結膜炎)	5	1.27	0	0.00	4	1.02	0	0.00	3	0.77	0	0.00
Pneumonia bacterial(細菌性肺炎)	3	0.76	0	0.00	6	1.53	2	0.51	3	0.77	1	0.26
Viral upper respiratory tract infection(ウイルス性上気道感染)	4	1.02	0	0.00	5	1.28	0	0.00	2	0.51	0	0.00
Respiratory tract infection viral(ウイルス性気道感染)	2	0.51	1	0.25	6	1.53	0	0.00	1	0.26	0	0.00
Skin infection(皮膚感染)	3	0.76	0	0.00	1	0.26	0	0.00	5	1.28	0	0.00
Viral infection(ウイルス感染)	3	0.76	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Gastroenteritis viral(ウイルス性胃腸炎)	4	1.02	0	0.00	1	0.26	0	0.00	3	0.77	0	0.00
Oral candidiasis(口腔カンジダ症)	0	0.00	0	0.00	2	0.51	0	0.00	6	1.53	0	0.00
Gingivitis(歯肉炎)	3	0.76	0	0.00	3	0.77	1	0.26	1	0.26	0	0.00
Pharyngitis(咽頭炎)	2	0.51	0	0.00	4	1.02	0	0.00	1	0.26	0	0.00
Coronavirus infection(コロナウイルス感染)	3	0.76	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Tooth infection(歯感染)	5	1.27	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hordeolum(麦粒腫)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Laryngitis(喉頭炎)	3	0.76	1	0.25	2	0.51	0	0.00	0	0.00	0	0.00
Otitis media(中耳炎)	2	0.51	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Respiratory syncytial virus infection(ＲＳウイルス感染)	0	0.00	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Septic shock(敗血症性ショック)	1	0.25	0	0.00	2	0.51	0	0.00	2	0.51	1	0.26
Cellulitis(蜂巣炎)	0	0.00	0	0.00	4	1.02	1	0.26	0	0.00	0	0.00
Diverticulitis(憩室炎)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	1	0.26
Ear infection(耳感染)	3	0.76	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Herpes simplex(単純ヘルペス)	1	0.25	0	0.00	1	0.26	1	0.26	2	0.51	0	0.00
Pulpitis dental(歯髄炎)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Atypical mycobacterial infection(非定型マイコバクテリア感染)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atypical pneumonia(異型肺炎)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Body tinea(体部白癬)	0	0.00	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00
Bronchitis viral(ウイルス性気管支炎)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Bronchopulmonary aspergillosis(気管支肺アスペルギルス症)	1	0.25	1	0.25	2	0.51	0	0.00	0	0.00	0	0.00
Chronic sinusitis(慢性副鼻腔炎)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Dengue fever(デング熱)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Folliculitis(毛包炎)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Helicobacter infection(ヘリコバクター感染)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Oral herpes(口腔ヘルペス)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	1	0.26
Post-acute COVID-19 syndrome(急性ＣＯＶＩＤ－１９後症候群)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Tinea pedis(足部白癬)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Tooth abscess(歯膿瘍)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Tracheobronchitis(気管気管支炎)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Acute sinusitis(急性副鼻腔炎)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Appendicitis(虫垂炎)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Bacterial infection(細菌感染)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Biliary tract infection(胆道感染)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Bronchitis bacterial(細菌性気管支炎)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
COVID-19 pneumonia(ＣＯＶＩＤ－１９肺炎)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Febrile infection(熱性感染症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Fungal foot infection(真菌性足感染)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Fungal skin infection(皮膚真菌感染)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Genital herpes(陰部ヘルペス)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hepatitis E(E型肝炎)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Infection(感染)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Laryngopharyngitis(咽喉頭炎)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oral fungal infection(口腔真菌感染)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oropharyngeal candidiasis(中咽頭カンジダ症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Periodontitis(歯周炎)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumonia haemophilus(ヘモフィルス性肺炎)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Pneumonia influenzal(インフルエンザ性肺炎)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Pneumonia pseudomonal(シュードモナス性肺炎)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumonia viral(ウイルス性肺炎)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pyelonephritis acute(急性腎盂腎炎)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sepsis(敗血症)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tonsillitis(扁桃炎)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Tuberculosis(結核)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Vulvovaginal candidiasis(外陰部腟カンジダ症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Acarodermatitis(ダニ皮膚炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Alveolar osteitis(歯槽骨炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Anal tinea(肛門白癬)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Appendiceal abscess(虫垂膿瘍)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Aspergillus infection(アスペルギルス感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bacterial tracheitis(細菌性気管炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bacterial vaginosis(細菌性腟症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Candida infection(カンジダ感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Dermatophytosis of nail(爪の皮膚糸状菌症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Device related infection(医療機器関連感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Endocarditis bacterial(細菌性心内膜炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Enteritis infectious(感染性腸炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eyelid infection(眼瞼感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Fungal balanitis(真菌性亀頭炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fungal infection(真菌感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Furuncle(せつ)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastroenteritis norovirus(ノロウイルス性胃腸炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastroenteritis salmonella(サルモネラ菌性胃腸炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastrointestinal bacterial infection(細菌性消化管感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gastrointestinal infection(消化管感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastrointestinal viral infection(ウイルス性消化管感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Groin abscess(鼠径部膿瘍)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
HCoV-OC43 infection(ＨＣｏＶ－ＯＣ４３感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hepatitis B reactivation(Ｂ型肝炎再活性化)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Herpes dermatitis(ヘルペス性皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Herpes simplex reactivation(単純ヘルペス再燃)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Impetigo(膿痂疹)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Infective glossitis(感染性舌炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Laryngitis viral(ウイルス性喉頭炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lice infestation(シラミ寄生)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Localised infection(限局性感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lyme disease(ライム病)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Medical device site infection(医療機器使用部位感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Metapneumovirus infection(メタニューモウイルス感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Mycobacterial disease carrier(マイコバクテリア性疾患キャリアー)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Norovirus infection(ノロウイルス感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Onychomycosis(爪真菌症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Otitis externa fungal(真菌性外耳炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Otitis externa(外耳炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Parainfluenzae virus infection(パラインフルエンザウイルス感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Paronychia(爪囲炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Perichondritis(軟骨膜炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pharyngitis bacterial(細菌性咽頭炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pilonidal disease(毛巣病)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pleurisy bacterial(細菌性胸膜炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumocystis jirovecii pneumonia(ニューモシスチス・イロベチイ肺炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumonia aspiration(誤嚥性肺炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumonia fungal(真菌性肺炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pneumonia mycoplasmal(マイコプラズマ性肺炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pneumonia pneumococcal(肺炎球菌性肺炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pyelonephritis(腎盂腎炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Rash pustular(膿疱性皮疹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rhinovirus infection(ライノウイルス感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Salmonellosis(サルモネラ症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin candida(皮膚カンジダ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Staphylococcal skin infection(ブドウ球菌皮膚感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Streptococcal infection(レンサ球菌感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Strongyloidiasis(糞線虫症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Subcutaneous abscess(皮下組織膿瘍)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Syphilis(梅毒)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tinea cruris(股部白癬)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tinea infection(白癬感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Tracheitis(気管炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Urinary tract infection pseudomonal(シュードモナス性尿路感染)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urosepsis(尿路性敗血症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Varicella zoster virus infection(水痘帯状疱疹ウイルス感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Wound infection bacterial(細菌性創感染)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastrointestinal disorders(胃腸障害)	164	41.73	73	18.58	209	53.32	128	32.65	231	58.93	158	40.31
Diarrhoea(下痢)	72	18.32	40	10.18	126	32.14	87	22.19	166	42.35	135	34.44
Nausea(悪心)	28	7.12	18	4.58	36	9.18	21	5.36	34	8.67	20	5.10
Vomiting(嘔吐)	19	4.83	7	1.78	20	5.10	9	2.30	22	5.61	10	2.55
Constipation(便秘)	20	5.09	1	0.25	7	1.79	1	0.26	13	3.32	0	0.00
Abdominal pain(腹痛)	12	3.05	6	1.53	11	2.81	6	1.53	16	4.08	8	2.04
Flatulence(鼓腸)	12	3.05	9	2.29	10	2.55	8	2.04	10	2.55	7	1.79

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Frequent bowel movements(排便回数増加)	7	1.78	3	0.76	11	2.81	8	2.04	13	3.32	10	2.55
Gastrooesophageal reflux disease(胃食道逆流性疾患)	10	2.54	3	0.76	18	4.59	6	1.53	2	0.51	0	0.00
Abdominal pain upper(上腹部痛)	6	1.53	0	0.00	14	3.57	7	1.79	8	2.04	3	0.77
Dyspepsia(消化不良)	8	2.04	1	0.25	12	3.06	4	1.02	8	2.04	3	0.77
Abdominal discomfort(腹部不快感)	4	1.02	3	0.76	7	1.79	4	1.02	7	1.79	4	1.02
Haemorrhoids(痔核)	3	0.76	1	0.25	6	1.53	1	0.26	5	1.28	0	0.00
Abdominal distension(腹部膨満)	4	1.02	2	0.51	3	0.77	2	0.51	5	1.28	2	0.51
Dry mouth(口内乾燥)	2	0.51	0	0.00	6	1.53	3	0.77	3	0.77	1	0.26
Faeces soft(軟便)	4	1.02	2	0.51	3	0.77	3	0.77	4	1.02	3	0.77
Inguinal hernia(鼠径ヘルニア)	4	1.02	0	0.00	3	0.77	0	0.00	4	1.02	0	0.00
Gastritis(胃炎)	2	0.51	0	0.00	6	1.53	1	0.26	1	0.26	0	0.00
Dental caries(齲歯)	1	0.25	0	0.00	3	0.77	0	0.00	4	1.02	0	0.00
Toothache(歯痛)	2	0.51	0	0.00	3	0.77	0	0.00	3	0.77	0	0.00
Diverticulum intestinal(腸憩室)	2	0.51	0	0.00	3	0.77	0	0.00	2	0.51	0	0.00
Large intestine polyp(大腸ポリープ)	1	0.25	0	0.00	5	1.28	0	0.00	1	0.26	0	0.00
Colitis(大腸炎)	1	0.25	0	0.00	4	1.02	2	0.51	1	0.26	0	0.00
Gastrointestinal disorder(胃腸障害)	1	0.25	1	0.25	4	1.02	1	0.26	1	0.26	0	0.00
Haematochezia(血便排泄)	1	0.25	0	0.00	5	1.28	0	0.00	0	0.00	0	0.00
Chronic gastritis(慢性胃炎)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Dysphagia(嚥下障害)	0	0.00	0	0.00	4	1.02	1	0.26	1	0.26	0	0.00
Hiatus hernia(裂孔ヘルニア)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Enteritis(小腸炎)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	1	0.26
Food poisoning(食中毒)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Odynophagia(嚥下痛)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Abdominal pain lower(下腹部痛)	1	0.25	1	0.25	0	0.00	0	0.00	1	0.26	0	0.00
Aerophagia(空気嚥下)	0	0.00	0	0.00	1	0.26	1	0.26	1	0.26	0	0.00
Diverticulum(憩室)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Enterocolitis(腸炎)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Eructation(おくび)	0	0.00	0	0.00	1	0.26	1	0.26	1	0.26	1	0.26
Gastric dilatation(胃拡張)	1	0.25	1	0.25	0	0.00	0	0.00	1	0.26	0	0.00
Gastrointestinal haemorrhage(胃腸出血)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Gastrointestinal pain(消化器痛)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Gingival bleeding(歯肉出血)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Irritable bowel syndrome(過敏性腸症候群)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Melaena(メレナ)	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Oral lichen planus(口腔扁平苔癬)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Small intestinal obstruction(小腸閉塞)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Anal fissure(裂肛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Angular cheilitis(口角口唇炎)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Anorectal discomfort(肛門直腸不快感)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aphthous ulcer(アフタ性潰瘍)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Ascites(腹水)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Breath odour(呼気臭)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Burning mouth syndrome(口腔灼熱感症候群)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Change of bowel habit(便習慣変化)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Cheilitis(口唇炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Defaecation urgency(便意切迫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Duodenogastric reflux(十二指腸胃逆流)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Ectopic gastric mucosa(異所性胃粘膜)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Faeces discoloured(変色便)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Feline oesophagus(食道多発輪状狭窄)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastric polyps(胃ポリープ)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastric ulcer(胃潰瘍)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastric varices(胃静脈瘤)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gastritis erosive(びらん性胃炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastrointestinal angiodysplasia(胃腸管血管異形成)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastrointestinal motility disorder(消化管運動障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastrointestinal oedema(消化管浮腫)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Gingival recession(歯肉退縮)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Glossodynia(舌痛)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Haematemesis(吐血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Haemorrhoidal haemorrhage(痔出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hyperaesthesia teeth(歯の知覚過敏)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypergastrinaemia(高ガストリン血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Intestinal dilatation(腸管拡張症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Intestinal mass(腸管腫瘤)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Intestinal obstruction(腸閉塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Leukoplakia oesophageal(食道白斑症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Leukoplakia oral(口腔白斑症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lip swelling(口唇腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lower gastrointestinal haemorrhage(下部消化管出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Mechanical ileus(機械的イレウス)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Mouth ulceration(口腔内潰瘍形成)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Mucous stools(粘液便)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Obstructive pancreatitis(閉塞性膵炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oesophageal rupture(食道破裂)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oesophageal stenosis(食道狭窄)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Oesophagitis(食道炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oronasal fistula(口腔鼻腔瘻)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pancreatic enlargement(膵腫大)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pancreatitis acute(急性膵炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pancreatitis(膵炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Paraesthesia oral(口の錯感覚)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Peptic ulcer(消化性潰瘍)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rectal haemorrhage(直腸出血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Salivary gland pain(唾液腺痛)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tongue geographic(地図状舌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tooth disorder(歯の障害)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tooth resorption(歯の吸収症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Umbilical hernia(臍ヘルニア)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Upper gastrointestinal haemorrhage(上部消化管出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Varices oesophageal(食道静脈瘤)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Volvulus(腸の軸捻転)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	179	45.55	15	3.82	172	43.88	13	3.32	148	37.76	11	2.81
Cough(咳嗽)	74	18.83	4	1.02	72	18.37	5	1.28	68	17.35	7	1.79
Dyspnoea(呼吸困難)	63	16.03	6	1.53	51	13.01	1	0.26	42	10.71	2	0.51
Productive cough(湿性咳嗽)	11	2.80	0	0.00	14	3.57	2	0.51	16	4.08	1	0.26
Pulmonary hypertension(肺高血圧症)	12	3.05	1	0.25	9	2.30	0	0.00	12	3.06	0	0.00
Rhinorrhoea(鼻漏)	8	2.04	0	0.00	11	2.81	1	0.26	14	3.57	0	0.00
Idiopathic pulmonary fibrosis(特発性肺線維症)	11	2.80	0	0.00	12	3.06	0	0.00	9	2.30	0	0.00
Epistaxis(鼻出血)	6	1.53	0	0.00	8	2.04	1	0.26	11	2.81	1	0.26
Dyspnoea exertional(労作性呼吸困難)	4	1.02	0	0.00	10	2.55	0	0.00	10	2.55	0	0.00
Oropharyngeal pain(口腔咽頭痛)	9	2.29	1	0.25	5	1.28	2	0.51	6	1.53	0	0.00
Hypoxia(低酸素症)	7	1.78	0	0.00	5	1.28	0	0.00	4	1.02	0	0.00
Pulmonary embolism(肺塞栓症)	7	1.78	1	0.25	5	1.28	0	0.00	4	1.02	0	0.00
Respiratory failure(呼吸不全)	8	2.04	2	0.51	4	1.02	0	0.00	2	0.51	0	0.00
Haemoptysis(喀血)	4	1.02	1	0.25	5	1.28	0	0.00	2	0.51	0	0.00
Pneumothorax(気胸)	1	0.25	0	0.00	3	0.77	0	0.00	7	1.79	0	0.00
Rhinitis allergic(アレルギー性鼻炎)	3	0.76	0	0.00	6	1.53	0	0.00	2	0.51	0	0.00
Acute respiratory failure(急性呼吸不全)	2	0.51	1	0.25	4	1.02	0	0.00	3	0.77	0	0.00
Dysphonia(発声障害)	1	0.25	0	0.00	4	1.02	0	0.00	4	1.02	0	0.00
Upper-airway cough syndrome(上気道咳症候群)	3	0.76	0	0.00	3	0.77	0	0.00	3	0.77	0	0.00
Sputum increased(喀痰増加)	2	0.51	0	0.00	1	0.26	0	0.00	5	1.28	0	0.00
Asthma(喘息)	3	0.76	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Nasal congestion(鼻閉)	1	0.25	0	0.00	3	0.77	0	0.00	3	0.77	0	0.00
Sleep apnoea syndrome(睡眠時無呼吸症候群)	1	0.25	0	0.00	5	1.28	0	0.00	1	0.26	0	0.00
Chronic respiratory failure(慢性呼吸不全)	3	0.76	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Interstitial lung disease(間質性肺疾患)	3	0.76	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Catarrh(カタル)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Pneumonitis(肺臓炎)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Pulmonary mass(肺腫瘤)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Respiratory disorder(呼吸障害)	1	0.25	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Upper respiratory tract inflammation(上気道の炎症)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Wheezing(喘鳴)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Aphonia(失声症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Chronic obstructive pulmonary disease(慢性閉塞性肺疾患)	1	0.25	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Painful respiration(呼吸時疼痛)	2	0.51	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Pneumomediastinum(気縦隔症)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary arterial hypertension(肺動脈性肺高血圧症)	3	0.76	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sinus congestion(副鼻腔うっ血)	1	0.25	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Cough variant asthma(咳喘息)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Hiccups(しゃっくり)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Hypersensitivity pneumonitis(過敏性肺臓炎)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Increased viscosity of bronchial secretion(高粘稠性気管支分泌物)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lung disorder(肺障害)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lung opacity(肺陰影)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Obstructive airways disorder(閉塞性気道障害)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Pleural effusion(胸水)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pneumothorax spontaneous(自然気胸)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary fibrosis(肺線維症)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Sneezing(くしゃみ)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sputum discoloured(変色痰)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Vocal cord leukoplakia(声帯白斑症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Allergic cough(アレルギー性咳嗽)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Atelectasis(無気肺)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bendopnoea(前屈呼吸困難)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bronchial hyperreactivity(気管支反応性亢進)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bronchiectasis(気管支拡張症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bronchospasm(気管支痙攣)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Choking(息詰まり)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Diaphragmalgia(横隔膜痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Emphysema(肺気腫)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Haemothorax(血胸)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hepatopulmonary syndrome(肝肺症候群)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Hyperactive pharyngeal reflex(咽頭反射亢進)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypercapnia(高炭酸ガス血症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hyperventilation(過換気)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Increased bronchial secretion(気管支分泌増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Increased upper airway secretion(上気道分泌増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Laryngospasm(喉頭痙攣)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lower respiratory tract congestion(下気道うっ血)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Nasal dryness(鼻乾燥)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Nasal mucosal hypertrophy(鼻粘膜肥厚)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nasal ulcer(鼻潰瘍)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Noninfective bronchitis(非感染性気管支炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Obstructive sleep apnoea syndrome(閉塞性睡眠時無呼吸症候群)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Organising pneumonia(器質化肺炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Paranasal sinus discomfort(副鼻腔不快感)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Pharyngeal inflammation(咽頭の炎症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pleuritic pain(胸膜痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary artery dilatation(肺動脈拡張)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pulmonary artery thrombosis(肺動脈血栓症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pulmonary venous hypertension(肺静脈性肺高血圧症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rales(ラ音)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Respiratory acidosis(呼吸性アシドーシス)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Respiratory distress(呼吸窮迫)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rheumatoid arthritis-associated interstitial lung disease(関節リウマチ関連間質性肺疾患)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Suffocation feeling(窒息感)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Throat clearing(咳払い)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Throat irritation(咽喉刺激感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Upper respiratory tract congestion(上気道うっ血)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vasomotor rhinitis(血管運動性鼻炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	119	30.28	18	4.58	110	28.06	21	5.36	122	31.12	15	3.83
Condition aggravated(状態悪化)	52	13.23	4	1.02	39	9.95	1	0.26	45	11.48	1	0.26
Fatigue(疲労)	23	5.85	9	2.29	32	8.16	13	3.32	30	7.65	7	1.79
Asthenia(無力症)	10	2.54	0	0.00	15	3.83	5	1.28	19	4.85	6	1.53
Chest pain(胸痛)	8	2.04	0	0.00	13	3.32	0	0.00	13	3.32	1	0.26
Oedema peripheral(末梢性浮腫)	10	2.54	0	0.00	12	3.06	2	0.51	10	2.55	1	0.26
Pyrexia(発熱)	8	2.04	1	0.25	6	1.53	1	0.26	10	2.55	0	0.00
Disease progression(疾患進行)	6	1.53	0	0.00	7	1.79	0	0.00	7	1.79	0	0.00
Chest discomfort(胸部不快感)	3	0.76	1	0.25	5	1.28	0	0.00	4	1.02	0	0.00
Influenza like illness(インフルエンザ様疾患)	7	1.78	0	0.00	3	0.77	0	0.00	2	0.51	0	0.00
Malaise(倦怠感)	2	0.51	1	0.25	1	0.26	0	0.00	4	1.02	0	0.00
Oedema(浮腫)	3	0.76	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Chills(悪寒)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
General physical health deterioration(全身健康状態悪化)	1	0.25	1	0.25	1	0.26	0	0.00	2	0.51	1	0.26
Peripheral swelling(末梢腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	4	1.02	0	0.00
Death(死亡)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Discomfort(不快感)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gait disturbance(歩行障害)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Hernia(ヘルニア)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Inflammation(炎症)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Non-cardiac chest pain(非心臓性胸痛)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pain(疼痛)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Vascular stent stenosis(血管ステント狭窄)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Adverse drug reaction(医薬品副作用)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Calcinosis(石灰沈着症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Face oedema(顔面浮腫)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Feeling hot(熱感)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Illness(疾患)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Infusion site extravasation(注入部位溢出)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Infusion site thrombosis(注入部位血栓)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Medical device pain(医療機器による疼痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Pacemaker generated arrhythmia(ペースメーカー原性不整脈)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Physical deconditioning(体調不良)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Secretion discharge(分泌物分泌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sluggishness(不活発)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Stent-graft endoleak(ステントグラフトエンドリーク)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Sudden death(突然死)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Swelling face(顔面腫脹)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vessel puncture site bruise(血管穿刺部位内出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vessel puncture site haematoma(血管穿刺部位血腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vessel puncture site pain(血管穿刺部位疼痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Investigations(臨床検査)	82	20.87	32	8.14	102	26.02	31	7.91	99	25.26	44	11.22
Weight decreased(体重減少)	38	9.67	16	4.07	43	10.97	18	4.59	48	12.24	28	7.14
C-reactive protein increased(Ｃ－反応性蛋白増加)	5	1.27	1	0.25	12	3.06	2	0.51	9	2.30	0	0.00
Aspartate aminotransferase increased(アスパラギン酸アミノトランスフェラーゼ増加)	3	0.76	1	0.25	6	1.53	1	0.26	10	2.55	5	1.28
Gamma-glutamyltransferase increased(γ－グルタミルトランスフェラーゼ増加)	4	1.02	3	0.76	7	1.79	2	0.51	4	1.02	1	0.26
Lipase increased(リパーゼ増加)	2	0.51	1	0.25	6	1.53	4	1.02	7	1.79	3	0.77
Alanine aminotransferase increased(アラニンアミノトランスフェラーゼ増加)	1	0.25	0	0.00	5	1.28	1	0.26	7	1.79	3	0.77
Depression rating scale score increased(抑うつ尺度スコア増加)	4	1.02	2	0.51	5	1.28	0	0.00	4	1.02	1	0.26
Amylase increased(アミラーゼ増加)	0	0.00	0	0.00	5	1.28	4	1.02	5	1.28	3	0.77

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
SARS-CoV-2 test positive(ＳＡＲＳ－ＣｏＶ－２検査陽性)	4	1.02	0	0.00	1	0.26	0	0.00	5	1.28	0	0.00
Hepatic enzyme increased(肝酵素上昇)	3	0.76	1	0.25	3	0.77	1	0.26	2	0.51	1	0.26
Blood glucose increased(血中ブドウ糖増加)	2	0.51	1	0.25	2	0.51	0	0.00	3	0.77	1	0.26
Blood creatine phosphokinase increased(血中クレアチンホスホキナーゼ増加)	1	0.25	1	0.25	3	0.77	0	0.00	2	0.51	0	0.00
Blood pressure decreased(血圧低下)	1	0.25	0	0.00	1	0.26	1	0.26	4	1.02	1	0.26
Interferon gamma release assay positive(インターフェロンγ応答測定陽性)	2	0.51	1	0.25	3	0.77	0	0.00	1	0.26	0	0.00
Protein urine present(尿中蛋白陽性)	2	0.51	1	0.25	2	0.51	1	0.26	2	0.51	2	0.51
Blood alkaline phosphatase increased(血中アルカリホスファターゼ増加)	2	0.51	2	0.51	1	0.26	1	0.26	2	0.51	1	0.26
Oxygen saturation decreased(酸素飽和度低下)	2	0.51	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Blood pressure increased(血圧上昇)	0	0.00	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Blood uric acid increased(血中尿酸増加)	2	0.51	1	0.25	1	0.26	0	0.00	1	0.26	0	0.00
Heart rate increased(心拍数増加)	1	0.25	0	0.00	2	0.51	1	0.26	1	0.26	0	0.00
Prothrombin time prolonged(プロトロンビン時間延長)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	1	0.26
Activated partial thromboplastin time prolonged(活性化部分トロンボプラスチン時間延長)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Blood creatinine increased(血中クレアチニン増加)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Blood thyroid stimulating hormone increased(血中甲状腺刺激ホルモン増加)	2	0.51	2	0.51	1	0.26	0	0.00	0	0.00	0	0.00
Occult blood positive(便潜血陽性)	1	0.25	1	0.25	2	0.51	0	0.00	0	0.00	0	0.00
Platelet count decreased(血小板数減少)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Troponin increased(トロポニン増加)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
White blood cells urine positive(尿中白血球陽性)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Blood potassium decreased(血中カリウム減少)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Cardiac murmur(心雑音)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Electrocardiogram QT prolonged(心電図ＱＴ延長)	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Eosinophil count increased(好酸球数増加)	1	0.25	1	0.25	1	0.26	0	0.00	0	0.00	0	0.00
False positive tuberculosis test(結核菌検査偽陽性)	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Heart rate irregular(心拍数不整)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
International normalised ratio increased(国際標準比増加)	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Mycobacterium tuberculosis complex test positive(結核菌群検査陽性)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Neutrophil count increased(好中球数増加)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Pulmonary arterial pressure increased(肺動脈圧上昇)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Urinary casts present(尿円柱陽性)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Allergy test positive(アレルギー検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Antineutrophil cytoplasmic antibody increased(抗好中球細胞質抗体増加)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blast cell count increased(芽球細胞数増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood calcium increased(血中カルシウム増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Blood cholesterol increased(血中コレステロール増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Blood folate decreased(血中葉酸減少)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Blood phosphorus decreased(血中リン減少)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood sodium decreased(血中ナトリウム減少)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood sodium increased(血中ナトリウム増加)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Body temperature increased(体温上昇)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bone density decreased(骨密度減少)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Carcinoembryonic antigen increased(癌胎児性抗原増加)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cardiac function test abnormal(心機能検査異常)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Clostridium test positive(クロストリジウム検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Creatinine renal clearance decreased(腎クレアチニン・クリアランス減少)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Electrocardiogram PR prolongation(心電図ＰＲ延長)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Electrocardiogram ST segment elevation(心電図ＳＴ部分上昇)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Electrocardiogram ST-T segment abnormal(心電図ＳＴ－Ｔ部分異常)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Faecal calprotectin increased(便中カルプロテクチン増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
False positive investigation result(検査結果偽陽性)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Forced vital capacity decreased(努力肺活量減少)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Glomerular filtration rate decreased(糸球体濾過率減少)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Glucose tolerance increased(耐糖能上昇)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Glucose urine present(尿中ブドウ糖陽性)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Haemoglobin decreased(ヘモグロビン減少)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Helicobacter test positive(ヘリコバクター検査陽性)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Influenza A virus test positive(A型インフルエンザウイルス検査陽性)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intraocular pressure increased(眼圧上昇)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Liver function test increased(肝機能検査値上昇)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Lymphocyte count increased(リンパ球数増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Mean cell volume increased(平均赤血球容積増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Prostatic specific antigen increased(前立腺特異性抗原増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Protein total increased(総蛋白増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary function test decreased(肺機能検査値低下)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Red blood cell sedimentation rate increased(血沈亢進)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Respiratory syncytial virus test positive(ＲＳウイルス検査陽性)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rheumatoid factor increased(リウマチ因子増加)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Serum ferritin decreased(血清フェリチン減少)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Staphylococcus test positive(ブドウ球菌検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tumour marker increased(腫瘍マーカー上昇)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Venous flow velocity increased(静脈血流速度上昇)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Weight increased(体重増加)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
White blood cell count increased(白血球数増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害)	87	22.14	6	1.53	94	23.98	6	1.53	98	25.00	7	1.79
Back pain(背部痛)	16	4.07	0	0.00	24	6.12	1	0.26	28	7.14	0	0.00
Arthralgia(関節痛)	25	6.36	3	0.76	23	5.87	2	0.51	15	3.83	0	0.00
Pain in extremity(四肢痛)	7	1.78	0	0.00	9	2.30	0	0.00	13	3.32	4	1.02
Myalgia(筋肉痛)	6	1.53	4	1.02	9	2.30	2	0.51	6	1.53	0	0.00
Muscle spasms(筋痙縮)	4	1.02	0	0.00	7	1.79	0	0.00	7	1.79	2	0.51
Neck pain(頚部痛)	9	2.29	0	0.00	2	0.51	0	0.00	4	1.02	0	0.00
Osteoarthritis(変形性関節症)	3	0.76	0	0.00	6	1.53	0	0.00	5	1.28	0	0.00
Tendonitis(腱炎)	5	1.27	0	0.00	3	0.77	0	0.00	4	1.02	0	0.00
Rotator cuff syndrome(肩回旋筋腱板症候群)	6	1.53	0	0.00	3	0.77	0	0.00	1	0.26	0	0.00
Arthritis(関節炎)	0	0.00	0	0.00	1	0.26	0	0.00	8	2.04	0	0.00
Joint swelling(関節腫脹)	2	0.51	0	0.00	6	1.53	2	0.51	0	0.00	0	0.00
Musculoskeletal chest pain(筋骨格系胸痛)	2	0.51	0	0.00	2	0.51	0	0.00	4	1.02	0	0.00
Intervertebral disc protrusion(椎間板突出)	2	0.51	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Rheumatoid arthritis(関節リウマチ)	2	0.51	1	0.25	1	0.26	0	0.00	3	0.77	0	0.00
Bursitis(滑液包炎)	1	0.25	0	0.00	3	0.77	0	0.00	1	0.26	0	0.00
Clubbing(ばち状指)	1	0.25	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Flank pain(側腹部痛)	1	0.25	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00
Muscular weakness(筋力低下)	0	0.00	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Lumbar spinal stenosis(腰部脊柱管狭窄症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Musculoskeletal pain(筋骨格痛)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Musculoskeletal stiffness(筋骨格硬直)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Osteopenia(骨減少症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Osteoporosis(骨粗鬆症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Periarthritis(関節周囲炎)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Polymyalgia rheumatica(リウマチ性多発筋痛)	1	0.25	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Spinal osteoarthritis(変形性脊椎症)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Bone pain(骨痛)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Coccydynia(尾骨痛)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Dupuytren's contracture(デュプイトラン拘縮)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Fibromyalgia(線維筋痛)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Gouty arthritis(痛風性関節炎)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Groin pain(鼠径部痛)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Muscle tightness(筋緊張)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Musculoskeletal discomfort(筋骨格不快感)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Trigger finger(弾発指)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Arthropathy(関節障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bone demineralisation(骨ミネラル喪失)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bone disorder(骨障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bone loss(骨喪失)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Chest wall mass(胸壁腫瘤)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Chondrocalcinosis(軟骨石灰化症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Chondromalacia(軟骨軟化症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Chondropathy(軟骨疾患)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Diastasis recti abdominis(腹直筋離開)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Exostosis(外骨腫)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Facet joint syndrome(椎間関節症候群)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Inguinal mass(鼠径部腫瘤)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intervertebral disc degeneration(椎間板変性症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intervertebral disc displacement(椎間板変位)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Joint effusion(関節滲出液)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Joint instability(関節不安定)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Limb discomfort(四肢不快感)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Limb mass(四肢腫瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lordosis(脊柱前弯症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Muscle atrophy(筋萎縮)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Osteonecrosis(骨壊死)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rhabdomyolysis(横紋筋融解症)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Sacral pain(仙骨痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Sacroiliac joint dysfunction(仙腸関節機能障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Sarcopenia(サルコペニア)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spinal pain(脊椎痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Systemic scleroderma(全身性強皮症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Temporomandibular pain and dysfunction syndrome(顎関節症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Torticollis(斜頸)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vertebral osteophyte(脊椎骨棘)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Nervous system disorders(神経系障害)	85	21.63	12	3.05	82	20.92	19	4.85	83	21.17	17	4.34
Headache(頭痛)	23	5.85	7	1.78	25	6.38	12	3.06	28	7.14	9	2.30
Dizziness(浮動性めまい)	22	5.60	5	1.27	27	6.89	3	0.77	19	4.85	4	1.02
Sciatica(坐骨神経痛)	4	1.02	0	0.00	7	1.79	0	0.00	3	0.77	0	0.00
Syncope(失神)	6	1.53	0	0.00	2	0.51	0	0.00	6	1.53	0	0.00
Paraesthesia(錯感覚)	2	0.51	0	0.00	6	1.53	1	0.26	4	1.02	0	0.00
Tremor(振戦)	3	0.76	0	0.00	3	0.77	0	0.00	4	1.02	0	0.00
Dysgeusia(味覚不全)	2	0.51	0	0.00	1	0.26	0	0.00	4	1.02	2	0.51
Hypoaesthesia(感覚鈍麻)	0	0.00	0	0.00	2	0.51	0	0.00	5	1.28	1	0.26
Loss of consciousness(意識消失)	2	0.51	0	0.00	0	0.00	0	0.00	4	1.02	0	0.00
Neuropathy peripheral(末梢性ニューロパチー)	3	0.76	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Transient ischaemic attack(一過性脳虚血発作)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	1	0.26
Carpal tunnel syndrome(手根管症候群)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Cerebrovascular accident(脳卒中)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Memory impairment(記憶障害)	4	1.02	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Presyncope(失神寸前の状態)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Balance disorder(平衡障害)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Post herpetic neuralgia(ヘルペス後神経痛)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Somnolence(傾眠)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cerebral infarction(脳梗塞)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cognitive disorder(認知障害)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Epilepsy(てんかん)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Lethargy(嗜眠)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Neuralgia(神経痛)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Peripheral sensory neuropathy(末梢性感覚ニューロパチー)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Ageusia(味覚消失)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Amnesia(健忘)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aphasia(失語症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aura(前兆)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Brain fog(ブレインフォグ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Carotid arteriosclerosis(頚動脈硬化症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Carotid artery dissection(頚動脈解離)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Carotid artery stenosis(頚動脈狭窄)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Central nervous system haemorrhage(中枢神経系出血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cerebral atrophy(大脳萎縮)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cerebral haemorrhage(脳出血)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cerebral small vessel ischaemic disease(虚血性脳小血管疾患)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cerebrovascular disorder(脳血管障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cerebrovascular insufficiency(脳血管不全)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cervical radiculopathy(頚髄神経根障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Cervicobrachial syndrome(頚腕症候群)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dementia Alzheimer's type(アルツハイマー型認知症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dementia(認知症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Diabetic neuropathy(糖尿病性ニューロパチー)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dizziness exertional(労作性めまい)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Encephalopathy(脳症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor(本態性振戦)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Facial paralysis(顔面麻痺)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Focal dyscognitive seizures(認知障害発作)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Haemorrhagic stroke(出血性卒中)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hyperaesthesia(知覚過敏)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Hypersomnia(過眠症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypogeusia(味覚減退)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyposmia(嗅覚減退)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Increased need for sleep(睡眠欲求の増加)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Intercostal neuralgia(肋間神経痛)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ischaemic stroke(虚血性脳卒中)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lacunar infarction(ラクナ梗塞)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lumbar radiculopathy(腰髄神経根障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Mental impairment(精神的機能障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Metabolic encephalopathy(代謝性脳症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Middle cerebral artery stroke(中大脳動脈性卒中)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Migraine(片頭痛)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Monoplegia(単麻痺)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Muscle tension dysphonia(筋緊張性発声障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Nervous system disorder(神経系障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Occipital neuralgia(後頭神経痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Parkinson's disease(パーキンソン病)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Parosmia(嗅覚錯誤)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Partial seizures(部分発作)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Polyneuropathy(多発ニューロパチー)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Psychomotor hyperactivity(精神運動亢進)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Restless legs syndrome(下肢静止不能症候群)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Senile dementia(老年認知症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sensory disturbance(感覚障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Spinal claudication(脊髄性跛行症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Subdural hygroma(硬膜下ヒグローマ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Taste disorder(味覚障害)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Tension headache(緊張性頭痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Trigeminal neuralgia(三叉神経痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Vascular cognitive impairment(血管性認知障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vertebrobasilar insufficiency(椎骨脳底動脈不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Psychiatric disorders(精神障害)	75	19.08	15	3.82	69	17.60	19	4.85	77	19.64	17	4.34
Depression(うつ病)	36	9.16	6	1.53	36	9.18	6	1.53	36	9.18	4	1.02
Anxiety(不安)	32	8.14	7	1.78	31	7.91	6	1.53	33	8.42	6	1.53
Insomnia(不眠症)	17	4.33	2	0.51	15	3.83	3	0.77	14	3.57	2	0.51
Sleep disorder(睡眠障害)	2	0.51	1	0.25	2	0.51	0	0.00	4	1.02	0	0.00
Suicidal ideation(自殺念慮)	2	0.51	0	0.00	3	0.77	3	0.77	3	0.77	2	0.51
Depressed mood(抑うつ気分)	2	0.51	1	0.25	0	0.00	0	0.00	5	1.28	1	0.26
Irritability(易刺激性)	0	0.00	0	0.00	1	0.26	0	0.00	3	0.77	2	0.51
Panic attack(パニック発作)	1	0.25	0	0.00	3	0.77	1	0.26	0	0.00	0	0.00
Adjustment disorder with depressed mood(抑うつ気分を伴う適応障害)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Depressive symptom(抑うつ症状)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Initial insomnia(初期不眠症)	0	0.00	0	0.00	2	0.51	2	0.51	0	0.00	0	0.00
Agitation(激越)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Alcohol abuse(アルコール乱用)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Alcohol withdrawal syndrome(アルコール離脱症候群)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bruxism(歯ぎしり)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Euphoric mood(多幸気分)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Flat affect(感情の平板化)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Generalised anxiety disorder(全般性不安障害)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Grief reaction(悲嘆反応)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hallucination(幻覚)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Hallucinations, mixed(混合性幻覚)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Libido decreased(リビドー減退)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Major depression(大うつ病)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Mixed anxiety and depressive disorder(混合性不安抑うつ障害)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Nervousness(神経過敏)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Nightmare(悪夢)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Psychiatric symptom(精神症状)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Restlessness(落ち着きのなさ)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Tobacco abuse(タバコ乱用)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Metabolism and nutrition disorders(代謝および栄養障害)	66	16.79	12	3.05	69	17.60	26	6.63	64	16.33	21	5.36
Decreased appetite(食欲減退)	27	6.87	10	2.54	38	9.69	22	5.61	40	10.20	19	4.85
Hypokalaemia(低カリウム血症)	5	1.27	0	0.00	5	1.28	0	0.00	6	1.53	0	0.00
Hyponatraemia(低ナトリウム血症)	2	0.51	1	0.25	6	1.53	0	0.00	4	1.02	0	0.00
Gout(痛風)	2	0.51	0	0.00	2	0.51	0	0.00	5	1.28	0	0.00
Hyperglycaemia(高血糖)	6	1.53	0	0.00	2	0.51	1	0.26	1	0.26	0	0.00
Hyperkalaemia(高カリウム血症)	5	1.27	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Dehydration(脱水)	1	0.25	0	0.00	2	0.51	0	0.00	3	0.77	1	0.26

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hypercholesterolaemia(高コレステロール血症)	4	1.02	0	0.00	1	0.26	1	0.26	1	0.26	0	0.00
Hyperlipidaemia(高脂血症)	1	0.25	0	0.00	4	1.02	0	0.00	1	0.26	0	0.00
Iron deficiency(鉄欠乏)	3	0.76	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Vitamin D deficiency(ビタミンＤ欠乏)	3	0.76	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Hyperuricaemia(高尿酸血症)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Dyslipidaemia(脂質異常症)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Electrolyte imbalance(電解質失調)	1	0.25	0	0.00	2	0.51	1	0.26	0	0.00	0	0.00
Hypervolaemia(血液量増加症)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Hypophosphataemia(低リン血症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Malnutrition(栄養障害)	1	0.25	1	0.25	1	0.26	0	0.00	1	0.26	1	0.26
Type 2 diabetes mellitus(２型糖尿病)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Abnormal loss of weight(異常体重減少)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Diabetes mellitus inadequate control(コントロール不良の糖尿病)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypoalbuminaemia(低アルブミン血症)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypocalcaemia(低カルシウム血症)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypoproteinaemia(低蛋白血症)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Impaired fasting glucose(空腹時血中ブドウ糖不良)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Steroid diabetes(ステロイド糖尿病)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Vitamin B12 deficiency(ビタミンＢ１２欠乏)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Adult failure to thrive(成人ＦＴＴ)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Alcohol intolerance(アルコール不耐性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Cachexia(悪液質)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Diabetes mellitus(糖尿病)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Fluid retention(体液貯留)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Folate deficiency(葉酸欠乏)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypercalcaemia(高カルシウム血症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperferritinaemia(高フェリチン血症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypertriglyceridaemia(高トリグリセリド血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypoglycaemia(低血糖)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypomagnesaemia(低マグネシウム血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Protein deficiency(蛋白欠乏症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Vitamin B complex deficiency(ビタミンＢ群欠乏)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Zinc deficiency(亜鉛欠乏)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin and subcutaneous tissue disorders(皮膚および皮下組織障害)	52	13.23	13	3.31	68	17.35	14	3.57	67	17.09	14	3.57
Rash(発疹)	12	3.05	3	0.76	16	4.08	4	1.02	9	2.30	1	0.26
Pruritus(そう痒症)	3	0.76	2	0.51	11	2.81	3	0.77	11	2.81	2	0.51
Dry skin(皮膚乾燥)	4	1.02	2	0.51	5	1.28	1	0.26	2	0.51	0	0.00
Photosensitivity reaction(光線過敏性反応)	2	0.51	0	0.00	7	1.79	1	0.26	2	0.51	0	0.00
Erythema(紅斑)	6	1.53	0	0.00	2	0.51	1	0.26	2	0.51	1	0.26
Dermatitis(皮膚炎)	3	0.76	1	0.25	4	1.02	1	0.26	2	0.51	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Eczema(湿疹)	4	1.02	1	0.25	3	0.77	0	0.00	2	0.51	1	0.26
Skin lesion(皮膚病変)	3	0.76	0	0.00	1	0.26	0	0.00	5	1.28	0	0.00
Actinic keratosis(光線角化症)	2	0.51	0	0.00	3	0.77	0	0.00	3	0.77	0	0.00
Rosacea(酒さ)	1	0.25	0	0.00	5	1.28	1	0.26	2	0.51	0	0.00
Urticaria(蕁麻疹)	0	0.00	0	0.00	2	0.51	1	0.26	5	1.28	3	0.77
Decubitus ulcer(褥瘡性潰瘍)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Night sweats(寝汗)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Dermatitis contact(接触皮膚炎)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Ecchymosis(斑状出血)	0	0.00	0	0.00	3	0.77	1	0.26	1	0.26	0	0.00
Rash macular(斑状皮疹)	2	0.51	1	0.25	1	0.26	0	0.00	1	0.26	0	0.00
Rash papular(丘疹性皮疹)	2	0.51	1	0.25	0	0.00	0	0.00	2	0.51	1	0.26
Alopecia(脱毛症)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	2	0.51
Dermatitis allergic(アレルギー性皮膚炎)	0	0.00	0	0.00	2	0.51	1	0.26	1	0.26	0	0.00
Rash maculo-papular(斑状丘疹状皮疹)	1	0.25	0	0.00	1	0.26	1	0.26	1	0.26	0	0.00
Rash pruritic(そう痒性皮疹)	1	0.25	1	0.25	0	0.00	0	0.00	2	0.51	1	0.26
Telangiectasia(毛細血管拡張症)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Acne(ざ瘡)	0	0.00	0	0.00	1	0.26	1	0.26	1	0.26	0	0.00
Dermal cyst(皮膚嚢腫)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Drug eruption(薬疹)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Miliaria(汗疹)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Skin discolouration(皮膚変色)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Skin ulcer(皮膚潰瘍)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Subcutaneous emphysema(皮下気腫)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Asteatosis(皮脂欠乏症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Blister(水疱)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dermatitis acneiform(ざ瘡様皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dermatitis atopic(アトピー性皮膚炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Erythema nodosum(結節性紅斑)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Hyperkeratosis(過角化)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Ingrown hair(内方発育毛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lichen planus(扁平苔癬)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lichen sclerosus(硬化性苔癬)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lichenoid keratosis(苔癬様角化症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nail discolouration(爪変色)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Onychoclasis(爪破損)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Onychomadesis(爪甲脱落症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Papule(丘疹)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Perioral dermatitis(口囲皮膚炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Petechiae(点状出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Post inflammatory pigmentation change(炎症後色素沈着変化)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Psoriasis(乾癬)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Seborrhoeic dermatitis(脂漏性皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Skin disorder(皮膚障害)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Skin exfoliation(皮膚剥脱)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin fissures(皮膚亀裂)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Skin fragility(皮膚脆弱性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin haemorrhage(皮膚出血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Skin odour abnormal(皮膚臭異常)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Solar dermatitis(日光皮膚炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Transient acantholytic dermatosis(一過性棘融解性皮膚症)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Urticaria papular(丘疹状蕁麻疹)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Injury, poisoning and procedural complications(傷害、中毒および処置合併症)	52	13.23	2	0.51	47	11.99	0	0.00	56	14.29	1	0.26
Fall(転倒)	8	2.04	0	0.00	9	2.30	0	0.00	7	1.79	0	0.00
Contusion(挫傷)	4	1.02	0	0.00	3	0.77	0	0.00	6	1.53	0	0.00
Limb injury(四肢損傷)	2	0.51	0	0.00	3	0.77	0	0.00	4	1.02	0	0.00
Skin laceration(皮膚裂傷)	5	1.27	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Ligament sprain(靱帯捻挫)	5	1.27	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Rib fracture(肋骨骨折)	1	0.25	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Muscle strain(肉離れ)	3	0.76	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Thermal burn(熱傷)	3	0.76	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00
Tooth fracture(歯牙破折)	1	0.25	0	0.00	3	0.77	0	0.00	2	0.51	0	0.00
Joint injury(関節損傷)	1	0.25	0	0.00	1	0.26	0	0.00	3	0.77	0	0.00
Muscle rupture(筋断裂)	1	0.25	0	0.00	3	0.77	0	0.00	1	0.26	0	0.00
Procedural pain(処置による疼痛)	0	0.00	0	0.00	3	0.77	0	0.00	1	0.26	0	0.00
Road traffic accident(交通事故)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Spinal compression fracture(脊椎圧迫骨折)	1	0.25	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Accidental overdose(偶発的過量投与)	2	0.51	1	0.25	0	0.00	0	0.00	1	0.26	0	0.00
Animal bite(動物咬傷)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Face injury(顔面損傷)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Foot fracture(足骨折)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Humerus fracture(上腕骨骨折)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Medication error(投薬過誤)	1	0.25	1	0.25	0	0.00	0	0.00	2	0.51	1	0.26
Skin abrasion(皮膚擦過傷)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Accident(事故)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bone contusion(骨挫傷)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Chest injury(胸部損傷)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Head injury(頭部損傷)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Hip fracture(股関節部骨折)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Immunisation reaction(免疫反応)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Lumbar vertebral fracture(腰椎骨折)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Muscle contusion(筋挫傷)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Muscle injury(筋損傷)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Pelvic fracture(骨盤骨折)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Stress fracture(ストレス骨折)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Sunburn(サンバーン)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Tendon rupture(腱断裂)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ankle fracture(足関節部骨折)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arthropod bite(節足動物咬傷)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arthropod sting(節足動物刺傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Burns second degree(第２度熱傷)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cervical vertebral fracture(頚椎骨折)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Clavicle fracture(鎖骨骨折)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Compression fracture(圧迫骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Concussion(脳振盪)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Coronary artery restenosis(冠動脈再狭窄)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dental restoration failure(歯科修復不成功)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Epicondylitis(上顆炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Femur fracture(大腿骨骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Fibula fracture(腓骨骨折)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Foreign body in eye(眼内異物)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Fractured sacrum(仙骨骨折)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Heat illness(熱中症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Heat oedema(熱性浮腫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypobarism(低圧症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Joint dislocation(関節脱臼)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lip injury(口唇損傷)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lower limb fracture(下肢骨折)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Meniscus injury(半月板損傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Overdose(過量投与)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Periorbital haematoma(眼窩周囲血腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Post procedural haematuria(処置後血尿)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Post procedural haemorrhage(処置後出血)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Post procedural inflammation(処置後炎症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Radius fracture(橈骨骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Reactive gastropathy(反応性胃障害)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Repetitive strain injury(反復性挫傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin injury(皮膚損傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Soft tissue injury(軟部組織損傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Superficial injury of eye(眼の擦過傷)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Surgical procedure repeated(反復手術手技)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Underdose(過少量投与)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Upper limb fracture(上肢骨折)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Vascular pseudoaneurysm(血管偽動脈瘤)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Venomous bite(有毒性咬傷)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Wound complication(創合併症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Wound(創傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Wrist fracture(手首関節骨折)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cardiac disorders(心臓障害)	50	12.72	4	1.02	33	8.42	5	1.28	48	12.24	4	1.02
Atrial fibrillation(心房細動)	5	1.27	0	0.00	7	1.79	1	0.26	10	2.55	0	0.00
Coronary artery disease(冠動脈疾患)	5	1.27	0	0.00	2	0.51	0	0.00	5	1.28	0	0.00
Cardiac failure(心不全)	3	0.76	0	0.00	1	0.26	1	0.26	5	1.28	0	0.00
Ventricular extrasystoles(心室性期外収縮)	5	1.27	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Acute myocardial infarction(急性心筋梗塞)	2	0.51	0	0.00	3	0.77	0	0.00	2	0.51	0	0.00
Palpitations(動悸)	2	0.51	1	0.25	3	0.77	1	0.26	2	0.51	1	0.26
Bradycardia(徐脈)	1	0.25	0	0.00	1	0.26	0	0.00	4	1.02	0	0.00
Myocardial ischaemia(心筋虚血)	1	0.25	1	0.25	2	0.51	0	0.00	3	0.77	1	0.26
Arrhythmia(不整脈)	2	0.51	1	0.25	1	0.26	1	0.26	2	0.51	0	0.00
Arteriosclerosis coronary artery(冠動脈硬化症)	1	0.25	0	0.00	1	0.26	0	0.00	3	0.77	0	0.00
Sinus tachycardia(洞性頻脈)	0	0.00	0	0.00	0	0.00	0	0.00	5	1.28	1	0.26
Supraventricular extrasystoles(上室性期外収縮)	0	0.00	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Angina pectoris(狭心症)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Atrial flutter(心房粗動)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Right ventricular failure(右室不全)	3	0.76	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Supraventricular tachycardia(上室性頻脈)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Tachycardia(頻脈)	1	0.25	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Bundle branch block right(右脚ブロック)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cardiac arrest(心停止)	2	0.51	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Cardiac failure chronic(慢性心不全)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Coronary artery stenosis(冠動脈狭窄)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ischaemic cardiomyopathy(虚血性心筋症)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Acute coronary syndrome(急性冠動脈症候群)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Angina unstable(不安定狭心症)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aortic valve incompetence(大動脈弁閉鎖不全症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Aortic valve stenosis(大動脈弁狭窄)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiogenic shock(心原性ショック)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Diastolic dysfunction(拡張機能障害)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Extrasystoles(期外収縮)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Heart failure with preserved ejection fraction(駆出率の保たれた心不全)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Left atrial enlargement(左房拡大)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Left ventricular failure(左室不全)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Myocardial infarction(心筋梗塞)	1	0.25	1	0.25	1	0.26	0	0.00	0	0.00	0	0.00
Tricuspid valve incompetence(三尖弁閉鎖不全症)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Acute right ventricular failure(急性右室不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Aortic valve sclerosis(大動脈弁硬化症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Atrial tachycardia(心房頻脈)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Atrioventricular block first degree(第一度房室ブロック)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atrioventricular block second degree(第二度房室ブロック)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Atrioventricular block(房室ブロック)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiac failure acute(急性心不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiac valve disease(心臓弁膜疾患)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiomegaly(心拡大)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiomyopathy(心筋症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cor pulmonale chronic(慢性肺性心)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cor pulmonale(肺性心)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Coronary artery dissection(冠動脈解離)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Coronary artery occlusion(冠動脈閉塞)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Heart failure with reduced ejection fraction(駆出率低下を伴う心不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Left ventricular dysfunction(左室機能不全)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pericardial effusion(心嚢液貯留)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pericarditis(心膜炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Right ventricular dilatation(右室拡張)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sinus bradycardia(洞性徐脈)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Ventricular fibrillation(心室細動)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Ventricular hypertrophy(心室肥大)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Ventricular hypokinesia(心室壁運動低下)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vascular disorders(血管障害)	34	8.65	3	0.76	32	8.16	5	1.28	35	8.93	7	1.79
Hypertension(高血圧)	10	2.54	2	0.51	11	2.81	1	0.26	14	3.57	1	0.26
Hypotension(低血圧)	5	1.27	1	0.25	4	1.02	2	0.51	4	1.02	0	0.00
Vasculitis(血管炎)	1	0.25	0	0.00	2	0.51	0	0.00	4	1.02	3	0.77
Aortic stenosis(大動脈狭窄)	0	0.00	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Haematoma(血腫)	2	0.51	0	0.00	1	0.26	1	0.26	2	0.51	0	0.00
Aortic aneurysm(大動脈瘤)	1	0.25	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00
Aortic arteriosclerosis(大動脈硬化症)	3	0.76	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Deep vein thrombosis(深部静脈血栓症)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Orthostatic hypotension(起立性低血圧)	1	0.25	0	0.00	3	0.77	0	0.00	0	0.00	0	0.00
Flushing(潮紅)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	1	0.26
Arteriosclerosis(動脈硬化症)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lymphoedema(リンパ浮腫)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Aortic dilatation(大動脈拡張)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aortic dissection(大動脈解離)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Arterial disorder(動脈障害)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arterial spasm(動脈攣縮)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Capillary fragility(毛細血管脆弱)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Circulatory collapse(循環虚脱)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Cyanosis(チアノーゼ)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Essential hypertension(本態性高血圧症)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Granulomatosis with polyangiitis(多発血管炎性肉芽腫症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Haemorrhage(出血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypertensive urgency(高血圧切迫症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypovolaemic shock(血液量減少性ショック)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Iliac artery stenosis(腸骨動脈狭窄)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intermittent claudication(間欠性跛行)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Microscopic polyangiitis(顕微鏡的多発血管炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Peripheral artery occlusion(末梢動脈閉塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Phlebitis(静脈炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Phlebolith(静脈結石)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Raynaud's phenomenon(レイノー現象)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Varicose vein(静脈瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Venous thrombosis(静脈血栓症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Renal and urinary disorders(腎および尿路障害)	24	6.11	3	0.76	24	6.12	1	0.26	37	9.44	4	1.02
Haematuria(血尿)	3	0.76	0	0.00	5	1.28	0	0.00	6	1.53	1	0.26
Acute kidney injury(急性腎障害)	3	0.76	1	0.25	4	1.02	0	0.00	3	0.77	0	0.00
Proteinuria(蛋白尿)	3	0.76	0	0.00	2	0.51	1	0.26	5	1.28	1	0.26
Nephrolithiasis(腎結石症)	2	0.51	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Pollakiuria(頻尿)	2	0.51	0	0.00	1	0.26	0	0.00	3	0.77	0	0.00
Leukocyturia(白血球尿)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Renal colic(腎仙痛)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Renal cyst(腎嚢胞)	1	0.25	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Urinary retention(尿閉)	1	0.25	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Chronic kidney disease(慢性腎臓病)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Dysuria(排尿困難)	1	0.25	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Glycosuria(糖尿)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Renal failure(腎不全)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Renal impairment(腎機能障害)	2	0.51	1	0.25	0	0.00	0	0.00	1	0.26	0	0.00
Ureterolithiasis(尿管結石症)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Urinary incontinence(尿失禁)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Albuminuria(アルブミン尿)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bladder dysfunction(膀胱機能障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Calculus urinary(尿路結石)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Chromaturia(着色尿)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Detrusor sphincter dyssynergia(排尿筋の括約筋失調)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypercalciuria(高カルシウム尿症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypertonic bladder(緊張性膀胱)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lower urinary tract symptoms(下部尿路症状)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Nephritis(腎炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Nephropathy toxic(中毒性腎症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Polyuria(多尿)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Renal disorder(腎障害)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urethral haemorrhage(尿道出血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Urethral stenosis(尿道狭窄)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	31	7.89	1	0.25	27	6.89	0	0.00	20	5.10	1	0.26
Lung neoplasm malignant(肺の悪性新生物)	3	0.76	0	0.00	4	1.02	0	0.00	3	0.77	0	0.00
Squamous cell carcinoma of skin(皮膚有棘細胞癌)	4	1.02	0	0.00	4	1.02	0	0.00	1	0.26	0	0.00
Basal cell carcinoma(基底細胞癌)	1	0.25	0	0.00	4	1.02	0	0.00	3	0.77	1	0.26
Prostate cancer(前立腺癌)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Bowen's disease(ボーエン病)	2	0.51	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Seborrhoeic keratosis(脂漏性角化症)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Squamous cell carcinoma(扁平上皮癌)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lipoma(脂肪腫)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Lung adenocarcinoma(肺腺癌)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Metastases to liver(肝転移)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin papilloma(皮膚乳頭腫)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Squamous cell carcinoma of lung(肺扁平上皮癌)	1	0.25	1	0.25	0	0.00	0	0.00	1	0.26	0	0.00
Transitional cell carcinoma(移行上皮癌)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Acute leukaemia(急性白血病)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atypical fibroxanthoma(異型線維黄色腫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Benign breast neoplasm(乳房の良性新生物)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bladder cancer stage 0, with cancer in situ(膀胱癌第０期、上皮内癌を伴う)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Bladder papilloma(膀胱乳頭腫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Cholangiocarcinoma(胆管細胞癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chronic myeloid leukaemia(慢性骨髄性白血病)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Clear cell renal cell carcinoma(腎明細胞癌)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Colon cancer(結腸癌)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Colorectal adenoma(結腸直腸腺腫)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ductal adenocarcinoma of pancreas(膵腺管癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extranodal marginal zone B-cell lymphoma (MALT type)(節外性辺縁帯Ｂ細胞リンパ腫（ＭＡＬＴ型）)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Eyelid seborrhoeic keratosis(眼瞼脂漏性角化症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Gastrointestinal tract adenoma(胃腸管腺腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hepatocellular carcinoma(肝細胞癌)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hodgkin's disease(ホジキン病)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hypergammaglobulinaemia benign monoclonal(良性単クローン性高γグロブリン血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Laryngeal neoplasm(喉頭新生物)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Lip squamous cell carcinoma(口唇扁平上皮癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lung cancer metastatic(遠隔転移を伴う肺癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lung neoplasm(肺新生物)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Metastases to bone(骨転移)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Metastases to lung(肺転移)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neuroendocrine carcinoma of the skin(皮膚神経内分泌癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oesophageal papilloma(食道乳頭腫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Rectal adenocarcinoma(直腸腺癌)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Rectal cancer(直腸癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rectal neoplasm(直腸新生物)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sarcomatoid carcinoma(肉腫様癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin cancer(皮膚癌)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sweat gland tumour(汗腺腫瘍)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Eye disorders(眼障害)	27	6.87	0	0.00	14	3.57	0	0.00	23	5.87	2	0.51
Cataract(白内障)	12	3.05	0	0.00	6	1.53	0	0.00	5	1.28	0	0.00
Dry eye(ドライアイ)	3	0.76	0	0.00	3	0.77	0	0.00	3	0.77	1	0.26
Conjunctival haemorrhage(結膜出血)	1	0.25	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Eye pruritus(眼そう痒症)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Vision blurred(霧視)	1	0.25	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Visual impairment(視力障害)	1	0.25	0	0.00	1	0.26	0	0.00	1	0.26	1	0.26
Chalazion(霰粒腫)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Eye inflammation(眼の炎症)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Macular oedema(黄斑浮腫)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Retinal haemorrhage(網膜出血)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Retinal tear(網膜裂孔)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Retinal vein occlusion(網膜静脈閉塞)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vitreous detachment(硝子体剥離)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Amaurosis(黒内障)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Asthenopia(眼精疲労)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blepharitis(眼瞼炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Contact lens acute red eye(コンタクトレンズによる急性眼充血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Diabetic retinopathy(糖尿病網膜症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Dry age-related macular degeneration(乾性加齢黄斑変性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Epiretinal membrane(網膜上膜)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Eye discharge(眼脂)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eye pain(眼痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Glaucoma(緑内障)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypotony of eye(低眼圧)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lacrimation increased(流涙増加)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ocular hypertension(高眼圧症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Posterior capsule opacification(後嚢部混濁)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Retinal infarction(網膜梗塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Retinopathy(網膜症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Visual field defect(視野欠損)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Vitreous floaters(硝子体浮遊物)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Reproductive system and breast disorders(生殖系および乳房障害)	15	3.82	1	0.25	13	3.32	1	0.26	24	6.12	0	0.00
Benign prostatic hyperplasia(良性前立腺肥大症)	7	1.78	0	0.00	3	0.77	0	0.00	9	2.30	0	0.00
Prostatitis(前立腺炎)	3	0.76	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Gynaecomastia(女性化乳房)	0	0.00	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Prostatomegaly(前立腺腫大)	2	0.51	1	0.25	0	0.00	0	0.00	3	0.77	0	0.00
Erectile dysfunction(勃起不全)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Atrophic vulvovaginitis(萎縮性外陰膣炎)	1	0.25	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Balanoposthitis(亀頭包皮炎)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Breast enlargement(乳房腫大)	0	0.00	0	0.00	1	0.26	1	0.26	0	0.00	0	0.00
Calculus prostatic(前立腺結石)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cystocele(膀胱瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Genital prolapse(性器脱)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Genital rash(性器発疹)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Nipple pain(乳頭痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ovarian cyst(卵巣嚢胞)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Perineal pain(会陰痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Sexual dysfunction(性機能不全)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Testicular cyst(精巣嚢胞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Testis discomfort(精巣不快感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Varicocele(精索静脈瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood and lymphatic system disorders(血液およびリンパ系障害)	20	5.09	5	1.27	14	3.57	1	0.26	12	3.06	0	0.00
Anaemia(貧血)	6	1.53	1	0.25	4	1.02	0	0.00	6	1.53	0	0.00
Thrombocytopenia(血小板減少症)	3	0.76	0	0.00	3	0.77	1	0.26	1	0.26	0	0.00
Iron deficiency anaemia(鉄欠乏性貧血)	2	0.51	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Eosinophilia(好酸球増加症)	2	0.51	1	0.25	1	0.26	0	0.00	0	0.00	0	0.00
Lymphopenia(リンパ球減少症)	2	0.51	2	0.51	0	0.00	0	0.00	1	0.26	0	0.00
Lymphadenopathy mediastinal(縦隔リンパ節腫脹)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lymphadenopathy(リンパ節症)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Neutropenia(好中球減少症)	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Abdominal lymphadenopathy(腹部リンパ節腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Anaemia macrocytic(大球性貧血)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Anaemia megaloblastic(巨赤芽球性貧血)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Autoimmune haemolytic anaemia(自己免疫性溶血性貧血)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Bicytopenia(二血球減少症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood loss anaemia(失血性貧血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bone marrow oedema(骨髄浮腫)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Clonal haematopoiesis(クローン性造血)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Leukocytosis(白血球増加症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Leukopenia(白血球減少症)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Lymph node pain(リンパ節痛)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Macrocytosis(大赤血球症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pancytopenia(汎血球減少症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Retroperitoneal lymphadenopathy(後腹膜リンパ節腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ear and labyrinth disorders(耳および迷路障害)	15	3.82	1	0.25	10	2.55	2	0.51	19	4.85	2	0.51
Vertigo(回転性めまい)	8	2.04	0	0.00	5	1.28	2	0.51	12	3.06	2	0.51
Cerumen impaction(耳垢栓塞)	2	0.51	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Ear pain(耳痛)	0	0.00	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Ear congestion(耳閉)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Presbyacusis(老人性難聴)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Tinnitus(耳鳴)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vertigo positional(頭位性回転性めまい)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.26	0	0.00
Ear discomfort(耳不快感)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ear inflammation(耳の炎症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ear pruritus(耳そう痒症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypoacusis(聴力低下)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Middle ear inflammation(中耳の炎症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Motion sickness(乗物酔い)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Otolithiasis(耳石症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Otorrhoea(耳漏)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatobiliary disorders(肝胆道系障害)	21	5.34	7	1.78	9	2.30	2	0.51	13	3.32	2	0.51
Hepatic function abnormal(肝機能異常)	5	1.27	1	0.25	0	0.00	0	0.00	2	0.51	1	0.26
Cholelithiasis(胆石症)	3	0.76	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Cholecystitis acute(急性胆嚢炎)	2	0.51	0	0.00	1	0.26	0	0.00	2	0.51	0	0.00
Cholecystitis(胆嚢炎)	0	0.00	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Hepatic steatosis(脂肪肝)	3	0.76	1	0.25	1	0.26	0	0.00	0	0.00	0	0.00
Suspected drug-induced liver injury(薬物性肝障害の疑い)	2	0.51	2	0.51	1	0.26	1	0.26	1	0.26	1	0.26
Bile duct stone(胆管結石)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Drug-induced liver injury(薬物性肝障害)	0	0.00	0	0.00	1	0.26	1	0.26	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hypertransaminasaemia(高トランスアミナーゼ血症)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Liver injury(肝損傷)	1	0.25	1	0.25	1	0.26	0	0.00	0	0.00	0	0.00
Autoimmune hepatitis(自己免疫性肝炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Biliary dilatation(胆管拡張)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Biliary obstruction(胆道閉塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cholangitis(胆管炎)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatic cirrhosis(肝硬変)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatic cyst(肝嚢胞)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hepatic failure(肝不全)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hepatitis toxic(中毒性肝炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hyperbilirubinaemia(高ビリルビン血症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperplastic cholecystopathy(過形成性胆嚢症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Liver disorder(肝障害)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Portal vein thrombosis(門脈血栓症)	1	0.25	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00
Immune system disorders(免疫系障害)	7	1.78	0	0.00	6	1.53	0	0.00	10	2.55	0	0.00
Seasonal allergy(季節性アレルギー)	4	1.02	0	0.00	2	0.51	0	0.00	6	1.53	0	0.00
Hypersensitivity(過敏症)	1	0.25	0	0.00	4	1.02	0	0.00	0	0.00	0	0.00
Allergy to arthropod sting(節足動物刺傷アレルギー)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Anaphylactic shock(アナフィラキシーショック)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Drug hypersensitivity(薬物過敏症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypogammaglobulinaemia(低γグロブリン血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Multiple allergies(複合アレルギー)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sunscreen sensitivity(日焼け止め過敏症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Endocrine disorders(内分泌障害)	3	0.76	0	0.00	0	0.00	0	0.00	5	1.28	1	0.26
Hyperthyroidism(甲状腺機能亢進症)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Thyroid mass(甲状腺腫瘤)	1	0.25	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Goitre(甲状腺腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Graves' disease(グレーブス病)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperparathyroidism primary(原発性副甲状腺機能亢進症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypogonadism(性腺機能低下)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Hypothyroidism(甲状腺機能低下症)	1	0.25	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Thyroid disorder(甲状腺障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Congenital, familial and genetic disorders(先天性、家族性および遺伝性障害)	0	0.00	0	0.00	3	0.77	0	0.00	2	0.51	0	0.00
Cystic fibrosis(嚢胞性線維症)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Dolichocolon(過長結腸)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Hypertrophic cardiomyopathy(肥大型心筋症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Retinopathy congenital(先天性網膜症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 99.2 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Thyroglossal cyst(甲状舌管嚢胞)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Social circumstances(社会環境)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	2	0.51
Inadequate diet(不適切な食事)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	2	0.51
Product issues(製品の問題)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Device leakage(医療機器リーク)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Surgical and medical procedures(外科および内科処置)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00
Tooth extraction(抜歯)	0	0.00	0	0.00	1	0.26	0	0.00	0	0.00	0	0.00

16.1.13.1.12.5.2 Listings of deaths - other serious adverse events - adverse events of special interest and other significant adverse events

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Blood and lymphatic system disorders(血液およびリンパ系障害) Anaemia(貧血)	Placebo	[redacted]	Nintedanib	8[redacted]/M	324	327	4	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Other respiratory causes
Blood and lymphatic system disorders(血液およびリンパ系障害) Autoimmune haemolytic anaemia(自己免疫性溶血性貧血)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	492			Grade 3	Yes	NoChg	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Acute coronary syndrome(急性冠動脈症候群)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	370			Grade 3	No	NoChg	Yes	Nrec	OTHER	non-fatal MACE	
Cardiac disorders(心臓障害) Acute myocardial infarction(急性心筋梗塞)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	368	412	45	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	111	114	4	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders(心臓障害) Angina unstable(不安定狭心症)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	64	98	35	Grade 3	No	NoChg	Yes	Rcver	OTHER	not MACE	
	Placebo	[redacted]	None	7[redacted]/M	174			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Aortic valve stenosis(大動脈弁狭窄)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	26	119	94	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Arteriosclerosis coronary artery(冠動脈硬化症)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	107	109	3	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Atrial fibrillation(心房細動)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	211	212	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Atrial flutter(心房粗動)	Placebo	[redacted]	Nintedanib	5[redacted]/M	125	125	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	272	274	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	247	249	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	482	484	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Bradycardia(徐脈)	Placebo	[redacted]	Nintedanib	7[redacted]/M	488	582	95	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Bundle branch block right(右脚ブロック)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	357	362	6	Grade 1	No	NoChg	No	Seq	REQ/PROL HSP		
Cardiac disorders(心臓障害) Cardiac arrest(心停止)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	346	346	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
	Placebo	[redacted]	Nintedanib	7[redacted]/M	284			Grade 4	No	NA	No	UNK	LIFE THR		
Cardiac disorders(心臓障害) Cardiac failure chronic(慢性心不全)	Placebo	[redacted]	Nintedanib	7[redacted]/M	391			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Cardiac failure(心不全)	Placebo	[redacted]	Nintedanib	5[redacted]/M	127	253	127	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/F	219			Grade 1	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Cardiac failure(心不全)	Residual effect	[redacted]	Nintedanib	6[redacted]/M	330			Grade 2	No	NA	Yes	Nrec	OTHER		
Cardiac disorders(心臓障害) Cardiogenic shock(心原性ショック)	Residual effect	[redacted]	None	7[redacted]/M	192			Grade 4	No	NA	No	Nrec	LIFE THR		
Cardiac disorders(心臓障害) Cor pulmonale chronic(慢性肺性心)	Residual effect	[redacted]	Nintedanib	6[redacted]/M	590			Grade 2	No	NoChg	No	Nrec	OTHER		
Cardiac disorders(心臓障害) Cor pulmonale(肺性心)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	311			Grade 2	No	NoChg	No	Nrec	OTHER		
Cardiac disorders(心臓障害) Coronary artery disease(冠動脈疾患)	Interruption (residual effect)	[redacted]	Nintedanib	5[redacted]/M	129			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	219	346	128	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Coronary artery dissection(冠動脈解離)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	228	346	119	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP/OTHER		
Cardiac disorders(心臓障害) Coronary artery stenosis(冠動脈狭窄)	Placebo	[redacted]	Nintedanib	6[redacted]/M	171	178	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Heart failure with preserved ejection fraction(駆出率の保たれた心不全)	Off-treatment	[redacted]	None	7[redacted]/F	483	492	10	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Left ventricular failure(左室不全)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	203	303	101	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Cardiac disorders(心臓障害) Myocardial infarction(心筋梗塞)	Placebo	[redacted]	None	6[redacted]/M	189	189	1	Grade 5	Yes	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Cardiac disorders(心臓障害) Pericarditis(心膜炎)	Residual effect	[redacted]	None	7[redacted]/M	192			Grade 4	No	NA	No	Nrec	LIFE THR/REQ/PROL HSP		
Cardiac disorders(心臓障害) Right ventricular failure(右室不全)	Placebo	[redacted]	Nintedanib	7[redacted]/M	309			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	None	7[redacted]/M	437			Grade 3	No	NoChg	No	Nrec	OTHER		
	Residual effect		Nintedanib	5[redacted]/M	122	126	5	Grade 4	No	NA	No	Rcver	LIFE THR/OTHER		
Ear and labyrinth disorders(耳および迷路障害) Vertigo(回転性めまい)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	259	260	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Eye disorders(眼障害) Cataract(白内障)	Placebo	[redacted]	None	8[redacted]/M	199	255	57	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders(眼障害) Hypotony of eye(低眼圧)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	163	167	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders(眼障害) Retinal vein occlusion(網膜静脈閉塞)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	114			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害) Abdominal pain(腹痛)	Interruption (residual effect)	[redacted]	None	6[redacted]/M	251	254	4	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	87	113	27	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Constipation(便秘)	Interruption (residual effect)	[redacted]	None	6[redacted]/M	251	254	4	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Diarrhoea(下痢)	Placebo	[redacted]	Nintedanib	7[redacted]/M	488	489	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Obstructive pancreatitis(閉塞性膵炎)	Placebo	[redacted]	Nintedanib	5[redacted]/F	47	57	11	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	Nintedanib	5[redacted]/F	57	253	197	Grade 2	No	NoChg	No	Rcver	OTHER		
Gastrointestinal disorders(胃腸障害) Oronasal fistula(口腔鼻腔瘻)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	332	332	1	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Gastrointestinal disorders(胃腸障害) Pancreatitis acute(急性膵炎)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	262	265	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Small intestinal obstruction(小腸閉塞)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	17	85	69	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害)	Placebo	[redacted]	Nintedanib	5[redacted]/M	344			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Varices oesophageal(食道静脈瘤)															
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	497	509	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Asthenia(無力症)															
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	370	371	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Chest pain(胸痛)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	214	219	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	17	92	76	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Condition aggravated(状態悪化)	Interruption (residual effect)	[redacted]	Pirfenidone	6[redacted]/M	237	251	15	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Pirfenidone	6[redacted]/M	509			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	6[redacted]/M	286	363	78	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Placebo	[redacted]	None	6[redacted]/M	165	173	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	498	545	48	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	None	5[redacted]/M	472	485	14	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	5[redacted]/M	78	212	135	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	319	326	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	190	200	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	218	240	23	Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/M	318	320	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	545	591	47	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	257	283	27	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	317	329	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	84	145	62	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	324			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	324	330	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Placebo	[redacted]	Nintedanib	5[redacted]/M	358	370	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	402	410	9	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	443	452	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	473			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	303	317	15	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	77	83	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	115	116	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	74	100	27	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Placebo		Nintedanib	7[redacted]/M	103	184	82	Grade 3	No	Withdr	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	261	299	39	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	99	162	64	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	521	533	13	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	None	7[redacted]/F	86	87	2	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Other respiratory causes
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	57	63	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Placebo	[redacted]	Pirfenidone	[redacted]/M	514	575	62	Grade 5	No	NoChg	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Pirfenidone	[redacted]/M	478	481	4	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Pneumonia
	Placebo	[redacted]	Nintedanib	[redacted]/F	527			Grade 4	Yes	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	[redacted]/M	201	248	48	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	None	[redacted]/F	565	593	29	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	[redacted]/M	364	377	14	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	[redacted]/M	152	223	72	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Pirfenidone	[redacted]/M	92	121	30	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	[redacted]/M	3	18	16	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Death(死亡)	Placebo	[redacted]	None	[redacted]/M	514	514	1	Grade 5		NA	No	Fatal	FATAL	Undetermined	Undetermined

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Disease progression(疾患進行)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	274	415	142	Grade 5	No	NoChg	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Nintedanib	7[redacted]/M	422	422	1	Grade 5	No	NoChg	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Pyrexia(発熱)	Placebo	[redacted]	Nintedanib	6[redacted]/M	417	427	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Sudden death(突然死)	Placebo	[redacted]	Nintedanib	7[redacted]/M	136	136	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Hepatobiliary disorders(肝胆道系障害) Bile duct stone(胆管結石)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	494	502	9	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Cholangitis(胆管炎)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	494	502	9	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	149	156	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Hepatobiliary disorders(肝胆道系障害)	Interruption (residual effect)	[redacted]	None	7[redacted]/M	216	254	39	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cholecystitis acute(急性胆嚢炎)	Interruption (residual effect)	[redacted]	None	7[redacted]/M	329	331	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	5[redacted]/F	374	380	7	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
Cholelithiasis(胆石症)															
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	5[redacted]/M	288			Grade 3	No	NoChg	No	Nrec	OTHER		
Hepatic cirrhosis(肝硬変)															
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	279			Grade 3	Yes	Withdr	Yes	UNK	REQ/PROL HSP		
Hepatic function abnormal(肝機能異常)															
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	7[redacted]/F	527			Grade 3	Yes	NA	Yes	Nrec	REQ/PROL HSP		
Liver injury(肝損傷)															
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	6[redacted]/M	156	340	185	Grade 2	Yes	NoChg	Yes	Rcver	OTHER		
Portal vein thrombosis(門脈血栓症)															
Hepatobiliary disorders(肝胆道系障害)	Placebo	[redacted]	Nintedanib	8[redacted]/M	127			Grade 2	Yes	Withdr	No	UNK	OTHER		
Suspected drug-induced liver injury(薬物性肝障害の疑い)															

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Hepatobiliary disorders(肝胆道系障害) Suspected drug-induced liver injury(薬物性肝障害の疑い)	Placebo	[redacted]	None	6[redacted]/M	358	416	59	Grade 3	Yes	NoChg	No	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) Atypical pneumonia(異型肺炎)	Placebo	[redacted]	None	7[redacted]/M	371	406	36	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Bronchitis(気管支炎)	Off-treatment	[redacted]	None	7[redacted]/F	481	492	12	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/F	234	254	21	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) COVID-19 pneumonia(ＣＯＶＩＤ－１９肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	371	381	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) COVID-19(ＣＯＶＩＤ－１９)	Interruption (residual effect)	[redacted]	Pirfenidone	6[redacted]/M	168	169	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	282	287	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Gastrointestinal bacterial infection(細菌性消化管感染)	Placebo	[redacted]	Nintedanib	6[redacted]/M	158	169	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Hepatitis E(E型肝炎)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	266	291	26	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) Influenza(インフルエンザ)	Placebo	[redacted]	None	5[redacted]/M	472	485	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	6[redacted]/M	97	100	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	229	233	5	Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	233	233	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Pneumonia
Infections and infestations(感染症および寄生虫症) Laryngitis(喉頭炎)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	166	189	24	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	482	504	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Lower respiratory tract infection(下気道感染)	Placebo	[redacted]	Nintedanib	7[redacted]/M	99	132	34	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Nasopharyngitis(上咽頭炎)	Placebo	[redacted]	None	6[redacted]/M	306	316	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Placebo	[redacted]	Nintedanib	8[redacted]/M	6	21	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Pneumonia mycoplasmal(マイコプラズマ性肺炎)	Placebo	[redacted]	Nintedanib	7[redacted]/M	329	337	9	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	391	402	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	407			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia viral(ウイルス性肺炎)	Placebo	[redacted]	Nintedanib	6[redacted]/M	9	15	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Interruption (residual effect)	[redacted]	None	7[redacted]/M	77	127	51	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	7[redacted]/M	476	483	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	20	26	7	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	282	291	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	289	307	19	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/M	388	393	6	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症)	Placebo	[redacted]	None	7[redacted]/M	136	155	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia(肺炎)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	332	337	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	5[redacted]/M	13	15	3	Grade 2	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/F	139	149	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	220	222	3	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/F	16	29	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/F	78			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	136	140	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	160	166	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	514			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	308	372	65	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	444	497	54	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	478			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/F	527	533	7	Grade 4	Yes	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	47	58	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	239			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	153			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	357	362	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	5[redacted]/M	15	15	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Pneumonia
	Residual effect	[redacted]	Nintedanib	7[redacted]/F	533	533	1	Grade 5	Yes	NA	No	Fatal	FATAL	Respiratory	Pneumonia
Infections and infestations(感染症および寄生虫症) Pyelonephritis acute(急性腎盂腎炎)	Residual effect	[redacted]	Pirfenidone	6[redacted]/M	431			Grade 4	No	NA	No	Nrec	LIFE THR/REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Respiratory tract infection(気道感染)	Placebo	[redacted]	None	7[redacted]/M	363	375	13	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	7[redacted]/M	472	483	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	75	89	15	Grade 2	No	NoChg	Yes	Seq	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Sepsis(敗血症)	Placebo	[redacted]	Nintedanib	7[redacted]/M	407			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Septic shock(敗血症性ショック)	Residual effect	[redacted]	Pirfenidone	6[redacted]/M	431	431	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Non-cardiovascular/non-respiratory	Infection (including sepsis)

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Tuberculosis(結核)	Placebo	[redacted]	None	[redacted]/F	491			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Infections and infestations(感染症および寄生虫症) Urinary tract infection(尿路感染)	Interruption (residual effect)	[redacted]	None	[redacted]/M	251	254	4	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	[redacted]/M	428			Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Urosepsis(尿路性敗血症)	Interruption (residual effect)	[redacted]	Nintedanib	[redacted]/M	450	459	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Cervical vertebral fracture(頚椎骨折)	Placebo	[redacted]	Pirfenidone	[redacted]/M	1			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Clavicle fracture(鎖骨骨折)	Placebo	[redacted]	Pirfenidone	[redacted]/M	19			Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Fall(転倒)	Placebo	[redacted]	None	[redacted]/M	187			Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ/PROL HSP		

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Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Fractured sacrum(仙骨骨折)	Placebo	[redacted]	Pirfenidone	8[redacted]/F	328	370	43	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Hip fracture(股関節部骨折)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	362	393	32	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Humerus fracture(上腕骨骨折)	Placebo	[redacted]	Nintedanib	5[redacted]/M	290	294	5	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Lower limb fracture(下肢骨折)	Placebo	[redacted]	None	6[redacted]/M	433	474	42	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Pelvic fracture(骨盤骨折)	Placebo	[redacted]	Pirfenidone	8[redacted]/F	328	370	43	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	19			Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Road traffic accident(交通事故)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	362	362	1	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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Investigations(臨床検査) False positive investigation result(検査結果偽陽性)	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	457			Grade 1	No	NA	No	Nrec	OTHER		
Investigations(臨床検査) Influenza A virus test positive(A型インフルエンザウイルス検査陽性)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	322	327	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Oxygen saturation decreased(酸素飽和度低下)	Placebo	[redacted]	Nintedanib	5[redacted]/M	445	446	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Troponin increased(トロポニン増加)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	240	244	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Metabolism and nutrition disorders(代謝および栄養障害) Dehydration(脱水)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	315	321	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	289	314	26	Grade 2	No	NA	No	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders(代謝および栄養障害) Diabetes mellitus inadequate control(コントロール不良の糖尿病)	Placebo	[redacted]	Nintedanib	6[redacted]/F	183	218	36	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders(代謝および栄養障害) Hyperglycaemia(高血糖)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	241			Grade 3	No	NA	Yes	UNK	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Metabolism and nutrition disorders(代謝および栄養障害) Hyperkalaemia(高カリウム血症)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	242	246	5	Grade 3	No	NA	Yes	Rcver	OTHER		
Metabolism and nutrition disorders(代謝および栄養障害) Hypokalaemia(低カリウム血症)	Placebo	[redacted]	Nintedanib	7[redacted]/M	407			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	243	306	64	Grade 4	No	NoChg	Yes	Rcver	LIFE THR		
Metabolism and nutrition disorders(代謝および栄養障害) Hyponatraemia(低ナトリウム血症)	Placebo	[redacted]	Nintedanib	7[redacted]/M	39	49	11	Grade 3	Yes	Withdr	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Chondropathy(軟骨疾患)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	174	176	3	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Intervertebral disc protrusion(椎間板突出)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	223	227	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Polymyalgia rheumatica(リウマチ性多発筋痛)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	326	337	12	Grade 2	No	NoChg	Yes	Rcver	OTHER	not Vasculitis	

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Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Rotator cuff syndrome(肩回旋筋腱板症候群)	Placebo	[redacted]	Nintedanib	6[redacted]/M	93	94	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Systemic scleroderma(全身性強皮症)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	128			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Basal cell carcinoma(基底細胞癌)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	119	119	1	Grade 1	No	NoChg	No	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Bowen's disease(ボーエン病)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	184	225	42	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	243	243	1	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Cholangiocarcinoma(胆管細胞癌)	Placebo	[redacted]	None	7[redacted]/M	589			Grade 2	No	NoChg	No	Nrec	OTHER		

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Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Chronic myeloid leukaemia(慢性骨髄性白血病)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	310			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Ductal adenocarcinoma of pancreas(膵腺管癌)	Residual effect	[redacted]	None	7[redacted]/M	303	387	85	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP/OTHER	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Hodgkin's disease(ホジキン病)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	180	209	30	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP/OTHER	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Lip squamous cell carcinoma(口唇扁平上皮癌)	Placebo	[redacted]	Nintedanib	7[redacted]/M	381	422	42	Grade 2	No	Withdr	Yes	Rcver	OTHER		

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Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Nintedanib	6[redacted]/M	309			Grade 2	No	Withdr	Yes	Nrec	OTHER		
Lung adenocarcinoma(肺腺癌)	Placebo	[redacted]	Nintedanib	5[redacted]/M	232	295	64	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Nintedanib	7[redacted]/M	389			Grade 2	No	Withdr	No	Nrec	OTHER		
Lung neoplasm malignant(肺の悪性新生物)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	383			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
	Residual effect	[redacted]	None	8[redacted]/F	582			Grade 3	No	NA	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	None	7[redacted]/M	136	171	36	Grade 5	No	NoChg	No	Fatal	FATAL	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Metastases to bone(骨転移)															

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Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Residual effect	[redacted]	None	7[redacted]/M	303			Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ/PROL HSP/OTHER		
Metastases to liver(肝転移)	Residual effect	[redacted]	None	8[redacted]/F	582			Grade 3	No	NA	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Residual effect	[redacted]	None	7[redacted]/M	303			Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ/PROL HSP/OTHER		
Metastases to lung(肺転移)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	121	150	30	Grade 3	No	Withdr	Yes	Rcver	OTHER		
Neuroendocrine carcinoma of the skin(皮膚神経内分泌癌)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Nintedanib	7[redacted]/M	78	355	278	Grade 2	No	Withdr	Yes	Seq	REQ/PROL HSP/OTHER		
Prostate cancer(前立腺癌)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	385			Grade 2	No	Withdr	No	Nrec	OTHER		

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Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	None	[redacted]/M	232	407	176	Grade 3	No	Withdr	Yes	Rcver	OTHER		
Rectal cancer(直腸癌)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Nintedanib	[redacted]/M	448			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Skin cancer(皮膚癌)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Pirfenidone	[redacted]/M	491			Grade 3	Yes	NA	Yes	Nrec	OTHER		
Squamous cell carcinoma of lung(肺扁平上皮癌)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Placebo	[redacted]	Nintedanib	[redacted]/M	15	15	1	Grade 3	No	Withdr	Yes	Rcver	OTHER		
Squamous cell carcinoma of skin(皮膚有棘細胞癌)															
	Placebo	[redacted]	Nintedanib	[redacted]/M	254	301	48	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Placebo		None	[redacted]/M	81	90	10	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Placebo		Nintedanib	[redacted]/M	103	197	95	Grade 1	No	Withdr	Yes	Rcver	OTHER		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Squamous cell carcinoma(扁平上皮癌)	Placebo	[redacted]	None	8[redacted]/F	392			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	495	495	1	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Transitional cell carcinoma(移行上皮癌)	Placebo	[redacted]	None	7[redacted]/M	233	263	31	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	8[redacted]/M	23	23	1	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP/OTHER		
Nervous system disorders(神経系障害) Cerebral haemorrhage(脳出血)	Residual effect	[redacted]	Nintedanib	5[redacted]/M	151	159	9	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Nervous system disorders(神経系障害) Cerebral infarction(脳梗塞)	Placebo	[redacted]	Nintedanib	8[redacted]/M	21	28	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Nervous system disorders(神経系障害) Cerebrovascular accident(脳卒中)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	133	134	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
	Residual effect	[redacted]	Nintedanib	6[redacted]/M	252	260	9	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Dementia(認知症)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	415			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Nervous system disorders(神経系障害) Dizziness(浮動性めまい)	Residual effect	[redacted]	Nintedanib	8[redacted]/M	608			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Nervous system disorders(神経系障害) Encephalopathy(脳症)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	359	426	68	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Undetermined	Undetermined
Nervous system disorders(神経系障害) Loss of consciousness(意識消失)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	189	192	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Nervous system disorders(神経系障害) Partial seizures(部分発作)	Placebo	[redacted]	None	6[redacted]/M	150	151	2	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Nervous system disorders(神経系障害) Spinal claudication(脊髄性跛行症)	Placebo	[redacted]	Nintedanib	6[redacted]/M	62	68	7	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Nervous system disorders(神経系障害) Syncope(失神)	Placebo	[redacted]	None	6[redacted]/M	531	532	2	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP	not MACE	
	Placebo	[redacted]	Pirfenidone	8[redacted]/M	196	198	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	137	137	1	Grade 2	No	NoChg	No	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害)	Placebo	[redacted]	None	7[redacted]/M	430	443	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Transient ischaemic attack(一過性脳虚血発作)	Placebo	[redacted]	None	7[redacted]/M	113	113	1	Grade 2	No	NoChg	No	Rcver	OTHER	not MACE	
Nervous system disorders(神経系障害)	Placebo	[redacted]	None	8[redacted]/M	193			Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		
Tremor(振戦)															
Psychiatric disorders(精神障害)	Residual effect	[redacted]	Pirfenidone	6[redacted]/F	50			Grade 3	No	NoChg	No	Nrec	OTHER		
Depression(うつ病)															
Psychiatric disorders(精神障害)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	350	356	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hallucinations, mixed(混合性幻覚)															
Psychiatric disorders(精神障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	303	359	57	Grade 1	No	NoChg	No	Rcver	OTHER		
Suicidal ideation(自殺念慮)	Residual effect	[redacted]	Pirfenidone	6[redacted]/F	50			Grade 3	No	NoChg	No	Nrec	OTHER		
Renal and urinary disorders(腎および尿路障害)	Placebo	[redacted]	Nintedanib	7[redacted]/F	527			Grade 2	Yes	NA	Yes	Nrec	REQ/PROL HSP		
Acute kidney injury(急性腎障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	336	338	3	Grade 4	No	NoChg	No	Rcver	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	7[redacted]/M	241	246	6	Grade 3	No	NA	Yes	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Reproductive system and breast disorders(生殖系および乳房障害)	Interruption (residual effect)	[redacted]	None	6[redacted]/M	251	254	4	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Prostatomegaly(前立腺腫大)															
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	407			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Acute respiratory failure(急性呼吸不全)															
	Residual effect	[redacted]	None	8[redacted]/M	38	39	2	Grade 5	Yes	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	287	289	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Chronic obstructive pulmonary disease(慢性閉塞性肺疾患)															
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	5[redacted]/F	532	538	7	Grade 4	No	NA	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Chronic respiratory failure(慢性呼吸不全)															
	Residual effect	[redacted]	Pirfenidone	6[redacted]/M	552			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	7[redacted]/M	417	424	8	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Dyspnoea(呼吸困難)															
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	330	331	2	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Dyspnoea(呼吸困難)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	61	62	2	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	279	294	16	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	501	503	3	Grade 3	Yes	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	239	244	6	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	246	259	14	Grade 3	No	NA	No	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	49			Grade 4	Yes	Withdr	Yes	Nrec	LIFE THR/OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Emphysema(肺気腫)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	357	362	6	Grade 3	No	NA	No	Seq	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hepatopulmonary syndrome(肝肺症候群)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	230	518	289	Grade 3	Yes	Withdr	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypersensitivity pneumonitis(過敏性肺臓炎)	Interruption (residual effect)	[redacted]	None	7[redacted]/F	383	395	13	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Off-treatment	[redacted]	None	7[redacted]/F	395			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	None	8[redacted]/M	450			Grade 1	No	NoChg	No	Nrec	OTHER		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypoxia(低酸素症)	Placebo	[redacted]	Nintedanib	7[redacted]/M	550			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	6[redacted]/M	150	151	2	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Placebo	[redacted]	Nintedanib	6[redacted]/M	168			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	6[redacted]/M	343	516	174	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	490			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	29	145	117	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Placebo		Nintedanib	5[redacted]/M	289			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Placebo		None	5[redacted]/M	395			Grade 3	No	NoChg	No	Nrec	OTHER		
	Placebo		Pirfenidone	8[redacted]/M	139			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo		None	5[redacted]/M	455			Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo		Nintedanib	7[redacted]/M	386			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo		Pirfenidone	8[redacted]/M	90			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Residual effect		None	5[redacted]/M	534	535	2	Grade 1	No	NA	No	Nrec	OTHER		
	Residual effect	[redacted]	None	5[redacted]/M	535	543	9	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP/OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Interstitial lung disease(間質性肺疾患)	Placebo	[redacted]	Nintedanib	7[redacted]/M	405	420	16	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumomediastinum(気縦隔症)	Placebo	[redacted]	Nintedanib	5[redacted]/M	257	363	107	Grade 1	No	NoChg	No	Rcver	OTHER		
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	502	521	20	Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo		Pirfenidone	6[redacted]/M	521	533	13	Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP/OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax spontaneous(自然気胸)	Placebo	[redacted]	None	6[redacted]/M	356	369	14	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax(気胸)	Placebo	[redacted]	Nintedanib	7[redacted]/M	176			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary arterial hypertension(肺動脈性肺高血圧症)	Placebo	[redacted]	Nintedanib	6[redacted]/M	540[a]			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	354			Grade 2	No	NoChg	No	Nrec	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	177			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary artery dilatation(肺動脈拡張)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	240	241	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

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Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary embolism(肺塞栓症)	Interruption (residual effect)	[redacted]	Pirfenidone	6[redacted]/M	168			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	229	397	169	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	384	509	126	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Placebo	[redacted]	Nintedanib	6[redacted]/M	324			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	None	7[redacted]/F	63			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	None	7[redacted]/M	192			Grade 4	No	NA	No	Nrec	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	6[redacted]/M	252	260	9	Grade 3	No	NA	Yes	Rcver	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary fibrosis(肺線維症)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	311			Grade 3	No	NoChg	No	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary hypertension(肺高血圧症)	Placebo	[redacted]	Nintedanib	6[redacted]/M	381			Grade 2	No	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	5[redacted]/M	280			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	360			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	99			Grade 1	No	NA	No	UNK	OTHER		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Pirfenidone	7[redacted]/F	377			Grade 1	No	NoChg	No	Nrec	OTHER		
Pulmonary hypertension(肺高血圧症)															
	Placebo	[redacted]	Pirfenidone	6[redacted]/F	365			Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo		Nintedanib	7[redacted]/F	527			Grade 4	Yes	NoChg	No	UNK	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	515			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	8[redacted]/M	182			Grade 3	No	NoChg	No	Nrec	OTHER		
	Placebo		None	7[redacted]/M	457			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Placebo		Pirfenidone	8[redacted]/M	91			Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo		Pirfenidone	7[redacted]/M	392			Grade 1	No	NoChg	No	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	8[redacted]/M	141			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Pulmonary venous hypertension(肺静脈性肺高血圧症)															
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	6[redacted]/M	344	344	1	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Respiratory distress(呼吸窮迫)															
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	5[redacted]/M	95			Grade 1	Yes	Withdr	No	Nrec	OTHER		
Respiratory failure(呼吸不全)															

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	5[redacted]/M	107	145	39	Grade 4	No	Withdr	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Respiratory failure(呼吸不全)															
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	177			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo		None	7[redacted]/M	181	194	14	Grade 1	No	NoChg	No	Rcver	OTHER		
	Placebo		Pirfenidone	8[redacted]/M	311			Grade 3	No	NoChg	No	Nrec	OTHER		
	Placebo		Nintedanib	7[redacted]/F	527			Grade 4	Yes	NA	No	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	7[redacted]/M	221			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo		Nintedanib	7[redacted]/M	284	284	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Skin and subcutaneous tissue disorders(皮膚および皮下組織障害)	Placebo	[redacted]	Pirfenidone	6[redacted]/M	157	191	35	Grade 2	Yes	NoChg	Yes	Rcver	OTHER		
Rash(発疹)															
Vascular disorders(血管障害)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	453	456	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Aortic aneurysm(大動脈瘤)															
Vascular disorders(血管障害)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	357	362	6	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Aortic dilatation(大動脈拡張)															
Vascular disorders(血管障害)	Placebo	[redacted]	Nintedanib	6[redacted]/M	324	324	1	Grade 1	No	NoChg	No	Rcver	OTHER	not MACE	
Circulatory collapse(循環虚脱)															

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity- (CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Vascular disorders(血管障害) Deep vein thrombosis(深部静脈血栓症)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	387	539	153	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	249	438	190	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Vascular disorders(血管障害) Granulomatosis with polyangiitis(多発血管炎性肉芽腫症)	Placebo	[redacted]	Nintedanib	6[redacted]/M	37			Grade 3	No	Withdr	Yes	Nrec	OTHER	Vasculitis	
Vascular disorders(血管障害) Hypovolaemic shock(血液量減少性ショック)	Placebo	[redacted]	None	7[redacted]/M	188	192	5	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined	Undetermined
Vascular disorders(血管障害) Iliac artery stenosis(腸骨動脈狭窄)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	430	432	3	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Blood and lymphatic system disorders(血液およびリンパ系障害) Pancytopenia(汎血球減少症)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	416			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Cardiac disorders(心臓障害) Acute coronary syndrome(急性冠動脈症候群)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	214	219	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders(心臓障害) Acute myocardial infarction(急性心筋梗塞)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	532	549	18	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER	non-fatal MACE	
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	383	383	1	Grade 5	No	NA	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Acute myocardial infarction
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	449	452	4	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders(心臓障害) Atrial fibrillation(心房細動)	Nera 9mg bid	[redacted]	None	8[redacted]/F	358			Grade 2	Yes	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/F	317	318	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Atrial flutter(心房粗動)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	449	452	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders(心臓障害) Atrioventricular block second degree(第二度房室ブロック)	Nera 9mg bid	[redacted]	None	7[redacted]/M	300	302	3	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Cardiac arrest(心停止)	Residual effect	[redacted]	Nintedanib	6[redacted]/M	16	16	1	Grade 5	Yes	NA	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Cardiac disorders(心臓障害) Cardiac failure(心不全)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	308	347	40	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Cardiogenic shock(心原性ショック)	Nera 9mg bid	[redacted]	None	8[redacted]/F	278	279	2	Grade 5	No	NA	No	Fatal	FATAL	Undetermined	Undetermined
Cardiac disorders(心臓障害) Coronary artery occlusion(冠動脈閉塞)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	546			Grade 1	No	NoChg	No	Nrec	OTHER	non-fatal MACE	
Cardiac disorders(心臓障害) Heart failure with preserved ejection fraction(駆出率の保たれた心不全)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	453			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Cardiac disorders(心臓障害) Ischaemic cardiomyopathy(虚血性心筋症)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	362	363	2	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Cardiovascular (fatal MACE)	Sudden cardiac death
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	501	503	3	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
Cardiac disorders(心臓障害) Left ventricular failure(左室不全)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	429			Grade 2	No	NoChg	No	Nrec	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Myocardial infarction(心筋梗塞)	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	105	110	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER	non-fatal MACE	
Cardiac disorders(心臓障害) Myocardial ischaemia(心筋虚血)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	10	11	2	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Ventricular fibrillation(心室細動)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	215	215	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Cardiac disorders(心臓障害) Ventricular hypertrophy(心室肥大)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	362	363	2	Grade 4	No	NA	Yes	UNK	LIFE THR/REQ/PROL HSP		
Eye disorders(眼障害) Retinal tear(網膜裂孔)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/F	83	83	1	Grade 3	No	NoChg	No	Rcver	OTHER		
Gastrointestinal disorders(胃腸障害) Dysphagia(嚥下障害)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	497			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Enterocolitis(腸炎)	Nera 9mg bid	[redacted]	None	7[redacted]/F	193			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Gastritis(胃炎)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	456	473	18	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害) Gastrointestinal haemorrhage(胃腸出血)	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/M	306	317	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Gastrooesophageal reflux disease(胃食道逆流性疾患)	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/F	432	437	6	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Haematochezia(血便排泄)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	366	416	51	Grade 2	No	NA	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Hiatus hernia(裂孔ヘルニア)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	162	216	55	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Intestinal mass(腸管腫瘤)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	559			Grade 3	No	NoChg	No	Nrec	OTHER		
Gastrointestinal disorders(胃腸障害) Large intestine polyp(大腸ポリープ)	Nera 9mg bid	[redacted]	None	[redacted]/M	545	550	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Mechanical ileus(機械的イレウス)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	395	400	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害) Small intestinal obstruction(小腸閉塞)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	395	400	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Volvulus(腸の軸捻転)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	246	247	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	327	329	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Vomiting(嘔吐)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	293	293	1	Grade 3	Yes	NoChg	No	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Asthenia(無力症)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	191	210	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	238			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Chest pain(胸痛)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/F	93	94	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	6[redacted]/F	280	283	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	6[redacted]/M	339	341	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	362			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	21	64	44	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	131[a]	183		Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	31	62	32	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	6[redacted]/M	10			Grade 3	No	NoChg	No	UNK	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	358	374	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	221	226	6	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	262	267	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	239	260	22	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	73	86	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	10	44	35	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	295	316	22	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	372	382	11	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	436	452	17	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	168	204	37	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	357	378	22	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	263	274	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	427	434	8	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	511	517	7	Grade 4	Yes	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/F	352	354	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	318	368	51	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	330	375	46	Grade 4	No	NoChg	No	Rcver	LIFE THR/REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	54	85	32	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	107	125	19	Grade 3	No	NA	No	Seq	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	8[redacted]/M	499	510	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	7[redacted]/F	198			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	5[redacted]/M	375			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Residual effect	[redacted]	Pirfenidone	5[redacted]/M	517	517	1	Grade 5	Yes	NA	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Death(死亡)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	506[a]			Grade 5	No	NA	No	Fatal	FATAL	Undetermined	Undetermined
General disorders and administration site conditions(一般・全身障害および投与部位の状態) General physical health deterioration(全身健康状態悪化)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	197	199	3	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Pyrexia(発熱)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	23	30	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Vascular stent stenosis(血管ステント狭窄)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	216	218	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER	not MACE	
Hepatobiliary disorders(肝胆道系障害) Biliary dilatation(胆管拡張)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	352	360	9	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Hepatobiliary disorders(肝胆道系障害) Cholecystitis acute(急性胆嚢炎)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	199	204	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Cholecystitis(胆嚢炎)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	92	110	19	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	352	385	34	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Drug-induced liver injury(薬物性肝障害)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	10	44	35	Grade 3	Yes	Withdr	No	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Hepatic failure(肝不全)	Residual effect	[redacted]	None	7[redacted]/F	200			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Suspected drug-induced liver injury(薬物性肝障害の疑い)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	145	152	8	Grade 2	Yes	NoChg	No	Rcver	OTHER		
Immune system disorders(免疫系障害) Hypersensitivity(過敏症)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	306	308	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Appendiceal abscess(虫垂膿瘍)	Interruption (residual effect)	[redacted]	Pirfenidone	6[redacted]/F	410	411	2	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Appendicitis(虫垂炎)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/F	409	411	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) COVID-19(ＣＯＶＩＤ－１９)	Interruption (residual effect)	[redacted]	Pirfenidone	8[redacted]/M	456	497	42	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	138	145	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	464	474	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	8[redacted]/M	133	160	28	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Cellulitis(蜂巣炎)	Nera 9mg bid	[redacted]	None	6[redacted]/M	416	418	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Febrile infection(熱性感染症)	Nera 9mg bid	[redacted]	None	6[redacted]/M	233	238	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Gastroenteritis salmonella(サルモネラ菌性胃腸炎)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/F	38	49	12	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Influenza(インフルエンザ)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	10	44	35	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	6	8	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Latent tuberculosis(潜伏結核)	Interruption (residual effect)	[redacted]	None	[redacted]/F	365			Grade 3	No	NoChg	No	Nrec	OTHER		
Infections and infestations(感染症および寄生虫症) Lower respiratory tract infection(下気道感染)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	224	353	130	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	402			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pleurisy bacterial(細菌性胸膜炎)	Nera 9mg bid	[redacted]	None	[redacted]/M	509	528	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumocystis jirovecii pneumonia(ニューモシスチス・イロベチイ肺炎)	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/F	165	253	89	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia aspiration(誤嚥性肺炎)	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/M	497			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Interruption (residual effect)	[redacted]	Pirfenidone	[redacted]/M	371	380	10	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	149	206	58	Grade 3	Yes	Withdr	Yes	Nrec	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	295	316	22	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	374	384	11	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	7[redacted]/M	509	528	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	356	358	3	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Off-treatment	[redacted]	Nintedanib	8[redacted]/M	315	337	23	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia haemophilus(ヘモフィルス性肺炎)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	8	20	13	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
Infections and infestations(感染症および寄生虫症) Pneumonia influenzal(インフルエンザ性肺炎)	Nera 9mg bid	[redacted]	None	6[redacted]/M	292	300	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia pseudomonal(シュードモナス性肺炎)	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	473	496	24	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Interruption (residual effect)	[redacted]	None	6[redacted]/M	487	492	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Pirfenidone	5[redacted]/M	280	291	12	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Pneumonia(肺炎)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	155	165	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/F	444	448	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	14	64	51	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	257	264	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	357	450	94	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/F	21	21	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Pneumonia
	Nera 9mg bid	[redacted]	None	7[redacted]/F	75	76	2	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	6[redacted]/M	471	474	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	205	214	10	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	17	35	19	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Nera 9mg bid	[redacted]	None	7[redacted]/M	360	365	6	Grade 4	No	NoChg	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	8[redacted]/M	499	510	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	369	394	26	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	451	451	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Pneumonia

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Respiratory tract infection(気道感染)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	364	371	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Septic shock(敗血症性ショック)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	356	358	3	Grade 4	No	NA	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	None	7[redacted]/F	200			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Upper respiratory tract infection(上気道感染)	Nera 9mg bid	[redacted]	None	6[redacted]/M	403[a]			Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	6[redacted]/M	453	460	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Viral infection(ウイルス感染)	Nera 9mg bid	[redacted]	Nintedanib	5[redacted]/M	334[a]			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Fall(転倒)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	293	510	218	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Hip fracture(股関節部骨折)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	174			Grade 2	No	NoChg	Yes	UNK	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Humerus fracture(上腕骨骨折)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	280	289	10	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Rib fracture(肋骨骨折)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	321	322	2	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Venomous bite(有毒性咬傷)	Nera 9mg bid	[redacted]	None	6[redacted]/M	57	62	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症) Wrist fracture(手首関節骨折)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	78	84	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Interferon gamma release assay positive(インターフェロンγ応答測定陽性)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	384	399	16	Grade 2	No	NA	No	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Weight decreased(体重減少)	Residual effect	[redacted]	Pirfenidone	6[redacted]/F	239			Grade 2	Yes	Withdr	No	Nrec	OTHER		
Metabolism and nutrition disorders(代謝および栄養障害) Decreased appetite(食欲減退)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	42	57	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	86	108	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Metabolism and nutrition disorders(代謝および栄養障害) Dehydration(脱水)	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	480	496	17	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders(代謝および栄養障害) Fluid retention(体液貯留)	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	511			Grade 4	Yes	NoChg	Yes	UNK	LIFE THR/REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Arthralgia(関節痛)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	236	239	4	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Osteoarthritis(変形性関節症)	Interruption (residual effect)	[redacted]	Nintedanib	5[redacted]/F	274			Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Polymyalgia rheumatica(リウマチ性多発筋痛)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	138			Grade 2	No	NoChg	Yes	Nrec	OTHER	not Vasculitis	
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	259	345	87	Grade 2	No	NoChg	Yes	Rcver	OTHER	not Vasculitis	
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Rhabdomyolysis(横紋筋融解症)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	183	450	268	Grade 1	Yes	NoChg	No	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	372	394	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Rotator cuff syndrome(肩回旋筋腱板症候群)															
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	79	110	32	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	351	414	64	Grade 1	No	Withdr	Yes	Rcver	OTHER		
Atypical fibroxanthoma(異型線維黄色腫)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	15	15	1	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Basal cell carcinoma(基底細胞癌)															
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	414	477	64	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	None	8[redacted]/M	252	282	31	Grade 1	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	130	140	11	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	130	242	113	Grade 1	No	NoChg	Yes	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Bladder cancer stage 0, with cancer in situ(膀胱癌第０期、上皮内癌を	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	272			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Bladder papilloma(膀胱乳頭腫)	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	492			Grade 2	No	NA	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Bowen's disease(ボーエン病)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	156	156	1	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Clear cell renal cell carcinoma(腎明細胞癌)	Nera 9mg bid	[redacted]	None	6[redacted]/M	501			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Colon cancer(結腸癌)	Nera 9mg bid	[redacted]	None	7[redacted]/M	213			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Extranodal marginal zone B-cell lymphoma (MALT type)(節外性辺縁帯B	Nera 9mg bid	[redacted]	Nintedanib	5[redacted]/M	339			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Hepatocellular carcinoma(肝細胞癌)	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	64			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Laryngeal neoplasm(喉頭新生物)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	456			Grade 3	No	NoChg	No	Nrec	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 9mg bid	[redacted]	None	7[redacted]/M	297			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Lung neoplasm malignant(肺の悪性新生物)															
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	222			Grade 2	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	469			Grade 2	No	Withdr	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	187	304	118	Grade 5	No	Withdr	No	Fatal	FATAL/OTHER	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	315			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Prostate cancer(前立腺癌)															
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	269			Grade 3	No	Withdr	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 9mg bid	[redacted]	Nintedanib	5[redacted]/M	559			Grade 3	No	NoChg	No	Nrec	OTHER		
Rectal adenocarcinoma(直腸腺癌)															

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Squamous cell carcinoma of skin(皮膚有棘細胞癌)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	7	7	1	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/F	274	274	1	Grade 2	No	Withdr	Yes	Seq	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	8[redacted]/M	346	381	36	Grade 2	No	Withdr	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	159	209	51	Grade 2	No	Withdr	Yes	Rcver	OTHER		
Nervous system disorders(神経系障害) Central nervous system haemorrhage(中枢神経系出血)	Residual effect	[redacted]	Nintedanib	8[redacted]/M	208	211	4	Grade 5	No	NA	No	Fatal	FATAL/DISABL/REQ/PROL HSP	Cardiovascular (fatal MACE)	Hemorrhagic stroke
Nervous system disorders(神経系障害) Cerebrovascular accident(脳卒中)	Interruption (residual effect)	[redacted]	None	7[redacted]/F	120	122	3	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP	non-fatal MACE	
Nervous system disorders(神経系障害) Dizziness(浮動性めまい)	Nera 9mg bid	[redacted]	None	8[redacted]/M	51	67	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	8[redacted]/M	118	129	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	293	297	5	Grade 3	Yes	NoChg	No	Rcver	REQ/PROL HSP		
Nervous system disorders(神経系障害) Epilepsy(てんかん)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	183	225	43	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Ischaemic stroke(虚血性脳卒中)	Residual effect	[redacted]	Nintedanib	8[redacted]/M	206			Grade 4	No	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP	non-fatal MACE	
Nervous system disorders(神経系障害) Lacunar infarction(ラクナ梗塞)	Nera 9mg bid	[redacted]	None	7[redacted]/M	474			Grade 1	No	NoChg	No	Nrec	OTHER	not MACE	
Nervous system disorders(神経系障害) Presyncope(失神寸前の状態)	Nera 9mg bid	[redacted]	None	5[redacted]/M	463	463	1	Grade 4	No	NoChg	Yes	Rcver	LIFE THR	not MACE	
Nervous system disorders(神経系障害) Syncope(失神)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	321	322	2	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP	not MACE	
Nervous system disorders(神経系障害) Transient ischaemic attack(一過性脳虚血発作)	Nera 9mg bid	[redacted]	None	7[redacted]/F	94	94	1	Grade 2	No	NoChg	No	Rcver	OTHER	not MACE	
	Nera 9mg bid	[redacted]	None	6[redacted]/M	489	517	29	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Psychiatric disorders(精神障害) Alcohol abuse(アルコール乱用)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	226	278	53	Grade 3	Yes	NoChg	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	279	485	207	Grade 2	Yes	NoChg	No	Rcver	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Psychiatric disorders(精神障害)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	358	383	26	Grade 1	No	NoChg	No	Rcver	OTHER		
Depressive symptom(抑うつ症状)															
Psychiatric disorders(精神障害)	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	511			Grade 2	Yes	NA	Yes	UNK	OTHER		
Major depression(大うつ病)															
Psychiatric disorders(精神障害)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	336	344	9	Grade 3	Yes	Withdr	Yes	Rcver	REQ/PROL HSP		
Suicidal ideation(自殺念慮)															
	Nera 9mg bid	[redacted]	None	8[redacted]/M	176[a]	310		Grade 2	Yes	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	278	311	34	Grade 2	Yes	Withdr	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	None	8[redacted]/M	245			Grade 3	Yes	Withdr	No	Nrec	OTHER		
Psychiatric disorders(精神障害)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	226	278	53	Grade 3	Yes	NoChg	No	Rcver	OTHER		
Tobacco abuse(タバコ乱用)															
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	279			Grade 2	Yes	NoChg	No	Nrec	OTHER		
Renal and urinary disorders(腎および尿路障害)	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	497			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Acute kidney injury(急性腎障害)															
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	179	254	76	Grade 1	No	NoChg	No	Rcver	OTHER		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	480	496	17	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Renal and urinary disorders(腎および尿路障害) Acute kidney injury(急性腎障害)	Residual effect	[redacted]	None	[redacted]/F	200	212	13	Grade 4	No	NA	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Renal and urinary disorders(腎および尿路障害) Nephrolithiasis(腎結石症)	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/M	100	107	8	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Renal and urinary disorders(腎および尿路障害) Renal failure(腎不全)	Residual effect	[redacted]	Nintedanib	[redacted]/M	19			Grade 4	No	NA	No	UNK	LIFE THR		
Renal and urinary disorders(腎および尿路障害) Urethral stenosis(尿道狭窄)	Interruption (residual effect)	[redacted]	Pirfenidone	[redacted]/M	266	267	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Reproductive system and breast disorders(生殖系および乳房障害) Benign prostatic hyperplasia(良性前立腺肥大症)	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	204	254	51	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Acute respiratory failure(急性呼吸不全)	Interruption (residual effect)	[redacted]	Nintedanib	[redacted]/M	362			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	[redacted]/M	404	407	4	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	[redacted]/M	497			Grade 4	No	NoChg	Yes	Nrec	LIFE THR		
	Nera 9mg bid	[redacted]	None	[redacted]/M	309	314	6	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Acute respiratory failure(急性呼吸不全)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	292			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Chronic respiratory failure(慢性呼吸不全)	Nera 9mg bid	[redacted]	None	7[redacted]/M	360	365	6	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Dyspnoea(呼吸困難)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	236			Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	8[redacted]/M	413	419	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	274	363	90	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	483			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	7[redacted]/F	264	508	245	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Off-treatment	[redacted]	None	6[redacted]/F	383	391	9	Grade 3	No	NA	No	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypercapnia(高炭酸ガス血症)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	414	423	10	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypoxia(低酸素症)	Residual effect	[redacted]	None	8[redacted]/M	54	66	13	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	355	390	36	Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	390	393	4	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	393			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	124	129	6	Grade 4	No	Withdr	Yes	Seq	LIFE THR		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	532			Grade 3	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	280[a]	319		Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	74	191	118	Grade 3	No	Withdr	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	359			Grade 1	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	330			Grade 4	No	NoChg	No	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	7[redacted]/F	75	76	2	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	294	308	15	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	452			Grade 4	No	NoChg	No	Nrec	LIFE THR		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	93	406	314	Grade 3	No	NoChg	No	Nrec	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	129	129	1	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	593			Grade 3	No	NA	No	Nrec	OTHER		
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	319	356	38	Grade 4	No	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Interstitial lung disease(間質性肺疾患)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	376	393	18	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Painful respiration(呼吸時疼痛)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	293	297	5	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pleural effusion(胸水)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	358			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumonitis(肺臓炎)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	465	467	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	211	224	14	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumothorax(気胸)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	254	287	34	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	5[redacted]/M	308	388	81	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	84			Grade 2	No	NoChg	Yes	UNK	OTHER		
Pulmonary artery thrombosis(肺動脈血栓症)															
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	4[redacted]/M	378			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Pulmonary embolism(肺塞栓症)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	6	13	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	414			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	295			Grade 2	No	NA	Yes	UNK	OTHER		
	Residual effect	[redacted]	Pirfenidone	6[redacted]/M	234	262	29	Grade 4	No	NA	Yes	Seq	LIFE THR/REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary fibrosis(肺線維症)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	79			Grade 2	No	NoChg	No	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pulmonary hypertension(肺高血圧症)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	458			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	243			Grade 2	No	NoChg	No	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	375	394	20	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	360			Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	532			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	253			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	367	543	177	Grade 2	No	NA	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	389			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	7[redacted]/F	190	405	216	Grade 2	No	NoChg	No	Rcver	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Respiratory failure(呼吸不全)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	1	365	365	Grade 1	No	NoChg	Yes	Rcver	OTHER		
	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	408	416	9	Grade 4	No	NoChg	Yes	Rcver	LIFE THR		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Respiratory failure(呼吸不全)	Off-treatment	[redacted]	Nintedanib	8[redacted]/M	499	510	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	7[redacted]/M	526			Grade 4	No	Withdr	No	Nrec	LIFE THR		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Vocal cord leukoplakia(声帯白斑症)	Nera 9mg bid	[redacted]	None	7[redacted]/M	103	265	163	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders(血管障害) Aortic stenosis(大動脈狭窄)	Residual effect	[redacted]	Pirfenidone	8[redacted]/M	78	130	53	Grade 4	No	NA	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Vascular disorders(血管障害) Deep vein thrombosis(深部静脈血栓症)	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	184			Grade 2	No	NA	Yes	UNK	OTHER		
Vascular disorders(血管障害) Vasculitis(血管炎)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	81	180	100	Grade 1	No	NoChg	Yes	Rcver	OTHER	not assessable	

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Blood and lymphatic system disorders(血液およびリンパ系障害) Anaemia(貧血)	Nera 18mg bid	[redacted]	None	8[redacted]/M	288	288	1	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Blood and lymphatic system disorders(血液およびリンパ系障害) Blood loss anaemia(失血性貧血)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	473			Grade 2	No	NA	No	Nrec	REQ/PROL HSP/OTHER		
Cardiac disorders(心臓障害) Acute myocardial infarction(急性心筋梗塞)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	285	285	1	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	150	151	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders(心臓障害) Acute right ventricular failure(急性右室不全)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	383	385	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Aortic valve incompetence(大動脈弁閉鎖不全症)	Nera 18mg bid	[redacted]	None	8[redacted]/M	360	366	7	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	361			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Aortic valve stenosis(大動脈弁狭窄)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	605	632	28	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Arrhythmia(不整脈)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	446			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Atrial fibrillation(心房細動)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	150	151	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	103	108	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	358			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Atrial flutter(心房粗動)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	442	445	4	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Atrioventricular block(房室ブロック)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	48	55	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders(心臓障害) Bradycardia(徐脈)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	257	282	26	Grade 1	No	NoChg	No	Rcver	OTHER		
Cardiac disorders(心臓障害) Cardiac failure acute(急性心不全)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	48	55	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders(心臓障害) Cardiac failure chronic(慢性心不全)	Residual effect	[redacted]	Nintedanib	8[redacted]/M	150			Grade 3	No	NA	Yes	Nrec	OTHER		
Cardiac disorders(心臓障害) Cardiac failure(心不全)	Nera 18mg bid	[redacted]	None	7[redacted]/M	33			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	431	432	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,REQ/PROL HSP=Requires or Prolongs Hospitalization,
CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Cardiac failure(心不全)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	284			Grade 2	No	NoChg	No	UNK	OTHER		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	50	54	5	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Residual effect	[redacted]	Nintedanib	8[redacted]/M	147	161	15	Grade 3	No	NA	Yes	Seq	REQ/PROL HSP		
Cardiac disorders(心臓障害) Cardiac valve disease(心臓弁膜疾患)	Nera 18mg bid	[redacted]	None	8[redacted]/M	358			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Coronary artery disease(冠動脈疾患)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	239	258	20	Grade 4	No	Withdr	Yes	Rcver	LIFE THR/REQ/PROL HSP	not MACE	
	Nera 18mg bid	[redacted]	Pirfenidone	8[redacted]/M	66			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	6[redacted]/M	261	269	9	Grade 4	No	NA	No	Rcver	LIFE THR/REQ/PROL HSP		
Cardiac disorders(心臓障害) Heart failure with reduced ejection fraction(駆出率低下を伴う心不全)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	329	341	13	Grade 2	No	Withdr	Yes	Rcver	REQ/PROL HSP/OTHER		
Cardiac disorders(心臓障害) Myocardial ischaemia(心筋虚血)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	323			Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		
	Off-treatment	[redacted]	None	8[redacted]/M	65	95	31	Grade 3	Yes	NA	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders(心臓障害) Right ventricular failure(右室不全)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	445			Grade 3	No	NoChg	Yes	Nrec	DISABL		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Sinus tachycardia(洞性頻脈)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	165	167	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Congenital, familial and genetic disorders(先天性、家族性および遺伝性障害) Hypertrophic cardiomyopathy(肥大型心筋症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	287			Grade 3	No	NoChg	Yes	UNK	OTHER		
Congenital, familial and genetic disorders(先天性、家族性および遺伝性障害) Retinopathy congenital(先天性網膜症)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	491			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Ear and labyrinth disorders(耳および迷路障害) Presbyacusis(老人性難聴)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	154	370	217	Grade 2	No	NoChg	Yes	Seq	DISABL		
Endocrine disorders(内分泌障害) Hyperparathyroidism primary(原発性副甲状腺機能亢進症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	201	260	60	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders(眼障害) Amaurosis(黒内障)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	230	232	3	Grade 1	No	NoChg	No	Rcver	OTHER		
Eye disorders(眼障害) Cataract(白内障)	Nera 18mg bid	[redacted]	None	7[redacted]/M	65	280	216	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	5[redacted]/M	261	267	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders(眼障害) Dry age-related macular degeneration(乾性加齢黄斑変性)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	491			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Eye disorders(眼障害) Glaucoma(緑内障)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	321			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Eye disorders(眼障害) Retinal infarction(網膜梗塞)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	14[a]			Grade 1	No	NoChg	No	Nrec	OTHER		
Eye disorders(眼障害) Retinal tear(網膜裂孔)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	19	23	5	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Eye disorders(眼障害) Retinal vein occlusion(網膜静脈閉塞)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	37	93	57	Grade 1	No	NoChg	Yes	Seq	DISABL/OTHER		
Gastrointestinal disorders(胃腸障害) Abdominal pain upper(上腹部痛)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	338	338	1	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Abdominal pain(腹痛)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	334	335	2	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Constipation(便秘)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	333	335	3	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Diarrhoea(下痢)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	378	385	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Enteritis(小腸炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	184	205	22	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害) Enterocolitis(腸炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	195	215	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Gastrointestinal haemorrhage(胃腸出血)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	473			Grade 1	No	NA	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Haemorrhoids(痔核)	Nera 18mg bid	[redacted]	None	6[redacted]/M	272	310	39	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Hiatus hernia(裂孔ヘルニア)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/F	256	311	56	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Inguinal hernia(鼠径ヘルニア)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	350	353	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	125	162	38	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	141	143	3	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Intestinal obstruction(腸閉塞)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	405	413	9	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Nausea(悪心)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	334	335	2	Grade 2	Yes	NoChg	No	Rcver	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Gastrointestinal disorders(胃腸障害) Oesophageal rupture(食道破裂)	Nera 18mg bid	[redacted]	None	8[redacted]/M	346	347	2	Grade 1	No	NoChg	No	Rcver	OTHER		
Gastrointestinal disorders(胃腸障害) Oesophagitis(食道炎)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/F	320			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Pancreatitis(膵炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	49	60	12	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Upper gastrointestinal haemorrhage(上部消化管出血)	Off-treatment	[redacted]	None	8[redacted]/M	68	76	9	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders(胃腸障害) Vomiting(嘔吐)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	334	334	1	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Asthenia(無力症)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	269	280	12	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	289			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/F	312	331	20	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	475	485	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	5[redacted]/M	506	514	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	164	166	3	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	162			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	376	378	3	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	4	43	40	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	185	203	19	Grade 3	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	29	31	3	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	477			Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	333			Grade 4	No	NoChg	No	Nrec	LIFE THR		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Nera 18mg bid	[redacted]	None	8[redacted]/F	121	127	7	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	422	427	6	Grade 2	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	496	498	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	5[redacted]/M	300	340	41	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	137	152	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	9	145	137	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	38	102	65	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	383	395	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	486	522	37	Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	179			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	251	257	7	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	151	201	51	Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	127	129	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	238	268	31	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	268	369	102	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	192	197	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	486	505	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	91	103	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	5[redacted]/M	419	427	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	425	442	18	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	244	246	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	67			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	296	367	72	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	282			Grade 4	No	NoChg	No	UNK	LIFE THR		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	43	91	49	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	230	243	14	Grade 4	No	Withdr	No	Rcver	LIFE THR/REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	303	361	59	Grade 2	No	NA	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	7[redacted]/M	522	522	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	253			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Disease progression(疾患進行)	Nera 18mg bid	[redacted]	None	7[redacted]/F	394			Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	5[redacted]/M	622			Grade 3	No	NoChg	No	Nrec	OTHER		
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/F	312	331	20	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Gait disturbance(歩行障害)															
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	176[a]			Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General physical health deterioration(全身健康状態悪化)															
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	23			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Inflammation(炎症)															
General disorders and administration site conditions(一般・全身障害および投与部位の状態)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	250	251	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pyrexia(発熱)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	243	258	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Vascular stent stenosis(血管ステント狭窄)	Nera 18mg bid	[redacted]	None	8[redacted]/M	360	366	7	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	361			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Biliary obstruction(胆道閉塞)	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	200	211	12	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Cholecystitis acute(急性胆嚢炎)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/F	214	257	44	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Drug-induced liver injury(薬物性肝障害)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	377			Grade 3	No	NA	No	UNK	OTHER		
Hepatobiliary disorders(肝胆道系障害) Hepatitis toxic(中毒性肝炎)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	388	401	14	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Hepatobiliary disorders(肝胆道系障害) Suspected drug-induced liver injury(薬物性肝障害の疑い)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	335	351	17	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Immune system disorders(免疫系障害) Anaphylactic shock(アナフィラキシーショック)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	124	134	11	Grade 4	No	NoChg	Yes	Rcver	LIFE THR		
Infections and infestations(感染症および寄生虫症) Appendicitis(虫垂炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	293	298	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Atypical mycobacterial infection(非定型マイコバクテリア感染)	Residual effect	[redacted]	Nintedanib	5[redacted]/M	451	473	23	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Atypical pneumonia(異型肺炎)	Interruption (residual effect)	[redacted]	None	5[redacted]/M	506	514	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Interruption (residual effect)	[redacted]	None	7[redacted]/M	431			Grade 4	No	NoChg	Yes	UNK	LIFE THR/REQ/PROL HSP/OTHER		
	Nera 18mg bid	[redacted]	None	5[redacted]/M	419	474	56	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) Biliary tract infection(胆道感染)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/F	411	415	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Bronchitis(気管支炎)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	98	102	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	505	535	31	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) COVID-19 pneumonia(ＣＯＶＩＤ－１９肺炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	70	74	5	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) COVID-19(ＣＯＶＩＤ－１９)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	337	357	21	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	371	377	7	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	107	155	49	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Diverticulitis(憩室炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	20	23	4	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Endocarditis bacterial(細菌性心内膜炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/F	168			Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Gastroenteritis norovirus(ノロウイルス性胃腸炎)	Nera 18mg bid	[redacted]	Pirfenidone	5[redacted]/M	567	577	11	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Gastroenteritis(胃腸炎)	Nera 18mg bid	[redacted]	None	7[redacted]/F	344	354	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	425[a]	433		Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) HCoV-OC43 infection(ＨＣｏＶ－ＯＣ４３感染)	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	258	264	7	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Infection(感染)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	225	233	9	Grade 3	No	NA	Yes	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) Influenza(インフルエンザ)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	250	255	6	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Latent tuberculosis(潜伏結核)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/F	306	312	7	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Norovirus infection(ノロウイルス感染)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	267	271	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	5[redacted]/M	136	144	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	444	473	30	Grade 3	Yes	Withdr	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia fungal(真菌性肺炎)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	253	263	11	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia influenzal(インフルエンザ性肺炎)	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	279	283	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia viral(ウイルス性肺炎)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	484	497	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	415	428	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	52	60	9	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	7[redacted]/M	125	127	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	281	297	17	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	388	401	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia(肺炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	79	97	19	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	7[redacted]/F	342	354	13	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	5[redacted]/M	300	340	41	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	337	372	36	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	119	125	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	410	418	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	212	220	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	342	352	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	510	517	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	337	351	15	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	258	264	7	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	241	251	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pyelonephritis acute(急性腎盂腎炎)															

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Respiratory tract infection(気道感染)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	245	252	8	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	133	147	15	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	35	56	22	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	273	294	22	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Salmonellosis(サルモネラ症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	267	271	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Sepsis(敗血症)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	388	401	14	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Infections and infestations(感染症および寄生虫症) Septic shock(敗血症性ショック)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	388	401	14	Grade 3	Yes	NoChg	Yes	Rcver	OTHER		
	Residual effect	[redacted]	Nintedanib	7[redacted]/M	272	289	18	Grade 2	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Infections and infestations(感染症および寄生虫症) Sinusitis(副鼻腔炎)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	204	212	9	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	112	124	13	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Upper respiratory tract infection(上気道感染)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	431	437	7	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	438	438	1	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Compression fracture(圧迫骨折)															
Injury, poisoning and procedural complications(傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	None	7[redacted]/M	95	97	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Coronary artery restenosis(冠動脈再狭窄)	Nera 18mg bid	[redacted]	None	7[redacted]/M	518	520	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Injury, poisoning and procedural complications(傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	212	242	31	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Femur fracture(大腿骨骨折)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	243			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Injury, poisoning and procedural complications(傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	39	42	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Skin laceration(皮膚裂傷)															

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Investigations(臨床検査) Amylase increased(アミラーゼ増加)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	207	221	15	Grade 2	No	NoChg	No	Rcver	OTHER		
Investigations(臨床検査) C-reactive protein increased (C－反応性蛋白増加)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	257	302	46	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	267	270	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Clostridium test positive(クロストリジウム検査陽性)	Interruption (residual effect)	[redacted]	Nintedanib	8[redacted]/M	396	410	15	Grade 3	Yes	NA	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Haemoglobin decreased(ヘモグロビン減少)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	191	249	59	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations(臨床検査) Heart rate irregular(心拍数不整)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	462			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Investigations(臨床検査) Lipase increased(リパーゼ増加)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	207	221	15	Grade 2	No	NoChg	No	Rcver	OTHER		
Investigations(臨床検査) Weight decreased(体重減少)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	263	270	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders(代謝および栄養障害) Dehydration(脱水)	Nera 18mg bid	[redacted]	None	7[redacted]/F	378	382	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Metabolism and nutrition disorders(代謝および栄養障害) Hyponatraemia(低ナトリウム血症)	Nera 18mg bid	[redacted]	None	7[redacted]/M	43	58	16	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Metabolism and nutrition disorders(代謝および栄養障害) Malnutrition(栄養障害)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	183[a]			Grade 2	Yes	NoChg	Yes	Nrec	OTHER		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Arthropathy(関節障害)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	168	181	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Intervertebral disc protrusion(椎間板突出)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	291	433	143	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	434	434	1	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	446	448	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders(筋骨格系および結合組織障害) Osteonecrosis(骨壊死)	Nera 18mg bid	[redacted]	Nintedanib	4[redacted]/M	209			Grade 1	No	NoChg	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Acute leukaemia(急性白血病)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	375	406	32	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	82	82	1	Grade 1	Yes	NoChg	Yes	Rcver	OTHER		
Basal cell carcinoma(基底細胞癌)															
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	462			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	73	176	104	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	73	366	294	Grade 1	No	NA	No	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	468	519	52	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Bowen's disease(ボーエン病)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/F	385	395	11	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Lung cancer metastatic(遠隔転移を伴う肺癌)															

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	None	4[redacted]/M	446			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Lung neoplasm malignant(肺の悪性新生物)															
	Nera 18mg bid	[redacted]	None	6[redacted]/M	551	558	8	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	310			Grade 2	No	Withdr	No	Nrec	OTHER		
	Residual effect	[redacted]	None	6[redacted]/M	558			Grade 2	No	NA	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	None	8[redacted]/M	93			Grade 2	No	Withdr	Yes	Nrec	OTHER		
Prostate cancer(前立腺癌)															
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	246	313	68	Grade 4	No	Withdr	Yes	Rcver	LIFE THR/OTHER		
Sarcomatoid carcinoma(肉腫様癌)															

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Squamous cell carcinoma of lung(肺扁平上皮癌)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	324[a]			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Squamous cell carcinoma of skin(皮膚有棘細胞癌)	Nera 18mg bid	[redacted]	Pirfenidone	5[redacted]/M	125[a]	147		Grade 2	No	Withdr	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Squamous cell carcinoma(扁平上皮癌)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	348			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Sweat gland tumour(汗腺腫瘍)	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	350	442	93	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Nervous system disorders(神経系障害) Carotid artery dissection(頚動脈解離)	Off-treatment	[redacted]	None	8[redacted]/M	52	76	25	Grade 4	Yes	NA	Yes	Rcver	REQ/PROL HSP not MACE		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Carotid artery stenosis(頚動脈狭窄)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	413	416	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Nervous system disorders(神経系障害) Cerebral infarction(脳梗塞)	Nera 18mg bid	[redacted]	None	7[redacted]/M	180	184	5	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Nervous system disorders(神経系障害) Cerebrovascular accident(脳卒中)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	474	481	8	Grade 4	No	NoChg	No	Rcver	LIFE THR/REQ/PROL HSP/OTHER	non-fatal MACE	
Nervous system disorders(神経系障害) Epilepsy(てんかん)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	302			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	302	303	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
Nervous system disorders(神経系障害) Focal dyscognitive seizures(認知障害発作)	Nera 18mg bid	[redacted]	None	8[redacted]/M	183			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Nervous system disorders(神経系障害) Haemorrhagic stroke(出血性卒中)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/M	371	479	109	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP	non-fatal MACE	

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Loss of consciousness(意識消失)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	301	301	1	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	306	306	1	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Nervous system disorders(神経系障害) Mental impairment(精神的機能障害)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	250	251	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Nervous system disorders(神経系障害) Metabolic encephalopathy(代謝性脳症)	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	275	283	9	Grade 4	No	NA	Yes	Seq	LIFE THR/REQ/ PROL HSP		
Nervous system disorders(神経系障害) Middle cerebral artery stroke(中大脳動脈性卒中)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	510			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	non-fatal MACE	
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	510	510	1	Grade 4	No	NoChg	Yes	Seq	LIFE THR/REQ/ PROL HSP/OTHER	non-fatal MACE	
Nervous system disorders(神経系障害) Monoplegia(単麻痺)	Nera 18mg bid	[redacted]	Pirfenidone	8[redacted]/M	408			Grade 2	No	NoChg	Yes	Nrec	DISABL	not MACE	
Nervous system disorders(神経系障害) Subdural hygroma(硬膜下ヒグローマ)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	50	142	93	Grade 3	No	NA	Yes	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Transient ischaemic attack(一過性脳虚血発作)	Nera 18mg bid	[redacted]	None	8[redacted]/M	40	76	37	Grade 1	Yes	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Psychiatric disorders(精神障害) Depression(うつ病)	Nera 18mg bid	[redacted]	Pirfenidone	8[redacted]/M	483	512	30	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Psychiatric disorders(精神障害) Suicidal ideation(自殺念慮)	Interruption (residual effect)	[redacted]	Nintedanib	6[redacted]/F	45	86	42	Grade 3	No	Withdr	No	Rcver	OTHER		
	Interruption (residual effect)	[redacted]	None	7[redacted]/M	419	419	1	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	12	33	22	Grade 2	Yes	Withdr	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	7[redacted]/M	176	177	2	Grade 1	Yes	NoChg	No	Rcver	OTHER		
Renal and urinary disorders(腎および尿路障害) Acute kidney injury(急性腎障害)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	415	417	3	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	428	433	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	388	401	14	Grade 3	No	NoChg	No	Rcver	OTHER		

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Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Renal and urinary disorders(腎および尿路障害) Nephritis(腎炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	11	64	54	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Reproductive system and breast disorders(生殖系および乳房障害) Benign prostatic hyperplasia(良性前立腺肥大症)	Nera 18mg bid	[redacted]	None	7[redacted]/M	245	496	252	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Reproductive system and breast disorders(生殖系および乳房障害) Genital prolapse(性器脱)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	124			Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		
Reproductive system and breast disorders(生殖系および乳房障害) Prostatitis(前立腺炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	64	72	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Acute respiratory failure(急性呼吸不全)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	48	55	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	8[redacted]/M	245	248	4	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	8[redacted]/M	250	255	6	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	8[redacted]/M	358			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		

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LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,REQ/PROL HSP=Requires or Prolongs Hospitalization,
CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Acute respiratory failure(急性呼吸不全)	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	275	283	9	Grade 4	No	NA	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Dyspnoea(呼吸困難)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	85	87	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	143	144	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	278	280	3	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	211	214	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	462			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	261			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP	not MACE	
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Epistaxis(鼻出血)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	221	230	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/F	144	148	5	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Haemothorax(血胸)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	222	227	6	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,REQ/PROL HSP=Requires or Prolongs Hospitalization,
CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	130[a]			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Hypoxia(低酸素症)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	217	219	3	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	365	484	120	Grade 1	No	NoChg	No	Nrec	OTHER		
Idiopathic pulmonary fibrosis(特発性肺線維症)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	484	497	14	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	484	497	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	497			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/F	253			Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	178	189	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	535	541	7	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	303			Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	182			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	None	6[redacted]/F	366			Grade 4	No	NoChg	No	Nrec	LIFE THR		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	534	535	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	222			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,REQ/PROL HSP=Requires or Prolongs Hospitalization,
CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	291	291	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumomediastinum(気縦隔症)	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	517			Grade 1	No	NoChg	No	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumonitis(肺臓炎)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/F	390	393	4	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax spontaneous(自然気胸)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	359	369	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax(気胸)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	190	307	118	Grade 1	No	NA	No	Rcver	OTHER		
	Interruption (residual effect)	[redacted]	None	5[redacted]/M	506	512	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	204	215	12	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/F	168	178	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	283	285	3	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
Pneumothorax(気胸)	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	351	359	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	5[redacted]/M	444	473	30	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	287	315	29	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	Pirfenidone	7[redacted]/M	487	494	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pulmonary embolism(肺塞栓症)	Interruption (residual effect)	[redacted]	None	7[redacted]/M	476	481	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	8[redacted]/M	245	335	91	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	7[redacted]/M	393			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	227	277	51	Grade 3	No	NA	Yes	Rcver	OTHER		
Pulmonary hypertension(肺高血圧症)															

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	384			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Pulmonary hypertension(肺高血圧症)															
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	445			Grade 3	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	146			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	103[a]			Grade 3	No	NoChg	No	UNK	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	8[redacted]/M	226			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	269	275	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	276			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	366	367	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	399	400	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	351			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/M	449			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	213			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	244			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	134			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Respiratory failure(呼吸不全)	Nera 18mg bid	[redacted]	None	5[redacted]/M	300	311	12	Grade 4	No	NoChg	No	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	6[redacted]/M	329	332	4	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Vocal cord leukoplakia(声帯白斑症)	Nera 18mg bid	[redacted]	None	6[redacted]/M	447	467	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders(血管障害) Aortic dissection(大動脈解離)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	618	627	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders(血管障害) Aortic stenosis(大動脈狭窄)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/M	113	117	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders(血管障害) Arteriosclerosis(動脈硬化症)	Nera 18mg bid	[redacted]	None	6[redacted]/M	169[a]	397		Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Vascular disorders(血管障害) Deep vein thrombosis(深部静脈血栓症)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	449			Grade 2	Yes	NoChg	Yes	Nrec	OTHER		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Outcome	Adjudi-cation Cause of Death
Vascular disorders(血管障害) Hypertension(高血圧)	Interruption (residual effect)	[redacted]	Nintedanib	7[redacted]/F	145	146	2	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Vascular disorders(血管障害) Hypertensive urgency(高血圧切迫症)	Interruption (residual effect)	[redacted]	None	8[redacted]/M	245	245	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders(血管障害) Microscopic polyangiitis(顕微鏡的多発血管炎)	Off-treatment	[redacted]	Pirfenidone	7[redacted]/M	211			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	Vasculitis	
Vascular disorders(血管障害) Peripheral artery occlusion(末梢動脈閉塞)	Nera 18mg bid	[redacted]	Nintedanib	6[redacted]/F	102	126	25	Grade 2	No	NoChg	Yes	Seq	OTHER		
Vascular disorders(血管障害) Vasculitis(血管炎)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	267	279	13	Grade 3	Yes	Withdr	Yes	Seq	REQ/PROL HSP	Vasculitis	
	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	224	346	123	Grade 2	No	Withdr	Yes	Rcver	OTHER	Vasculitis	
	Nera 18mg bid	[redacted]	None	7[redacted]/M	5	360	356	Grade 2	Yes	Withdr	Yes	Rcver	REQ/PROL HSP	Vasculitis	
Vascular disorders(血管障害) Venous thrombosis(静脈血栓症)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	194	388	195	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		

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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Blood and lymphatic system disorders(血液およびリンパ系障害) Anaemia(貧血)	Placebo	[redacted]	Nintedanib	8[redacted]/M	324	327	4	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Other respiratory causes
Cardiac disorders(心臓障害) Cardiac arrest(心停止)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	346	346	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Cardiac disorders(心臓障害) Myocardial infarction(心筋梗塞)	Placebo	[redacted]	None	6[redacted]/M	189	189	1	Grade 5	Yes	NA	No	Fatal	FATAL	Sudden cardiac death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Placebo	[redacted]	Nintedanib	6[redacted]/M	324	330	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	521	533	13	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Placebo	[redacted]	None	7[redacted]/F	86	87	2	Grade 5	No	NA	Yes	Fatal	FATAL	Other respiratory causes
	Placebo	[redacted]	Pirfenidone	6[redacted]/M	514	575	62	Grade 5	No	NoChg	Yes	Fatal	FATAL	Underlying interstitial lung disease
	Placebo	[redacted]	Pirfenidone	7[redacted]/M	478	481	4	Grade 5	No	NA	Yes	Fatal	FATAL	Pneumonia
	Placebo		Nintedanib	7[redacted]/M	201	248	48	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease

AE records may be intermittent, i.e. not always continuing from start to stop day.
[1] Related to start of treatment in the respective study.
Nrec=Not Recovered or Not Resolved, Rcver=Recovered or Resolved
Seq=Recovered or Resolved with Sequelae, UNK=Unknown. LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,
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MedDRA version used for reporting: 27.1

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Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	152	223	72	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Death(死亡)	Placebo	[redacted]	None	7[redacted]/M	514	514	1	Grade 5		NA	No	Fatal	FATAL	Undetermined
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Disease progression(疾患進行)	Placebo	[redacted]	Pirfenidone	7[redacted]/M	274	415	142	Grade 5	No	NoChg	No	Fatal	FATAL	Underlying interstitial lung disease
	Placebo	[redacted]	Nintedanib	7[redacted]/M	422	422	1	Grade 5	No	NoChg	No	Fatal	FATAL	Underlying interstitial lung disease
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Sudden death(突然死)	Placebo	[redacted]	Nintedanib	7[redacted]/M	136	136	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Infections and infestations(感染症および寄生虫症) Influenza(インフルエンザ)	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	233	233	1	Grade 5	No	NA	No	Fatal	FATAL	Pneumonia
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Residual effect	[redacted]	None	5[redacted]/M	15	15	1	Grade 5	No	NA	No	Fatal	FATAL	Pneumonia

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REQ/PROL HSP=Requires or Prolongs Hospitalization, CONG AB=Congenital Anomaly or Birth Defect, NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Residual effect	[redacted]	Nintedanib	[redacted]/F	533	533	1	Grade 5	Yes	NA	No	Fatal	FATAL	Pneumonia
Infections and infestations(感染症および寄生虫症) Septic shock(敗血症性ショック)	Residual effect	[redacted]	Pirfenidone	[redacted]/M	431	431	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Infection (including sepsis)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Ductal adenocarcinoma of pancreas(膵腺管癌)	Residual effect	[redacted]	None	[redacted]/M	303	387	85	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP/OTHER	Malignancy (new or worsening)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Hodgkin's disease(ホジキン病)	Placebo	[redacted]	Pirfenidone	[redacted]/M	180	209	30	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP/OTHER	Malignancy (new or worsening)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Metastases to bone(骨転移)	Placebo	[redacted]	None	[redacted]/M	136	171	36	Grade 5	No	NoChg	No	Fatal	FATAL	Malignancy (new or worsening)

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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Encephalopathy(脳症)	Placebo	[redacted]	Pirfenidone	8[redacted]/M	359	426	68	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Undetermined
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Acute respiratory failure(急性呼吸不全)	Residual effect	[redacted]	None	8[redacted]/M	38	39	2	Grade 5	Yes	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Interstitial lung disease(間質性肺疾患)	Placebo	[redacted]	Nintedanib	7[redacted]/M	405	420	16	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Respiratory failure(呼吸不全)	Placebo	[redacted]	Nintedanib	7[redacted]/M	284	284	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Vascular disorders(血管障害) Hypovolaemic shock(血液量減少性ショック)	Placebo	[redacted]	None	7[redacted]/M	188	192	5	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined

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REQ/PROL HSP=Requires or Prolongs Hospitalization, CONG AB=Congenital Anomaly or Birth Defect, NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Cardiac disorders(心臓障害) Acute myocardial infarction(急性心筋梗塞)	Nera 9mg bid	[redacted]	Pirfenidone	5[redacted]/M	383	383	1	Grade 5	No	NA	Yes	Fatal	FATAL	Acute myocardial infarction
Cardiac disorders(心臓障害) Cardiac arrest(心停止)	Residual effect	[redacted]	Nintedanib	6[redacted]/M	16	16	1	Grade 5	Yes	NA	Yes	Fatal	FATAL	Sudden cardiac death
Cardiac disorders(心臓障害) Cardiogenic shock(心原性ショック)	Nera 9mg bid	[redacted]	None	8[redacted]/F	278	279	2	Grade 5	No	NA	No	Fatal	FATAL	Undetermined
Cardiac disorders(心臓障害) Ischaemic cardiomyopathy(虚血性心筋症)	Nera 9mg bid	[redacted]	Nintedanib	6[redacted]/M	362	363	2	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Sudden cardiac death
	Nera 9mg bid	[redacted]	Pirfenidone	8[redacted]/M	501	503	3	Grade 5	No	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
Cardiac disorders(心臓障害) Ventricular fibrillation(心室細動)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/M	215	215	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Nera 9mg bid	[redacted]	Pirfenidone	6[redacted]/M	427	434	8	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Underlying interstitial lung disease
	Residual effect	[redacted]	Pirfenidone	5[redacted]/M	517	517	1	Grade 5	Yes	NA	No	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease

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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Death(死亡)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	506[a]			Grade 5	No	NA	No	Fatal	FATAL	Undetermined
Infections and infestations(感染症および寄生虫症) Pneumonia bacterial(細菌性肺炎)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	356	358	3	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Infections and infestations(感染症および寄生虫症) Pneumonia haemophilus(ヘモフィルス性肺炎)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	8	20	13	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Infections and infestations(感染症および寄生虫症) Pneumonia(肺炎)	Nera 9mg bid	[redacted]	Pirfenidone	7[redacted]/F	21	21	1	Grade 5	No	NA	No	Fatal	FATAL	Pneumonia
	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	17	35	19	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
	Residual effect	[redacted]	Pirfenidone	7[redacted]/M	451	451	1	Grade 5	No	NA	No	Fatal	FATAL	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Lung neoplasm malignant(肺の悪性新生物)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	187	304	118	Grade 5	No	Withdr	No	Fatal	FATAL/OTHER	Malignancy (new or worsening)

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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Nervous system disorders(神経系障害) Central nervous system haemorrhage(中枢神経系出血)	Residual effect	[redacted]	Nintedanib	8[redacted]/M	208	211	4	Grade 5	No	NA	No	Fatal	FATAL/DISABL/REQ/PROL HSP	Hemorrhagic stroke
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Chronic respiratory failure(慢性呼吸不全)	Nera 9mg bid	[redacted]	None	7[redacted]/M	360	365	6	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypercapnia(高炭酸ガス血症)	Nera 9mg bid	[redacted]	Nintedanib	7[redacted]/M	414	423	10	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Hypoxia(低酸素症)	Residual effect	[redacted]	None	8[redacted]/M	54	66	13	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	129	129	1	Grade 5	No	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax(気胸)	Residual effect	[redacted]	Nintedanib	5[redacted]/M	308	388	81	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease

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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
General disorders and administration site conditions(一般・全身障害および投与部位の状態) Condition aggravated(状態悪化)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	376	378	3	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	4	43	40	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	29	31	3	Grade 5	No	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
	Nera 18mg bid	[redacted]	None	7[redacted]/M	425	442	18	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	7[redacted]/M	522	522	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
Infections and infestations(感染症および寄生虫症) COVID-19(ＣＯＶＩＤ－１９)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/M	337	357	21	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Acute leukaemia(急性白血病)	Nera 18mg bid	[redacted]	Nintedanib	7[redacted]/M	375	406	32	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Malignancy (new or worsening)

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Seq=Recovered or Resolved with Sequelae, UNK=Unknown. LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,
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MedDRA version used for reporting: 27.1

Listing 12.5.2.8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adjudi-cation Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps)(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）) Lung cancer metastatic(遠隔転移を伴う肺癌)	Nera 18mg bid	[redacted]	Pirfenidone	6[redacted]/F	385	395	11	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Malignancy (new or worsening)
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Idiopathic pulmonary fibrosis(特発性肺線維症)	Residual effect	[redacted]	Nintedanib	7[redacted]/M	291	291	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Respiratory, thoracic and mediastinal disorders(呼吸器、胸郭および縦隔障害) Pneumothorax(気胸)	Nera 18mg bid	[redacted]	Pirfenidone	7[redacted]/M	287	315	29	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Vascular disorders(血管障害) Arteriosclerosis(動脈硬化症)	Nera 18mg bid	[redacted]	None	6[redacted]/M	169[a]	397		Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death

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4.3　国際共同第 III 相試験（1305-0023 試験［評価資料：CTD 5.3.5.1-03-01］）

4.3.1　計画

4.3.1.1　治験名

A double blind, randomised, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)

4.3.1.2　治験実施施設

北米，南米，欧州，アフリカ，アジア，中東及びオセアニアの 44 カ国，403 施設

4.3.1.3　公表文献

なし（2025 年 4 月時点）

4.3.1.4　治験フェーズ

第 III 相

4.3.1.5　目的

本治験の目的は，標準治療を受けている進行性線維化を伴う間質性肺疾患（PF-ILD）（進行性肺線維症［PPF］）患者を対象に，BI 1015550（ネランドミラスト［以下，本薬］）9 mg 1 日 2 回又は 18 mg 1 日 2 回投与を追加投与したときの有効性及び安全性をプラセボと比較評価することであった。

4.3.1.6　方法

本治験は，PPF 患者を対象とした多施設共同，ランダム化，二重盲検，プラセボ対照，プロスペクティブ，国際共同第 III 相試験であり，52 週間以上の投与期及び 7 日間の追跡調査期で構成された。被験者を本薬 9 mg 1 日 2 回経口投与，本薬 18 mg 1 日 2 回経口投与，又はプラセボ 1 日 2 回経口投与に 1:1:1 の比で割り付けた。ベースライン時の抗線維化薬（AF）（ニンテダニブ）使用の有無及び高分解能コンピュータ断層撮影（HRCT）パターン（通常型間質性肺炎［UIP］又は UIP 様の線維化パターン，その他の線維化パターン）を層別因子として割り付けた。本治験は，ランダム割付けから 52 週時までの Part A と，ランダム割付け及び盲検化された治験薬の投与を 52 週以降も継続する Part B で構成された。最後にランダム割付けされた被験者が 52 週時の評価を完了した時点で，初回データベースロック（DBL1）（20[redacted] 年[redacted] 月[redacted] 日）に基づき本治験の主要解析を実施した。すべての被験者が治験薬投与終了（EOT）Visit 及び治験終了（EOS）Visit（該当する場合に実施）を完了するまで治験を継続する。その後最終データベースロック（DBL2）後に治験全体のデータに基づく最終解析を実施する。

4.3.1.7　被験者数

計画時：組入れ 1041 名

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解析時：スクリーニング 1780 名，組入れ 1178 名

組入れ被験者数，投与被験者数及び主要評価項目の解析対象被験者数：

	組入れ	投与	解析 [1]
本薬 9 mg 群	393 名	393 名	393 名
本薬 18 mg 群	392 名	391 名	391 名
プラセボ群	393 名	392 名	392 名

1　最大の解析対象集団（FAS）

4.3.1.8　診断

治験対象集団は，HRCT で肺線維症が確認され，スクリーニング前の 24 カ月以内に事前に規定した基準（努力肺活量［FVC］の予測値に対する割合［%FVC］の臨床的に意味のある低下，呼吸器症状の悪化，及び画像上での線維化範囲の増加の組合せ）に基づく進行が確認された PPF/PF-ILD 患者とし，HRCT パターンは中央判定により確認された。「PPF」の用語は，米国胸部医学会/欧州呼吸器学会/日本呼吸器学会/ラテンアメリカ胸部医学会（ATS/ERS/JRS/ALAT）による 2022 年改訂の診断ガイドライン［CTD 5.4-40_P22-03204］に沿った適応症を表現するために選択した。「PPF」と「PF-ILD」は同義として使用した。

4.3.1.9　主な組入れ基準

同意書に署名した時点の年齢が 18 歳以上の IPF 以外の PPF 患者を組み入れた。スクリーニングでの%FVC が 45%以上，ヘモグロビン（Hb）で補正した一酸化炭素肺拡散能（DLCO）の予測値に対する割合（%DLCO）が 25%以上であることとした。スクリーニング時点で 12 週間以上ニンテダニブによる安定した治療を受けている患者，若しくは 8 週間以上ニンテダニブによる治療を受けていない患者を組み入れた。全身性の基礎疾患のため，許容された免疫抑制剤（コルチコステロイドを除く）を使用している患者は，スクリーニング前の 12 週間以上及びスクリーニング期に安定した治療を受けていることとした。

4.3.1.10　治験薬

BI 被験薬　本薬 C1 製剤：フィルムコート錠
用量：9 mg 又は 18 mg 1 日 2 回
投与方法：経口投与

対照薬　本薬に対応するプラセボ：フィルムコート錠
用量：該当なし，1 日 2 回
投与方法：経口投与

4.3.1.11　投与期間

Part A：52 週間

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Part B：52 週以降，ランダム割付け及び盲検化された治験薬の投与の継続

Part A を含めた最大総投与期間は DBL1 で 25.0 カ月であった。

4.3.1.12　有効性/臨床薬理に関する評価基準

主要評価項目は，52 週時の FVC（mL）のベースラインからの絶対変化量であった。

重要な副次評価項目は複合評価項目であり，治験期間中に ILD の初回急性増悪，呼吸器疾患による初回入院，又は死亡のいずれかが最初に発生するまでの期間であった。

他の副次評価項目は，以下のとおりであった。

- 治験期間中の ILD の初回急性増悪又は死亡までの期間
- 治験期間中の呼吸器疾患による入院又は死亡までの期間
- 治験期間中の死亡までの期間
- 52 週時の%FVC のベースラインからの絶対変化量
- 治験期間中の%FVC のベースラインから 10%超（絶対変化量）の低下又は死亡までの期間
- 52 週時の%DLCO（Hb 補正）のベースラインからの絶対変化量
- 治験期間中の%DLCO（Hb 補正）のベースラインから 15%超（絶対変化量）の低下又は死亡までの期間
- 52 週時の Living with Pulmonary Fibrosis（L-PF）Symptoms 呼吸困難ドメインスコアのベースラインからの絶対変化量
- 52 週時の L-PF Symptoms 咳嗽ドメインスコアのベースラインからの絶対変化量
- 52 週時の L-PF Symptoms 疲労ドメインスコアのベースラインからの絶対変化量

その他の有効性評価項目には，FVC，DLCO，安静時酸素飽和度（SpO_2）及び L-PF 評価に基づく評価項目，複合評価項目の構成要素，非待機的入院，救援治療の使用，並びに L-PF 質問票に基づく酸素療法の使用が含まれた。

その他の評価項目として，本薬の定常状態での投与前の血漿中濃度（$C_{pre,ss}$）を評価した。

4.3.1.13　安全性に関する評価基準

安全性は，有害事象，特に注目すべき有害事象（AESI），並びに非臨床試験でみられた毒性所見，他のホスホジエステラーゼ（PDE）4 阻害薬の重要な潜在的リスク又は特定されたリスク，及び本薬の作用機序に基づく特記すべき安全性に関する項目に基づき評価した。治験実施計画書で「potential severe drug induced liver injury (DILI)」，「vasculitis」，「severe, serious, opportunistic, or *Mycobacterium tuberculosis* infections」，「new onset of severe depression」及び「new onset of severe anxiety」を AESI として事前に規定した。死亡した被験者の主な死因, 主要心血管イベント（MACE）及び血管炎イベントとして分類されたすべての有害事象を独立判定委員会が盲検下で判定した。自殺及び下痢について，事前に規定された追加解析を実施した。また，身体所見，臨床検査値及びバイタルサインの臨床的に問題となる所見又は変化を評価した。

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4.3.1.14　解析方法

主要評価項目の主要ストラテジーは，肺移植及び死亡以外のすべての中間事象を治療方針（treatment policy）ストラテジーに従って取り扱うアプローチに基づいた。肺移植は仮想アプローチ，死亡は複合アプローチで取り扱った。主要解析は，ランダム割付けされ，治験薬を 1 回以上投与されたすべての被験者を含む，最大の解析対象集団（FAS）を対象として実施した。主要解析では，混合効果反復測定モデル（MMRM）に基づく制限付き最尤法（REML）により，52 週時の FVC のベースラインからの変化量を投与群間で比較した。解析には，各 Visit 時の治療（カテゴリー変数）の効果，各 Visit 時のベースライン時の AF 投与（カテゴリー変数）の効果，各 Visit 時のベースライン時の HRCT パターン（カテゴリー変数）の効果及び各 Visit 時のベースライン時の FVC（連続変数）の効果を固定効果として含めた。Visit は反復測定とし，被験者内誤差のモデリングには無構造の共分散構造を用いた。肺移植後のデータは除外し，データは missing at random であると仮定し，MMRM で取り扱った。52 週時の解析対象期間の終了前に死亡し，肺移植を受けていなかった被験者の場合，死亡イベント発生日の当日又はそれ以降の Visit の FVC のベースラインからの変化量の欠測に対し，各投与群での各 Visit 時のすべての測定値（FVC のベースラインからの変化量）の 10 パーセンタイル値に基づき補完した。

主要評価項目と同様に，副次評価項目及びその他の有効性評価項目の解析は FAS を対象として実施した。

重要な副次評価項目の主要ストラテジーは，治療方針（treatment policy）ストラテジー（肺移植は除く）に従って取り扱い，治験期間全体のデータを用いた。

治験期間中にイベントが発生しなかった被験者は，イベントが認められないことが確認された最後の日で打ち切りとした。肺移植を受けた被験者は，肺移植を受けた時点で打ち切りとした。主要解析には，治療，ベースライン時の AF 投与，ベースライン時の HRCT パターン，年齢（連続変数），ベースライン時の%FVC 及びベースライン時の%DLCO（Hb 補正）を共変量として含めた Cox 比例ハザードモデルを用いた。本薬群のプラセボに対するハザード比の検定には，Wald 検定を用いた。グラフィカルアプローチによる検定手順を用いて，本薬の両用量を主要評価項目及び重要な副次評価項目について検定した。他の副次評価項目及びその他の有効性評価項目は探索的であり，多重性の調整は行わなかった。

4.3.2　結果

4.3.2.1　治験対象及び治験実施計画書の遵守状況

全体で 1780 名の被験者がスクリーニングされ，このうち 1178 名が 1:1:1 の比でプラセボの 1 日 2 回投与（393 名），本薬 9 mg の 1 日 2 回投与（393 名）又は本薬 18 mg の 1 日 2 回投与（392 名）のいずれかにランダム割付けされた。ランダム割付けされた被験者の多くがアジア（37.1%）及び欧州（32.5%）からの被験者であり，次いで西半球（米国を除く）（15.4%）及び米国（11.8%）からの被験者であった。適格基準に合致していなかった 2 名を除く 1176 名が治験薬の投与を受けた。

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ランダム割付けされ，治験薬の投与を受けた被験者の過半数が男性であった（男性 55.6%，女性 44.4%）。ほとんどの被験者が白人（58.2%）又はアジア人（アジア人，アメリカインディアン又はアラスカ先住民，及びハワイ先住民又は他の太平洋諸島民を含む）（39.1%）であった。黒人又はアフリカ系アメリカ人が 16 名（1.4%），マルチレイシャルが 15 名（1.3%）であった。被験者の平均年齢は 66.4 歳（標準偏差［SD］：10.0）であった。

初回の ILD 診断からの期間の中央値は，2.9 年（第 1 四分位数，第 3 四分位数：1.4，5.8）であった。ベースライン時に AF を使用していた被験者は 514 名（43.7%）であった。PPF を適応症として唯一承認されている治療薬であるニンテダニブをベースライン時に使用していた被験者は 512 名（43.5%）であった。ベースライン時にピルフェニドンを使用していた被験者は 2 名（0.2%）であり，治験実施計画書からの重要な逸脱として分類されたが，事前に規定したとおり治験を継続し，解析ではベースライン時にニンテダニブ使用ありの層に含めた。ベースライン時までのニンテダニブ使用（ピルフェニドンを使用していた 2 名を含む）の平均期間は，18.2 カ月（SD：17.8）であった。ベースライン時にニンテダニブ又はピルフェニドンを使用していなかった被験者は 662 名（56.3%）であり，この大部分（521 名，全体集団の 44.3%）は AF の使用歴のない被験者であった。ベースライン時に酸素療法を使用していた被験者の割合は 27.6%であり，ベースライン時に免疫抑制剤を使用していた被験者の割合は 24.1%であった。

ベースライン時に HRCT で UIP 又は UIP 様の線維化パターンが認められた被験者は 840 名（71.4%），その他の線維化パターンが認められた被験者は 336 名（28.6%）であった。最もよくみられた ILD 臨床診断の分類は自己免疫性 ILD（325 名［27.6%］）であり，次いで過敏性肺臓炎（233 名［19.8%］），分類不能型特発性間質性肺炎（231 名［19.6%］），特発性非特異的間質性肺炎（228 名［19.4%］），その他の ILD（159 名［13.5%］）であった。被験者の大部分（87.2%）は，ATS/ERS/JRS/ALAT による 2022 年改訂の診断ガイドラインに基づく PPF の基準を満たしていた。ベースラインの平均値は，%FVC が 70.1%（SD：15.8），%DLCO（Hb 補正）が 49.3%（SD：16.9）であった。これらのデータは投与群間でおおむね同様であった。

ベースライン時にニンテダニブ使用なしの集団と比較して，ニンテダニブ使用ありの集団では酸素療法を使用していた被験者の割合が 2 倍であり，%DLCO が低かった。ベースライン時にその他の線維化パターンの集団と比較して，UIP 又は UIP 様の線維化パターンの集団では酸素療法を使用していた被験者の割合が低く，%FVC が高かった。

本治験の主要解析（DBL1）は，最後にランダム割付けされた被験者が 52 週時の評価を完了した時点で実施した。

DBL1

52 週時までに計画された治験薬の投与を完了した被験者は，治験薬の投与を受けた 1176 名中 952 名（81.0%）であった。また，計画された主要評価項目のための観察を完了した被験者は，1064 名（90.5%）（52 週時の FVC の値が得られている被験者 975 名，肺移植を受けた被験者 15 名，及び死亡した被験者 80 名）であった。

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DBL1 までに計画された治験薬の投与を完了した被験者（DBL1 で治験薬投与継続中）は，867 名（73.7%）であった。DBL1 までに治験薬の投与を中止した被験者（26.3%）の中止理由は，有害事象（11.3%）が最も多く，次いで，被験者の意向による投与中止（8.1%）及びその他（6.4%）であった。また，DBL1 までに計画された観察を完了した被験者は，1123 名（95.5%）であった。その内訳は，DBL1 で治験薬投与継続中の被験者 995 名（84.6%），肺移植を受けた被験者 21 名（1.8%），及び死亡した被験者 107 名（9.1%）であった。投与群別では，DBL1 までに死亡した被験者の割合が本薬群で低く，本薬 18 mg 群で最も低かったが（プラセボ群 12.8%，本薬 9 mg 群 8.4%，本薬 18 mg 群 6.1%），これ以外の被験者の内訳については投与群間で同様であった。

治験薬を 52 週間（12 カ月）以上投与された被験者の割合は 80%超であった。DBL1 までの平均投与期間は，約 14 カ月（SD：5.3 カ月）であり，DBL1 までの投与期間が 15 カ月以上であった被験者の割合は約 53%であった。DBL1 までの投与期間の最大値は 25 カ月であった。投与期間のデータは投与群間で同様であった。DBL1 までの平均観察期間は，すべての投与群で約 15.4 カ月（SD：4 カ月）であった。

DBL1 までに治験実施計画書の重要な逸脱に該当した被験者の割合（全体集団の 17.3%）は，投与群間で同様であった。最もよくみられた治験実施計画書の重要な逸脱は，ランダム割付けから EOT までの期間中の prednisone 15 mg/日超又は他のステロイドであれば prednisone 換算で 15 mg/ 日超の使用（5.1%）であった。

4.3.2.2 有効性/臨床薬理

主要評価項目及び重要な副次評価項目

DBL1

主要評価項目は，52 週時の FVC（mL）のベースラインからの絶対変化量である。52 週時の FVC（mL）のベースラインからの調整済み平均絶対変化量は，プラセボ群−165.8 mL（95%信頼区間［CI］：−190.5〜−141.0），本薬 9 mg 群−84.6 mL（95% CI：−109.6〜−59.7），本薬 18 mg 群−98.6 mL（95% CI：−123.7〜−73.4）であった（表 4.3.2.2: 1）。以下に示すとおり，本薬 9 mg 群及び本薬 18 mg 群とプラセボ群との投与群間差はいずれも統計学的に有意であった。52 週時の FVC（mL）のベースラインからの絶対変化量のプラセボ群との調整済み平均値の差は，本薬 9 mg 群では 81.1 mL（95% CI：46.0〜116.3，p<0.0001），本薬 18 mg 群では 67.2 mL（95% CI：31.9〜102.5，p=0.0002）であった。

全体の第一種の過誤確率を 5%に保つためのグラフィカルアプローチによる検定手順に基づき，主要評価項目について，両用量で本薬のプラセボに対する優越性が示された（本薬 18 mg 群 p=0.0002 であり，最初に割り振られた α=0.04 を下回った；本薬 9 mg 群 p<0.0001 であり，更新された α=0.03 を下回った）。

FVC（mL）のベースラインからの調整済み平均絶対変化量の推移から，本薬 9 mg 群及び本薬 18 mg 群でランダム割付け後早期の 2 週時からプラセボ群と比較して FVC 低下抑制が認められ，52 週時まで維持された。FVC（mL）のベースラインからの調整済み平均絶対変化量の経時推移は，本薬 9 mg 群と本薬 18 mg 群でほぼ重複していた。

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事前に規定したすべての解析及びベースライン時にピルフェニドンを使用していた 2 名を除外した事後解析（本薬［薬理学的活性のある R 体のエナンチオマー］の投与前血漿中濃度を約 50%減少させる薬物相互作用を考慮）を含む，感度分析及び補足解析のすべての結果が，主要評価項目の主要解析の結果と一貫していた。

表 4.3.2.2: 1　　52 週時の FVC（mL）のベースラインからの絶対変化量－FAS（DBL1）

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
All patients (primary analysis), N analysed	391		390		390	
Baseline (mean, SD)	2353.6	766.2	2325.5	767.6	2381.4	722.8
Week 52 change from baseline						
Adjusted mean (95% CI)	−165.8	(−190.5, −141.0)	−84.6	(−109.6, −59.7)	−98.6	(−123.7, −73.4)
Comparison vs. placebo						
Adjusted mean (95% CI)	--		81.1	(46.0, 116.3)	67.2	(31.9, 102.5)
p-value			<0.0001		0.0002	

bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
引用元：CTD 5.3.5.1-03-01_1305-0023 試験_c43862464_Table 15.2.1.1: 1

主要評価項目の治療効果は，人口統計学的特性，ベースライン時の疾患特性（ILD 臨床診断の分類及び HRCT パターンを含む）及びベースライン時のニンテダニブ使用状況別に事前に規定した部分集団で，両用量の本薬群でおおむね一貫していた。本薬（9 mg 及び 18 mg の 1 日 2 回投与）の治療効果はベースライン時のニンテダニブ使用状況別の両部分集団で認められ，52 週時の FVC 減少量のプラセボ群に対する相対的な低下抑制率は同程度であった（両部分集団の両用量で 38%～51%）（表 4.3.2.2: 2）。全体として，ベースライン時の HRCT パターン別の両部分集団で，本薬（9 mg 及び 18 mg の 1 日 2 回投与）の治療効果は一貫していた。本薬 9 mg 群では，プラセボ群に対する治療効果は両部分集団で同様であった。本薬 18 mg 群では，両部分集団でプラセボ群に対して良好な治療効果が認められ，UIP 又は UIP 様の線維化パターンの集団と比較してその他の線維化パターンの集団で数値的に大きいことが示唆された（交互作用の p 値は 0.0384）（表 4.3.2.2: 3）。

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表 4.3.2.2: 2　ベースライン時のニンテダニブ使用状況別の 52 週時の FVC（mL）のベースラインからの絶対変化量－FAS（DBL1）

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients without background nintedanib therapy, N analysed	222		217		220	
Baseline (mean, SD)	2264.1	739.8	2243.7	758.6	2354.0	715.0
Week 52 change from baseline						
Adjusted mean (95% CI)	−154.1	(−187.1, −121.2)	−82.3	(−115.9, −48.8)	−95.2	(−128.6, −61.9)
Comparison vs. placebo						
Adjusted mean (95% CI)	--		71.8	(24.9, 118.8)	58.9	(12.1, 105.8)
Patients with background nintedanib therapy, N analysed	169		173		170	
Baseline (mean, SD)	2470.6	786.3	2429.6	768.7	2416.6	733.4
Week 52 change from baseline						
Adjusted mean (95% CI)	−180.9	(−218.6, −143.2)	−87.8	(−125.4, −50.2)	−102.9	(−141.2, −64.5)
Comparison vs. placebo						
Adjusted mean (95% CI)	--		93.1	(39.9, 146.3)	78.0	(24.2, 131.8)

bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
ベースライン時のニンテダニブ使用状況別の部分集団と投与群との交互作用は p=0.5555（本薬 9 mg 群 vs. プラセボ群）及び p=0.5997（本薬 18 mg 群 vs. プラセボ群）
引用元：CTD 5.3.5.1-03-01_1305-0023 試験_c43862464_Table 15.2.1.3.6: 1

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表 4.3.2.2: 3　ベースライン時の HRCT パターン別の 52 週時の FVC（mL）のベースラインからの絶対変化量－FAS（DBL1）

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients with UIP or UIP-like fibrotic pattern on baseline HRCT, N analysed	274		288		274	
Baseline (mean, SD)	2450.4	748.9	2364.5	751.9	2451.9	740.2
Week 52 change from baseline						
Adjusted mean (95% CI)	−156.4	(−185.9, −126.9)	−72.4	(−101.2, −43.7)	−113.3	(−143.3, −83.4)
Comparison vs. placebo						
Adjusted mean (95% CI)	--		83.9	(42.7, 125.1)	43.0	(1.1, 85.0)
Patients with other fibrotic patterns on baseline HRCT, N analysed	117		102		116	
Baseline (mean, SD)	2126.3	761.4	2215.9	804.1	2214.1	653.0
Week 52 change from baseline						
Adjusted mean (95% CI)	−188.7	(−234.3, −143.1)	−119.7	(−169.6, −69.7)	−64.1	(−110.3, −18.0)
Comparison vs. placebo						
Adjusted mean (95% CI)	--		69.02	(1.5, 136.5)	124.6	(59.9, 189.3)

bid：1 日 2 回投与，N：number，Nera：ネランドミラスト
ベースライン時の HRCT パターンによる部分集団と投与群との交互作用は p=0.7118（本薬 9 mg 群 vs. プラセボ群）及び p=0.0384（本薬 18 mg 群 vs. プラセボ群）
引用元：CTD 5.3.5.1-03-01_1305-0023 試験_c43862464_Table 15.2.1.3.8: 1

重要な副次評価項目は検証的な評価項目であり，DBL1 までの治験期間中に ILD の初回急性増悪，呼吸器疾患による初回入院，又は死亡のいずれかが最初に発生するまでの期間である。重要な副次評価項目のイベントが発生した被験者は，プラセボ群 122 名（31.1%），本薬 9 mg 群 110 名（28.0%），本薬 18 mg 群 95 名（24.3%）であり，プラセボ群と比較して本薬 9 mg 群及び本薬 18 mg 群で数値的に少なく，本薬 18 mg 群で最も少なかった。重要な副次評価項目への寄与が最も大きかったイベントは，呼吸器疾患による入院であり，重要な副次評価項目の最初に発生したイベントの半数を超えた。重要な副次評価項目について，プラセボ群に対するハザード比は本薬 9 mg 群で 0.88（95% CI：0.68～1.14，p=0.3398），本薬 18 mg 群で 0.77（95% CI：0.59～1.01，p=0.0602）であり，イベント発生リスクはプラセボ群と比較して両用量の本薬群で数値的に低く，本薬 18 mg 群で最も低かったが，プラセボ群と比較して両用量の本薬群で統計学的な有意差は認められなかった。

事前に規定したすべての解析及びベースライン時にピルフェニドンを使用していた 2 名を除外した事後解析を含む，感度分析及び補足解析のすべての結果が，重要な副次評価項目の主要解析の結果と一貫していた。

重要な副次評価項目の結果は，部分集団間でおおむね一貫していた。重要な副次評価項目について，ニンテダニブ使用なしの集団で，プラセボ群に対するハザード比は本薬 9 mg 群で 0.78（95% CI：0.55～1.11），本薬 18 mg 群で 0.70（95% CI：0.49～1.01）であった。ニンテダニブ使用あり

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の集団で，プラセボ群に対するハザード比は本薬 9 mg 群で 1.02（95% CI：0.69～1.50），本薬 18 mg 群で 0.87（95% CI：0.58～1.30）であった。交互作用の p 値は本薬の治療効果が部分集団間で異なることを示唆するものではなかった（本薬 9 mg 群とプラセボ群との比較：p=0.3157，本薬 18 mg 群とプラセボ群との比較：p=0.4513）。

重要な副次評価項目について，ベースライン時の HRCT パターンが UIP 又は UIP 様の線維化パターンであった集団で，プラセボ群に対するハザード比は本薬 9 mg 群で 0.82（95% CI：0.60～1.12），本薬 18 mg 群で 0.81（95% CI：0.59～1.12）であった。ベースライン時の HRCT パターンがその他の線維化パターンであった集団で，プラセボ群に対するハザード比は本薬 9 mg 群で 1.07（95% CI：0.67～1.71），本薬 18 mg 群で 0.68（95% CI：0.41～1.12）であった。交互作用の p 値は本薬の治療効果が部分集団間で異なることを示唆するものではなかった（本薬 9 mg 群とプラセボ群との比較：p=0.3480，本薬 18 mg 群とプラセボ群との比較：p=0.5533）。

<u>その他の有効性の副次評価項目</u>

検証的検定は重要な副次評価項目で中止した。他の副次評価項目及びその他の有効性評価項目のすべての解析は記述的であり，投与群間の比較での p 値は名目上の値とみなし，検定の多重性は調整しなかった。

<u>DBL1</u>

DBL1 までの治験期間中に ILD の急性増悪が認められた又は死亡した被験者の割合は，プラセボ群 21.2%，本薬 9 mg 群 16.5%，本薬 18 mg 群 12.3%であった。本薬 18 mg 群では，プラセボ群に対するハザード比は 0.59（95% CI：0.41～0.84）であり，ILD の急性増悪又は死亡のリスクは 41%低下した。本薬 9 mg 群では，プラセボ群に対するハザード比は 0.78（95% CI：0.56～1.08）であり，ILD の急性増悪又は死亡のリスクは数値的に低下した。

DBL1 までの治験期間中に呼吸器疾患による入院が発生した又は死亡した被験者の割合は，プラセボ群 28.1%，本薬 9 mg 群 24.7%，本薬 18 mg 群 21.5%であった。本薬 18 mg 群では，プラセボ群に対するハザード比は 0.75（95% CI：0.56～1.00）であり，呼吸器疾患による入院又は死亡のリスクはプラセボ群と比較して 25%低下した。本薬 9 mg 群では，プラセボ群に対するハザード比は 0.83（95% CI：0.63～1.10）であり，呼吸器疾患による入院又は死亡のリスクは数値的に低下した。

DBL1 までの治験期間中に死亡した被験者は，プラセボ群 50 名（12.8%），本薬 9 mg 群 33 名（8.4%）及び本薬 18 mg 群 24 名（6.1%）であった。本薬 9 mg 群では，プラセボ群に対するハザード比は 0.60（95% CI：0.38～0.95）であり，死亡のリスクはプラセボ群と比較して 40%低下した。本薬 18 mg 群では，プラセボ群に対するハザード比は 0.48（95% CI：0.30～0.79）であり，死亡のリスクはプラセボ群と比較して 52%低下した。呼吸器系が主な死因と判定された割合が高く（独立判定委員会により判定された 97 件の死亡のうち 66.0%），呼吸器系の死亡の減少が，プラセボ群と比較して本薬群で死亡のリスク低下が認められたことの主な要因であった。

52 週時の%FVC のベースラインからの調整済み平均絶対変化量は，プラセボ群−4.88%（95% CI：−5.61～−4.15），本薬 9 mg 群−2.69%（95% CI：−3.43～−1.95），本薬 18 mg 群−2.94%（95% CI：

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−3.68～−2.19）であった。52 週時の%FVC のベースラインからの絶対変化量のプラセボ群との調整済み平均値の差は，本薬 9 mg 群では 2.19%（95% CI：1.15～3.23），本薬 18 mg 群では 1.94%（95% CI：0.90～2.98）であった。

治験期間中に%FVC のベースラインからの 10%超（絶対変化量）の低下が発生した又は死亡した被験者の割合は，プラセボ群 36.2%，本薬 9 mg 群 27.7%，本薬 18 mg 群 27.4%であった。プラセボ群に対するハザード比は，本薬 9 mg 群で 0.71（95% CI：0.55～0.91），本薬 18 mg 群で 0.74（95% CI：0.57～0.95）であった。

52 週時の%DLCO（Hb 補正）のベースラインからの調整済み平均絶対変化量は，プラセボ群−2.48%（95% CI：−3.89～−1.07），本薬 9 mg 群−3.38%（95% CI：−4.80～−1.96），本薬 18 mg 群−2.97%（95% CI：−4.40～−1.53）であった。52 週時の%DLCO（Hb 補正）のベースラインからの絶対変化量のプラセボ群との調整済み平均値の差は，本薬 9 mg 群では−0.90%（95% CI：−2.90～1.11），本薬 18 mg 群では−0.49%（95% CI：−2.50～1.53）であった。

治験期間中（12，26，52 週時，及び EOT 時）に%DLCO（Hb 補正）のベースラインからの 15%超（絶対変化量）の低下が発生した又は死亡した被験者の割合は，プラセボ群 18.6%，本薬 9 mg 群 17.3%，本薬 18 mg 群 15.6%であった。プラセボ群に対するハザード比は，本薬 9 mg 群で 0.89（95% CI：0.64～1.25），本薬 18 mg 群で 1.03（95% CI：0.73～1.45）であった。

52 週時の L-PF Symptoms ドメインスコアのベースラインからの調整済み平均絶対変化量（95% CI）は，投与群間で同様であった。

- 52 週時の L-PF Symptoms 呼吸困難ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 5.75（95% CI：4.04～7.46），本薬 9 mg 群 4.87（95% CI：3.15～6.58）及び本薬 18 mg 群 4.48（95% CI：2.76～6.20）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では−0.88（95% CI：−3.30～1.54），本薬 18 mg 群では−1.27（95% CI：−3.69～1.15）であった。
- 52 週時の L-PF Symptoms 咳嗽ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 3.05（95% CI：0.79～5.31），本薬 9 mg 群 1.17（95% CI：−1.09～3.44）及び本薬 18 mg 群 3.19（95% CI：0.92～5.46）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では−1.88（95% CI：−5.08～1.33），本薬 18 mg 群では 0.14（95% CI：−3.07～3.35）であった。
- 52 週時の L-PF Symptoms 疲労ドメインスコアのベースラインからの調整済み平均絶対変化量は，プラセボ群 2.95（95% CI：1.18～4.73），本薬 9 mg 群 3.01（95% CI：1.23～4.78）及び本薬 18 mg 群 3.89（95% CI：2.11～5.68）であった。プラセボ群との調整済み平均値の差は，本薬 9 mg 群では 0.05（95% CI：−2.46～2.57），本薬 18 mg 群では 0.94（95% CI：−1.58～3.46）であった。

<u>その他の有効性評価項目</u>

主要評価項目及び副次評価項目と同様の medical concept を検討したその他の有効性評価項目で，上記の結果とおおむね一貫した傾向がみられた。

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ベースライン時に酸素療法を使用していなかった被験者のうち，DBL1 までの治験期間中に酸素療法を使用した被験者の割合は，プラセボ群で 21.2%，本薬 9 mg 群で 17.5%，本薬 18 mg 群で 15.2%であった。プラセボ群に対するハザード比は，本薬 9 mg 群では 0.83（95% CI : 0.57～1.22），本薬 18 mg 群で 0.80（95% CI : 0.53～1.19）であり，プラセボ群と比較して本薬群で酸素療法の使用を開始するリスクが数値的に低かった。被験者全体を対象として，DBL1 までの治験期間中に酸素療法を増量（使用開始又は流量増加）した被験者の割合は，プラセボ群で 35.5%，本薬 9 mg 群で 30.5%，本薬 18 mg 群で 30.9%であった。プラセボ群に対するハザード比は，本薬 9 mg 群で 0.82（95% CI：0.64～1.04），本薬 18 mg 群で 0.87（95% CI：0.68～1.11）であり，プラセボ群と比較して本薬群で酸素療法を増量するリスクが数値的に低かった。ベースライン時に酸素療法を使用していた被験者を対象とした，DBL1 までの睡眠時，身体活動中又は安静時の酸素流量のベースラインからの平均絶対変化量について，投与群間で意義のある差異はみられなかった。被験者全体を対象とした場合も同様の結果であった。

ニンテダニブ（ベースライン時にニンテダニブ使用なしの場合）又は免疫抑制剤の初回使用までの期間，52 週時の安静時 SpO_2 のベースラインからの変化量の平均値，L-PF 総スコア，L-PF Impact スコア及び L-PF Symptoms ドメインスコアのベースラインからの絶対変化量，若しくは，L-PF スコアに基づく症状（咳嗽，呼吸困難又は疲労）の悪化までの期間に，投与群間で意義のある差異はみられなかった。

<u>臨床薬理</u>

本薬の薬理学的活性のある R 体のエナンチオマー（以下，R-BI 1015550）の定常状態における投与前血漿中濃度は，測定が行われた投与期間にわたって安定していた。R-BI 1015550 の定常状態での投与前血漿中濃度の投与期間全体を通じた幾何平均は，本薬 9 mg 群で 84.8 nmol/L，本薬 18 mg 群で 172 nmol/L であった。投与前血漿中濃度は，本薬 9 mg 群及び本薬 18 mg 群で用量に比例した。

R-BI 1015550 の投与前血漿中濃度は，白人被験者と比較して，アジア人被験者では，本薬 9 mg 群で約 43%，本薬 18 mg 群で約 10%高かった。R-BI 1015550 の投与前血漿中濃度は，正常な腎機能を有する被験者と比較して中等度の腎機能障害を有する被験者で高い傾向がみられた（本薬 9 mg 群：36%，本薬 18 mg 群：35%）。また，65 歳未満の被験者と比較して 65 歳以上の被験者で，本薬 18 mg 群で R-BI 1015550 の投与前血漿中濃度がやや（31%）高かった。

R-BI 1015550 の投与前血漿中濃度は，ベースライン時にニンテダニブを使用していた被験者と，ベースライン時に AF を使用していなかった被験者で同様であった。投与前血漿中濃度に基づく探索的な部分集団解析により，性別，民族（ヒスパニック系又はラテン系 vs ヒスパニック系又はラテン系以外），ニンテダニブ及び制酸薬の使用は R-BI 1015550 の曝露量に影響しないことが示された。

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4.3.2.3　安全性

DBL1

DBL1 までの治験期間中の有害事象の概要を表 4.3.2.3: 1 に示す。有害事象の発現割合は投与群間で同程度であった。重篤な有害事象の発現割合はプラセボ群と比較して本薬群で数値的に低かった。死亡に至った有害事象の発現割合はプラセボ群と比較して本薬群で低く，本薬 18 mg 群で最も低かった。重度の有害事象及び投与中止に至った有害事象の発現割合は，投与群間でおおむね同程度であった。

表 4.3.2.3: 1　有害事象の要約－ Treated set（DBL1）

Category of AEs	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0
Patients with any AE	369	94.1	369	93.9	364	93.1
Severe AEs (CTCAE grade >2)	146	37.2	139	35.4	145	37.1
AEs leading to permanent treatment discontinuation	46	11.7	39	9.9	44	11.3
Serious AEs	168	42.9	150	38.2	154	39.4
Resulted in death	29	7.4	18	4.6	8	2.1

AE：有害事象，bid：1 日 2 回投与，CTCAE：有害事象共通用語規準，N：number，Nera：ネランドミラスト，
SAE：重篤な有害事象
引用元：CTD 5.3.5.1-03-01_1305-0023 試験_c43862464_Table 15.3.1.1.1: 1

DBL1 までに最もよくみられた有害事象は，器官別大分類（SOC）では「感染症および寄生虫症」（プラセボ群 67.1%，本薬 9 mg 群 60.8%，本薬 18 mg 群 63.9%；以下同順）であり，次いで「胃腸障害」（44.6%，48.9%，51.7%）及び「呼吸器、胸郭および縦隔障害」（39.5%，35.4%，35.8%）であった。最もよくみられた有害事象は，基本語（PT）では下痢（25.0%，30.8%，36.6%）であり，次いで咳嗽（15.3%，13.5%，15.6%）及び上気道感染（16.1%，10.7%，13.0%）であった。下痢の発現割合は，プラセボ群と比較して本薬群で高く，本薬 18 mg 群で最も高かった。また，体重減少（6.6%，9.2%，12.5%）及び背部痛（2.8%，3.8%，6.4%）の発現割合もプラセボ群と比較して本薬群で高く，本薬 18 mg 群で最も高かった。悪心の発現割合はプラセボ群と比較して本薬群で高かった（7.1%，8.9%，11.0%）。

DBL1 までによくみられた重篤な有害事象は，SOC では「感染症および寄生虫症」（15.6%，13.0%，13.8%），「呼吸器、胸郭および縦隔障害」（14.8%，10.4%，8.4%）及び「一般・全身障害および投与部位の状態」（13.0%，10.2%，6.1%）であった。PT では，最もよくみられた重篤な有害事象は状態悪化（ILD の急性増悪又はその疑いを含む）（11.2%，8.9%，5.4%）であり，次いで肺炎（7.1%，7.6%，6.9%）であった。その他の重篤な有害事象の発現割合は，各投与群で 3%未満であった。死亡に至った有害事象の発現割合は，プラセボ群と比較して本薬群で低く，本薬 18 mg 群で最も低かった（7.4%，4.6%，2.1%）。PT では，最もよくみられた死亡に至った有害事象は状態悪化であり，本薬 18 mg 群で最も低かった（2.3%，1.3%，0.5%）。

よくみられた投与中止に至った有害事象は，状態悪化（3.1%，1.5%，1.5%），下痢（0.5%，1.5%，2.6%）及び呼吸困難（1.3%，0%，0%）であった。

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52 週時点までの有害事象の概要には，上記の DBL1 までと一貫した傾向がみられた。

特記すべき安全性に関する項目及び AESI に基づく medical concept

本治験では，medical concept を表す特記すべき安全性に関する項目について解析した。特記すべき安全性に関する項目の定義の詳細は［CTD 2.7.4_2.1.1.8.1 項］を参照のこと。この medical concept には，治験実施計画書で AESI と定義した事象及び独立判定委員会により判定された結果も含む。

DBL1

「Gastrointestinal symptoms」

特記すべき安全性に関する項目の「Gastrointestinal symptoms」の発現割合は，プラセボ群と比較して本薬群で高く，本薬 18 mg 群で最も高かった（32.7%，37.2%，43.0%）。この結果は PT の下痢に起因しており，下痢の発現割合はプラセボ群と比較して本薬群で高かった（25.0%，30.8%，36.6%）。下痢の重症度は，大多数の被験者で軽度又は中等度であり，ほとんどの被験者で治験薬の投与の中止に至らなかった。特記すべき安全性に関する項目の「Gastrointestinal symptoms」の下痢以外の PT 及び HLT（PT の嘔吐［6.1%，4.8%，6.7%］及び HLT の腹痛［5.6%，5.9%，6.4%］など）の発現割合は，投与群間で同程度であった。特記すべき安全性に関する項目の「Gastrointestinal symptoms」の下痢以外の PT である悪心の発現割合は，プラセボ群と比較して本薬群で高かった（7.1%，8.9%，11.0%）。

「Weight decrease」

特記すべき安全性に関する項目の「Weight decrease」の発現割合は，プラセボ群と比較して本薬群で高かった（6.6%，9.2%，12.5%）。特記すべき安全性に関する項目の「Weight decrease」全体で，重篤な有害事象は認められず，ほとんどの事象が治験薬の投与を中止することなく，回復した。特記すべき安全性に関する項目の「Weight decrease」の重症度は，プラセボ群の 3 名（0.8%）及び本薬 9 mg 群の 1 名（0.3%）で報告された体重減少が重度であったのを除き，軽度又は中等度であった。

体重の治験薬投与下の最終値におけるベースラインからの絶対変化量の平均値は，プラセボ群−2.0 kg（SD：4.8），本薬 9 mg 群−2.2 kg（SD：4.3），本薬 18 mg 群−3.1 kg（SD：4.9）であり，いずれの投与群でもベースラインからの減少がみられた。体重のベースラインからの最大相対変化率の平均値は，プラセボ群−4.9%（SD：5.3），本薬 9 mg 群−5.4%（SD：5.0）及び本薬 18 mg 群−6.0%（SD：5.5）であった。プラセボ群と本薬 18 mg 群の平均体重減少の乖離は投与開始後早期の 2 週目からみられ，投与 18 週以降の群間差の拡大はみられなかった。

その他の特記すべき安全性に関する項目

本薬の作用機序，他の PDE4 阻害薬の重要な潜在的リスク又は特定されたリスク（心血管イベント及び精神関連症状，「Vasculitis」，「Severe, serious and opportunistic infections」，「Malignancies」，

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並びに，独立判定委員会により判定された「Vasculitis」及び「MACE」）若しくは「Potential DILI」に，投与群間で臨床的に意義のある差は認められなかった。AESI として治験担当医師により報告された事象の発現割合は，投与群間で同程度であった（20.2%，18.6%，19.4%）。

部分集団別の有害事象

人口統計学的特性及びベースライン特性別の部分集団の有害事象は，DBL1 までの治験期間中の全般的な安全性プロファイルとおおむね一貫していた。ベースライン時にニンテダニブ使用ありの集団では，重篤な有害事象及び投与中止に至った有害事象の傾向及び発現割合は全体集団とおおむね同様であった。全体集団と同様に，ベースライン時のニンテダニブ使用状況にかかわらず，死亡に至った有害事象の発現割合は本薬 18 mg 群で最も低かった。ニンテダニブ使用なしの集団では，重度の有害事象の発現割合は本薬 18 mg 群で最も低かった。ニンテダニブ使用ありの集団では，重度の有害事象の発現割合はプラセボ群及び本薬 9 mg 群と比較して本薬 18 mg 群で高かった。ニンテダニブ使用なしの集団では，投与中断に至った有害事象の発現割合は投与群間でおおむね同様であった。ニンテダニブ使用ありの集団では，投与中断に至った有害事象の発現割合はプラセボ群と比較して本薬群で高く，本薬 18 mg 群で最も高かった。

ニンテダニブ使用状況にかかわらず，特記すべき安全性に関する項目の「Gastrointestinal symptoms」の有害事象（PT の「下痢」，「悪心」，「嘔吐」，「腹痛」）の発現割合は，ニンテダニブ使用なしの集団（19.8%，20.9%，33.6%）と比較してニンテダニブ使用ありの集団（49.4%，57.8%，55.0%）で高かった。

臨床検査値及びバイタルサイン

DBL1

上述の体重減少を除き，治験期間中に臨床検査値又はバイタルサインに臨床的に意義のある経時的な変化及び臨床的に意味のある投与群間差は認められなかった。また，治験期間中に肝酵素値の上昇がみられた被験者の割合は低く，投与群間でおおむね同様であった。

4.3.2.4　結論

本治験は，PPF 患者に単独又はニンテダニブによる安定した治療と併用して，本薬 9 mg 及び本薬 18 mg を 1 日 2 回，52 週間以上投与し，プラセボと比較検討した。52 週時でのベースラインからの FVC 低下は，プラセボ群と比較して本薬 9 mg 群及び本薬 18 mg 群で統計学的に有意に抑制された。ベースライン時のニンテダニブ使用状況別のニンテダニブ使用ありの集団とニンテダニブ使用なしの集団，ベースライン時の HRCT パターン別の UIP 又は UIP 様の線維化パターンの集団とその他の線維化パターンの集団，並びに，ILD 臨床診断の分類別の集団で，本薬の治療効果が認められた。主要解析までに，重要な副次評価項目のイベント（治験期間中に ILD の初回急性増悪，呼吸器疾患による初回入院，又は死亡のいずれかが最初に発生するまでの期間）が発生するリスクは，統計学的な有意差は認められなかったが，プラセボ群と比較して両用量の本薬群で数値的に低く，本薬 18 mg 群で最も低かった。重要な副次評価項目のすべての構成要素が，本薬

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群でプラセボ群と比較して数値的に良好な傾向に寄与していた。死亡のリスクは両用量の本薬群で低下し，これは主に呼吸器系の死因による死亡の減少に起因していた。本薬 18 mg 群では，ILD の初回急性増悪又は死亡のリスク，呼吸器疾患による初回入院又は死亡のリスクも低下した。

被験者のほぼ半数がベースライン時にニンテダニブを使用していたにもかかわらず，プラセボ群では 52 週間にわたって FVC が低下し, 死亡に至った有害事象の発現割合が高かったことから，PPF 患者に対する有効な治療薬のアンメットニーズが強く示唆された。

本薬の両用量は，ベースライン時のニンテダニブ使用の有無にかかわらず，許容可能な安全性及び忍容性プロファイルを示した。重度の有害事象及び投与中止に至った有害事象の発現割合は，投与群間でおおむね同程度であった。重篤な有害事象の発現割合はプラセボ群と比較して本薬群で低かった。死亡に至った有害事象の発現割合はプラセボ群と比較して本薬群で低く，本薬 18 mg 群で最も低かった。最もよくみられた重篤な有害事象及び死亡に至った有害事象は状態悪化（ILD の急性増悪又はその疑いを含む）であり，発現割合はプラセボ群と比較して本薬群で低く，本薬 18 mg 群で最も低かった。最もよくみられた有害事象は下痢であり，下痢の発現割合はプラセボ群と比較して本薬群で高く，本薬 18 mg 群で最も高かった。最もよくみられた治験担当医師により治験薬と因果関係ありと判断された有害事象は，いずれの投与群でも下痢であった。下痢により投与中止に至った被験者の割合はいずれの投与群でも低かったが，本薬 18 mg 群で最も高かった。全体として，本薬の投与下で報告されたすべての下痢の有害事象は非重篤な有害事象であった。体重減少の PT の有害事象の発現割合はプラセボ群と比較して本薬群で高かったが，いずれの事象も非重篤であった。

本薬 9 mg 1 日 2 回及び本薬 18 mg 1 日 2 回投与は，疾患進行の指標である FVC 低下を抑制する効果を示し，患者にとって意味のあるイベント（すなわち，ILD の初回急性増悪，呼吸器疾患による初回入院，又は死亡）のリスクを低下させた。また，単独又はニンテダニブと併用したときの本薬の安全性及び忍容性は良好であった。

4.3.3　付録

本治験で認められたすべての有害事象及び治験担当医師により治験薬と因果関係ありと判断された有害事象を Table 15.3.99: 3 に, 重篤な有害事象が認められた被験者一覧を Listing 15.4.2: 1 に，死亡に至った有害事象が認められた被験者一覧を Listing 15.4.2: 8 に示す。

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	392	100.00	392	100.00	393	100.00	393	100.00	391	100.00	391	100.00
Total with adverse events	369	94.13	128	32.65	369	93.89	157	39.95	364	93.09	178	45.52
Infections and infestations (感染症および寄生虫症)	263	67.09	17	4.34	239	60.81	9	2.29	250	63.94	18	4.60
Upper respiratory tract infection (上気道感染)	63	16.07	5	1.28	42	10.69	2	0.51	51	13.04	3	0.77
COVID-19 (ＣＯＶＩＤ－１９)	63	16.07	1	0.26	44	11.20	0	0.00	47	12.02	1	0.26
Nasopharyngitis (上咽頭炎)	45	11.48	1	0.26	49	12.47	1	0.25	43	11.00	0	0.00
Pneumonia (肺炎)	40	10.20	2	0.51	41	10.43	2	0.51	45	11.51	3	0.77
Bronchitis (気管支炎)	27	6.89	0	0.00	31	7.89	0	0.00	23	5.88	0	0.00
Urinary tract infection (尿路感染)	24	6.12	1	0.26	24	6.11	1	0.25	20	5.12	0	0.00
Respiratory tract infection (気道感染)	17	4.34	0	0.00	25	6.36	0	0.00	25	6.39	1	0.26
Influenza (インフルエンザ)	22	5.61	1	0.26	18	4.58	0	0.00	21	5.37	0	0.00
Lower respiratory tract infection (下気道感染)	12	3.06	0	0.00	11	2.80	0	0.00	16	4.09	1	0.26
Sinusitis (副鼻腔炎)	8	2.04	0	0.00	7	1.78	0	0.00	8	2.05	1	0.26
Rhinitis (鼻炎)	8	2.04	0	0.00	4	1.02	0	0.00	10	2.56	1	0.26
Gastroenteritis (胃腸炎)	9	2.30	1	0.26	3	0.76	0	0.00	9	2.30	1	0.26
Pneumonia bacterial (細菌性肺炎)	8	2.04	0	0.00	5	1.27	0	0.00	4	1.02	0	0.00
Cystitis (膀胱炎)	8	2.04	0	0.00	3	0.76	0	0.00	4	1.02	0	0.00
Latent tuberculosis (潜伏結核)	4	1.02	1	0.26	8	2.04	1	0.25	3	0.77	0	0.00
Herpes zoster (帯状疱疹)	2	0.51	0	0.00	4	1.02	0	0.00	8	2.05	4	1.02
Pharyngitis (咽頭炎)	7	1.79	1	0.26	4	1.02	0	0.00	2	0.51	0	0.00
Viral infection (ウイルス感染)	3	0.77	0	0.00	6	1.53	0	0.00	4	1.02	0	0.00
Cellulitis (蜂巣炎)	1	0.26	0	0.00	3	0.76	0	0.00	4	1.02	0	0.00
Infection (感染)	5	1.28	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Oral herpes (口腔ヘルペス)	3	0.77	1	0.26	2	0.51	0	0.00	2	0.51	0	0.00
Candida infection (カンジダ感染)	2	0.51	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Conjunctivitis (結膜炎)	2	0.51	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Gingivitis (歯肉炎)	3	0.77	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Skin infection (皮膚感染)	0	0.00	0	0.00	5	1.27	1	0.25	1	0.26	0	0.00
Tooth infection (歯感染)	0	0.00	0	0.00	5	1.27	1	0.25	1	0.26	0	0.00
Viral upper respiratory tract infection (ウイルス性上気道感染)	3	0.77	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Acute sinusitis (急性副鼻腔炎)	1	0.26	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Bronchopulmonary aspergillosis (気管支肺アスペルギルス症)	0	0.00	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Gastroenteritis viral (ウイルス性胃腸炎)	1	0.26	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Hordeolum (麦粒腫)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Oral candidiasis (口腔カンジダ症)	1	0.26	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Respiratory tract infection viral (ウイルス性気道感染)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	1	0.26
Sepsis (敗血症)	1	0.26	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Bacterial infection (細菌感染)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Diverticulitis (憩室炎)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Ear infection (耳感染)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Laryngopharyngitis (咽喉頭炎)	1	0.26	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Otitis externa (外耳炎)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Otitis media (中耳炎)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Respiratory syncytial virus infection (ＲＳウイルス感染)	2	0.51	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Bronchitis viral (ウイルス性気管支炎)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
COVID-19 pneumonia (ＣＯＶＩＤ－１９肺炎)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Gastrointestinal infection (消化管感染)	0	0.00	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Labyrinthitis (迷路炎)	1	0.26	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Laryngitis (喉頭炎)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Paronychia (爪囲炎)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Pharyngotonsillitis (咽頭扁桃炎)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Septic shock (敗血症性ショック)	0	0.00	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Sputum purulent (膿性痰)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Tinea infection (白癬感染)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	1	0.26
Tonsillitis (扁桃炎)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Tooth abscess (歯膿瘍)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Tracheobronchitis (気管気管支炎)	0	0.00	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Wound infection (創傷感染)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Abscess limb (四肢膿瘍)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Asymptomatic bacteriuria (無症候性細菌尿)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bacteraemia (菌血症)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chronic sinusitis (慢性副鼻腔炎)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Coronavirus infection (コロナウイルス感染)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Eye infection (眼感染)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Fungal skin infection (皮膚真菌感染)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Gastrointestinal viral infection (ウイルス性消化管感染)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Helicobacter gastritis (ヘリコバクター性胃炎)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Herpes simplex (単純ヘルペス)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lower respiratory tract infection bacterial (細菌性下気道感染)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Lower respiratory tract infection viral (ウイルス性下気道感染)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Medical device site infection (医療機器使用部位感染)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Mumps (ムンプス)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Onychomycosis (爪真菌症)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Periodontitis (歯周炎)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Pneumocystis jirovecii pneumonia (ニューモシスチス・イロベチイ肺炎)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Pneumonia aspiration (誤嚥性肺炎)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pneumonia fungal (真菌性肺炎)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pneumonia influenzal (インフルエンザ性肺炎)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Tinea pedis (足部白癬)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Tongue fungal infection (真菌性舌感染)	2	0.51	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Adenovirus infection (アデノウイルス感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Appendicitis (虫垂炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Aspergillus infection (アスペルギルス感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bacteriuria (細菌尿)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bronchiolitis (細気管支炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Bronchitis bacterial (細菌性気管支炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Campylobacter infection (カンピロバクター感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Citrobacter infection (シトロバクター感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dacryocystitis (涙嚢炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dengue fever (デング熱)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dermatophytosis of nail (爪の皮膚糸状菌症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ear, nose and throat infection (耳・鼻・咽喉の感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eczema infected (感染性湿疹)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Epstein-Barr virus infection (エプスタイン・バーウイルス感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Erysipelas (丹毒)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Erythema migrans (遊走性紅斑)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Escherichia urinary tract infection (大腸菌性尿路感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Folliculitis (毛包炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fungal infection (真菌感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Fungal oesophagitis (真菌性食道炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Furuncle (せつ)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gastric infection (胃感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Genitourinary tract infection (泌尿生殖器感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
H1N1 influenza (Ｈ１Ｎ１インフルエンザ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Haemophilus infection (ヘモフィルス感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Helicobacter infection (ヘリコバクター感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hepatitis E (Ｅ型肝炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hookworm infection (鉤虫感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Infection parasitic (寄生虫感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Klebsiella infection (クレブシエラ感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Lyme disease (ライム病)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mastitis fungal (真菌性乳腺炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Meningitis aseptic (無菌性髄膜炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Meningitis viral (ウイルス性髄膜炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nasal vestibulitis (鼻前庭炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oesophageal candidiasis (食道カンジダ症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ophthalmic herpes zoster (眼帯状疱疹)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Oral fungal infection (口腔真菌感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Orchitis (精巣炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oropharyngeal candidiasis (中咽頭カンジダ症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Osteomyelitis (骨髄炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Papilloma viral infection (乳頭腫ウイルス感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Parasitic gastroenteritis (寄生虫性胃腸炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Parotitis (耳下腺炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Peritonsillar abscess (扁桃周囲膿瘍)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pharyngitis streptococcal (レンサ球菌性咽頭炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pneumonia klebsiella (クレブシエラ菌性肺炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pneumonia necrotising (壊死性肺炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pneumonia pneumococcal (肺炎球菌性肺炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Post procedural infection (処置後感染)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Post-acute COVID-19 syndrome (急性ＣＯＶＩＤ－１９後症候群)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Prostate infection (前立腺感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pseudomonas infection (シュードモナス感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary sepsis (肺敗血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary tuberculosis (肺結核)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Pulpitis dental (歯髄炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pustule (膿疱)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pyelonephritis (腎盂腎炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rhinovirus infection (ライノウイルス感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Rubella (風疹)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Salmonellosis (サルモネラ症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Serratia infection (セラチア感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Soft tissue infection (軟部組織感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Spirochaetal infection (スピロヘータ感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Strongyloidiasis (糞線虫症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tracheitis (気管炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Trachoma (トラコーマ)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Tuberculosis (結核)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vaccine breakthrough infection (ワクチンブレイクスルー感染)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vaginal infection (膣感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Viral diarrhoea (ウイルス性下痢)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Viral rash (ウイルス性発疹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Viral sinusitis (ウイルス性副鼻腔炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vulvovaginal mycotic infection (外陰膣真菌感染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Gastrointestinal disorders (胃腸障害)	175	44.64	73	18.62	192	48.85	111	28.24	202	51.66	129	32.99
Diarrhoea (下痢)	98	25.00	52	13.27	121	30.79	83	21.12	143	36.57	106	27.11
Nausea (悪心)	28	7.14	12	3.06	35	8.91	18	4.58	43	11.00	25	6.39
Vomiting (嘔吐)	24	6.12	6	1.53	19	4.83	12	3.05	26	6.65	14	3.58
Gastrooesophageal reflux disease (胃食道逆流性疾患)	12	3.06	2	0.51	20	5.09	5	1.27	11	2.81	2	0.51
Frequent bowel movements (排便回数増加)	7	1.79	4	1.02	14	3.56	8	2.04	15	3.84	9	2.30
Constipation (便秘)	14	3.57	0	0.00	9	2.29	2	0.51	12	3.07	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Abdominal pain (腹痛)	10	2.55	4	1.02	11	2.80	5	1.27	12	3.07	7	1.79
Abdominal pain upper (上腹部痛)	9	2.30	4	1.02	10	2.54	4	1.02	11	2.81	2	0.51
Dyspepsia (消化不良)	6	1.53	2	0.51	8	2.04	5	1.27	10	2.56	5	1.28
Flatulence (鼓腸)	5	1.28	3	0.77	6	1.53	4	1.02	9	2.30	7	1.79
Dental caries (齲歯)	6	1.53	0	0.00	8	2.04	0	0.00	5	1.28	0	0.00
Abdominal distension (腹部膨満)	4	1.02	4	1.02	8	2.04	4	1.02	4	1.02	2	0.51
Haemorrhoids (痔核)	4	1.02	0	0.00	5	1.27	1	0.25	6	1.53	2	0.51
Gastritis (胃炎)	6	1.53	1	0.26	2	0.51	0	0.00	6	1.53	0	0.00
Toothache (歯痛)	6	1.53	0	0.00	3	0.76	0	0.00	3	0.77	0	0.00
Dry mouth (口内乾燥)	6	1.53	0	0.00	4	1.02	2	0.51	1	0.26	1	0.26
Abdominal discomfort (腹部不快感)	3	0.77	1	0.26	3	0.76	0	0.00	2	0.51	0	0.00
Abdominal pain lower (下腹部痛)	1	0.26	0	0.00	1	0.25	1	0.25	5	1.28	1	0.26
Diverticulum intestinal (腸憩室)	0	0.00	0	0.00	4	1.02	1	0.25	3	0.77	0	0.00
Inguinal hernia (鼠径ヘルニア)	2	0.51	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00
Colitis (大腸炎)	2	0.51	0	0.00	2	0.51	0	0.00	2	0.51	1	0.26
Dysphagia (嚥下障害)	3	0.77	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Large intestine polyp (大腸ポリープ)	0	0.00	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00
Chronic gastritis (慢性胃炎)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	1	0.26
Haematochezia (血便排泄)	1	0.26	0	0.00	1	0.25	0	0.00	2	0.51	1	0.26
Rectal haemorrhage (直腸出血)	1	0.26	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Enteritis (小腸炎)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Eructation (おくび)	1	0.26	0	0.00	1	0.25	1	0.25	1	0.26	0	0.00
Food poisoning (食中毒)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Haemorrhoidal haemorrhage (痔出血)	1	0.26	0	0.00	1	0.25	1	0.25	1	0.26	0	0.00
Hiatus hernia (裂孔ヘルニア)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Mouth ulceration (口腔内潰瘍形成)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Stomatitis (口内炎)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Anal incontinence (肛門失禁)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Cheilitis (口唇炎)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Defaecation urgency (便意切迫)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Faeces discoloured (変色便)	1	0.26	1	0.26	1	0.25	0	0.00	0	0.00	0	0.00
Gastric antral vascular ectasia (胃前庭部毛細血管拡張症)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Gastritis erosive (びらん性胃炎)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Gastrointestinal haemorrhage (胃腸出血)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Gastrointestinal pain (消化器痛)	2	0.51	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Lip dry (口唇乾燥)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Oesophageal stenosis (食道狭窄)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Pancreatic cyst (膵嚢胞)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Pancreatitis (膵炎)	2	0.51	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Pancreatitis acute (急性膵炎)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Periodontal disease (歯周病)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Post-tussive vomiting (咳嗽後嘔吐)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Rectal polyp (直腸ポリープ)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Abdominal rigidity (腹部硬直)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Abdominal tenderness (腹部圧痛)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Aerophagia (空気嚥下)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Anal erythema (肛門紅斑)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Anal fissure (裂肛)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Anal haemorrhage (肛門出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Angular cheilitis (口角口唇炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Colitis microscopic (顕微鏡的大腸炎)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Colitis ulcerative (潰瘍性大腸炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Enterocolitis (腸炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Epigastric discomfort (心窩部不快感)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Erosive oesophagitis (びらん性食道炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Faeces hard (硬便)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Faeces soft (軟便)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Functional gastrointestinal disorder (機能性胃腸障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Gastric mucosa erythema (胃粘膜紅斑)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Gastric polyps (胃ポリープ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastric ulcer (胃潰瘍)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Gastrointestinal angiodysplasia (胃腸管血管異形成)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastrointestinal disorder (胃腸障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gastrointestinal mucosal disorder (胃腸粘膜障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gastrointestinal wall thickening (消化管壁肥厚)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gingival bleeding (歯肉出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gingival swelling (歯肉腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Glossitis (舌炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hyperaesthesia teeth (歯の知覚過敏)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hypoaesthesia oral (口の感覚鈍麻)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Intestinal obstruction (腸閉塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Intestinal polyp (腸管ポリープ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ischaemic enteritis (虚血性小腸炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Lumbar hernia (腰ヘルニア)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mallory-Weiss syndrome (マロリー・ワイス症候群)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Obstructive pancreatitis (閉塞性膵炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oesophageal spasm (食道痙攣)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oesophageal varices haemorrhage (食道静脈瘤出血)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Oesophagitis (食道炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Oral pain (口腔内痛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pancreatic failure (膵不全)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Peptic ulcer (消化性潰瘍)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Portal hypertensive gastropathy (門脈圧亢進性胃障害)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Subileus (亜イレウス)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	155	39.54	17	4.34	139	35.37	11	2.80	140	35.81	11	2.81
Cough (咳嗽)	60	15.31	5	1.28	53	13.49	7	1.78	61	15.60	4	1.02
Dyspnoea (呼吸困難)	38	9.69	5	1.28	36	9.16	2	0.51	37	9.46	4	1.02
Interstitial lung disease (間質性肺疾患)	17	4.34	1	0.26	8	2.04	0	0.00	6	1.53	2	0.51
Productive cough (湿性咳嗽)	7	1.79	0	0.00	14	3.56	1	0.25	8	2.05	0	0.00
Pulmonary hypertension (肺高血圧症)	10	2.55	0	0.00	7	1.78	0	0.00	10	2.56	0	0.00
Pneumothorax (気胸)	9	2.30	0	0.00	8	2.04	1	0.25	5	1.28	0	0.00
Rhinorrhoea (鼻漏)	7	1.79	0	0.00	10	2.54	1	0.25	4	1.02	0	0.00
Respiratory failure (呼吸不全)	8	2.04	2	0.51	4	1.02	0	0.00	6	1.53	0	0.00
Rhinitis allergic (アレルギー性鼻炎)	3	0.77	1	0.26	5	1.27	0	0.00	9	2.30	0	0.00
Oropharyngeal pain (口腔咽頭痛)	7	1.79	0	0.00	4	1.02	0	0.00	4	1.02	0	0.00
Dyspnoea exertional (労作性呼吸困難)	5	1.28	0	0.00	3	0.76	0	0.00	6	1.53	0	0.00
Acute respiratory failure (急性呼吸不全)	4	1.02	2	0.51	3	0.76	0	0.00	4	1.02	0	0.00
Asthma (喘息)	2	0.51	1	0.26	6	1.53	0	0.00	3	0.77	1	0.26
Hypoxia (低酸素症)	6	1.53	2	0.51	4	1.02	0	0.00	0	0.00	0	0.00
Epistaxis (鼻出血)	1	0.26	0	0.00	5	1.27	0	0.00	3	0.77	0	0.00
Pneumomediastinum (気縦隔症)	2	0.51	0	0.00	2	0.51	0	0.00	5	1.28	0	0.00
Pulmonary embolism (肺塞栓症)	2	0.51	0	0.00	5	1.27	0	0.00	2	0.51	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Dysphonia (発声障害)	2	0.51	0	0.00	2	0.51	0	0.00	4	1.02	0	0.00
Pulmonary fibrosis (肺線維症)	5	1.28	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Sputum increased (喀痰増加)	3	0.77	1	0.26	1	0.25	0	0.00	4	1.02	1	0.26
Haemoptysis (喀血)	3	0.77	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Obstructive sleep apnoea syndrome (閉塞性睡眠時無呼吸症候群)	3	0.77	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Pulmonary mass (肺腫瘤)	3	0.77	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Sputum discoloured (変色痰)	1	0.26	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Nasal congestion (鼻閉)	1	0.26	0	0.00	0	0.00	0	0.00	4	1.02	0	0.00
Wheezing (喘鳴)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Bronchospasm (気管支痙攣)	3	0.77	1	0.26	1	0.25	0	0.00	0	0.00	0	0.00
Hypersensitivity pneumonitis (過敏性肺臓炎)	1	0.26	0	0.00	3	0.76	1	0.25	0	0.00	0	0.00
Pulmonary arterial hypertension (肺動脈性肺高血圧症)	3	0.77	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Bronchiectasis (気管支拡張症)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Chronic obstructive pulmonary disease (慢性閉塞性肺疾患)	1	0.26	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Increased bronchial secretion (気管支分泌増加)	1	0.26	1	0.26	1	0.25	0	0.00	1	0.26	0	0.00
Bronchial obstruction (気管支閉塞)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Bronchitis chronic (慢性気管支炎)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chronic respiratory failure (慢性呼吸不全)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Emphysema (肺気腫)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Nasal dryness (鼻乾燥)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nasal obstruction (鼻閉塞)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pleural effusion (胸水)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Pulmonary oedema (肺水腫)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Rales (ラ音)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Sleep apnoea syndrome (睡眠時無呼吸症候群)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Throat irritation (咽喉刺激感)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Upper-airway cough syndrome (上気道咳症候群)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Vasomotor rhinitis (血管運動性鼻炎)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Acute respiratory distress syndrome (急性呼吸窮迫症候群)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Allergic sinusitis (アレルギー性副鼻腔炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Alveolar proteinosis (肺胞蛋白症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aphonia (失声症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Aspiration (誤嚥)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atopic cough (アトピー咳嗽)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Choking (息詰まり)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cough variant asthma (咳喘息)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dry throat (咽喉乾燥)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dyspnoea at rest (安静時呼吸困難)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Haemothorax (血胸)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypercapnia (高炭酸ガス血症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic interstitial pneumonia (特発性間質性肺炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Increased upper airway secretion (上気道分泌増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Increased viscosity of bronchial secretion (高粘稠性気管支分泌物)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nasal discharge discolouration (鼻汁変色)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nasal pruritus (鼻そう痒症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nasal septum perforation (鼻中隔穿孔)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nocturnal dyspnoea (夜間呼吸困難)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Noninfective bronchitis (非感染性気管支炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Obstructive airways disorder (閉塞性気道障害)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Painful respiration (呼吸時疼痛)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Paranasal sinus discomfort (副鼻腔不快感)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pleuritic pain (胸膜痛)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pleuroparenchymal fibroelastosis (胸膜肺実質線維弾性症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pulmonary cavitation (肺空洞形成)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pulmonary pain (肺痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Respiratory acidosis (呼吸性アシドーシス)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Respiratory disorder (呼吸障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Respiratory distress (呼吸窮迫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Respiratory symptom (呼吸器症状)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Rhinalgia (鼻痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sinus congestion (副鼻腔うっ血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sinus pain (副鼻腔痛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sneezing (くしゃみ)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tonsillar cyst (扁桃嚢胞)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Tonsillar erythema (扁桃紅斑)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tonsillar hypertrophy (扁桃肥大)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Upper respiratory tract inflammation (上気道の炎症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vocal cord leukoplakia (声帯白斑症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	144	36.73	17	4.34	123	31.30	17	4.33	117	29.92	27	6.91
Condition aggravated (状態悪化)	65	16.58	6	1.53	52	13.23	2	0.51	38	9.72	2	0.51
Fatigue (疲労)	24	6.12	7	1.79	24	6.11	8	2.04	21	5.37	9	2.30
Pyrexia (発熱)	23	5.87	2	0.51	11	2.80	0	0.00	16	4.09	2	0.51
Oedema peripheral (末梢性浮腫)	15	3.83	1	0.26	11	2.80	0	0.00	11	2.81	2	0.51
Asthenia (無力症)	10	2.55	1	0.26	11	2.80	2	0.51	10	2.56	4	1.02
Chest pain (胸痛)	6	1.53	0	0.00	7	1.78	1	0.25	12	3.07	0	0.00
Disease progression (疾患進行)	7	1.79	0	0.00	7	1.78	0	0.00	8	2.05	1	0.26
Influenza like illness (インフルエンザ様疾患)	5	1.28	0	0.00	8	2.04	1	0.25	6	1.53	2	0.51
Chest discomfort (胸部不快感)	4	1.02	0	0.00	5	1.27	1	0.25	4	1.02	2	0.51
Peripheral swelling (末梢腫脹)	2	0.51	1	0.26	2	0.51	0	0.00	9	2.30	2	0.51
Pain (疼痛)	5	1.28	0	0.00	3	0.76	0	0.00	4	1.02	1	0.26
Malaise (倦怠感)	0	0.00	0	0.00	6	1.53	3	0.76	2	0.51	1	0.26
Non-cardiac chest pain (非心臓性胸痛)	4	1.02	0	0.00	1	0.25	0	0.00	2	0.51	1	0.26
Chills (悪寒)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Oedema (浮腫)	1	0.26	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Death (死亡)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hernia (ヘルニア)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Fibrosis (線維症)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Adverse drug reaction (医薬品副作用)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Device related thrombosis (医療機器関連血栓症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Drug intolerance (薬物不耐性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Dysphagia (嚥下障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Early satiety (早期満腹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Exercise tolerance decreased (運動耐性低下)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Eyelid disorder (眼瞼障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Face oedema (顔面浮腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Facial pain (顔面痛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Feeling cold (冷感)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Feeling hot (熱感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gait disturbance (歩行障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
General physical health deterioration (全身健康状態悪化)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Inflammation (炎症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Interferon gamma release assay positive (インターフェロンγ応答測定陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26
Localised oedema (限局性浮腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Medical device site swelling (医療機器使用部位腫脹)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Post procedural haematoma (処置後血腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Prolapse (脱出症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Secretion discharge (分泌物分泌)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sensation of foreign body (異物感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Swelling face (顔面腫脹)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Thirst (口渇)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vaccination site pain (ワクチン接種部位疼痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	99	25.26	4	1.02	93	23.66	6	1.53	95	24.30	8	2.05
Arthralgia (関節痛)	20	5.10	2	0.51	28	7.12	3	0.76	29	7.42	1	0.26
Back pain (背部痛)	11	2.81	0	0.00	15	3.82	1	0.25	25	6.39	0	0.00
Myalgia (筋肉痛)	11	2.81	0	0.00	5	1.27	0	0.00	8	2.05	0	0.00
Muscle spasms (筋痙縮)	6	1.53	0	0.00	8	2.04	1	0.25	9	2.30	1	0.26
Pain in extremity (四肢痛)	6	1.53	0	0.00	7	1.78	0	0.00	9	2.30	3	0.77
Neck pain (頚部痛)	8	2.04	1	0.26	5	1.27	0	0.00	2	0.51	0	0.00
Rheumatoid arthritis (関節リウマチ)	3	0.77	0	0.00	9	2.29	0	0.00	3	0.77	1	0.26
Osteoarthritis (変形性関節症)	5	1.28	0	0.00	5	1.27	0	0.00	4	1.02	0	0.00
Arthritis (関節炎)	2	0.51	0	0.00	2	0.51	0	0.00	8	2.05	0	0.00
Intervertebral disc protrusion (椎間板突出)	3	0.77	0	0.00	3	0.76	0	0.00	4	1.02	0	0.00
Osteoporosis (骨粗鬆症)	3	0.77	0	0.00	3	0.76	0	0.00	4	1.02	0	0.00
Muscular weakness (筋力低下)	4	1.02	1	0.26	3	0.76	1	0.25	2	0.51	0	0.00
Spinal osteoarthritis (変形性脊椎症)	3	0.77	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Tendonitis (腱炎)	0	0.00	0	0.00	2	0.51	0	0.00	4	1.02	0	0.00
Musculoskeletal pain (筋骨格痛)	1	0.26	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Osteopenia (骨減少症)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Rotator cuff syndrome (肩回旋筋腱板症候群)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Spinal stenosis (脊柱管狭窄症)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Synovial cyst (滑液嚢腫)	2	0.51	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Systemic scleroderma (全身性強皮症)	3	0.77	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Intervertebral disc disorder (椎間板障害)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Joint swelling (関節腫脹)	0	0.00	0	0.00	0	0.00	0	0.00	3	0.77	0	0.00
Musculoskeletal chest pain (筋骨格系胸痛)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Musculoskeletal stiffness (筋骨格硬直)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Osteonecrosis (骨壊死)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Periarthritis (関節周囲炎)	3	0.77	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Antisynthetase syndrome (抗合成酵素症候群)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Bursitis (滑液包炎)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Connective tissue disorder (結合組織障害)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Costochondritis (肋軟骨炎)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Dermatomyositis (皮膚筋炎)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Flank pain (側腹部痛)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mobility decreased (運動性低下)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Muscle contracture (筋拘縮)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Osteoporotic fracture (骨粗鬆症性骨折)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Pain in jaw (顎痛)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Scleroderma (強皮症)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tendon disorder (腱障害)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bone lesion (骨病変)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bone loss (骨喪失)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bone pain (骨痛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bursal fluid accumulation (滑液貯留)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chondrocalcinosis (軟骨石灰化症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Clubbing (ばち状指)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Exostosis (外骨腫)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Facet joint syndrome (椎間関節症候群)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gouty arthritis (痛風性関節炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Greater trochanteric pain syndrome (大転子疼痛症候群)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic inflammatory myopathy (特発性炎症性ミオパチー)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Jaw cyst (顎骨嚢胞)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Limb mass (四肢腫瘤)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lumbar spinal stenosis (腰部脊柱管狭窄症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mixed connective tissue disease (混合性結合組織病)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Muscle atrophy (筋萎縮)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Muscle discomfort (筋不快感)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Muscle tightness (筋緊張)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Musculoskeletal discomfort (筋骨格不快感)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myopathy (ミオパチー)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Osteolysis (骨溶解)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pathological fracture (病的骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pes anserinus syndrome (鵞足炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Plantar fasciitis (足底筋膜炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Polymyositis (多発性筋炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Scoliosis (側弯症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Senile osteoporosis (老人性骨粗鬆症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Sjogren's syndrome (シェーグレン症候群)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Spinal pain (脊椎痛)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Spondylolisthesis (脊椎すべり症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Temporomandibular pain and dysfunction syndrome (顎関節症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tenosynovitis (腱鞘炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Tenosynovitis stenosans (狭窄性腱鞘炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Trigger finger (弾発指)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Investigations (臨床検査)	75	19.13	20	5.10	89	22.65	22	5.60	100	25.58	27	6.91
Weight decreased (体重減少)	26	6.63	8	2.04	36	9.16	11	2.80	49	12.53	19	4.86
C-reactive protein increased (Ｃ－反応性蛋白増加)	6	1.53	2	0.51	9	2.29	0	0.00	11	2.81	0	0.00
Alanine aminotransferase increased (アラニンアミノトランスフェラーゼ増加)	5	1.28	2	0.51	6	1.53	0	0.00	2	0.51	1	0.26
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)	7	1.79	4	1.02	6	1.53	1	0.25	0	0.00	0	0.00
Depression rating scale score increased (抑うつ尺度スコア増加)	3	0.77	1	0.26	4	1.02	0	0.00	6	1.53	0	0.00
Lipase increased (リパーゼ増加)	2	0.51	0	0.00	5	1.27	0	0.00	4	1.02	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Amylase increased (アミラーゼ増加)	3	0.77	2	0.51	3	0.76	0	0.00	4	1.02	2	0.51
Gamma-glutamyltransferase increased (γ－グルタミルトランスフェラーゼ増加)	5	1.28	2	0.51	4	1.02	0	0.00	1	0.26	1	0.26
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	6	1.53	3	0.77	3	0.76	0	0.00	0	0.00	0	0.00
Hepatic enzyme increased (肝酵素上昇)	3	0.77	2	0.51	3	0.76	2	0.51	3	0.77	1	0.26
Blood creatinine increased (血中クレアチニン増加)	2	0.51	0	0.00	4	1.02	1	0.25	1	0.26	1	0.26
Blood glucose increased (血中ブドウ糖増加)	0	0.00	0	0.00	3	0.76	0	0.00	4	1.02	0	0.00
Electrocardiogram QT prolonged (心電図ＱＴ延長)	0	0.00	0	0.00	3	0.76	3	0.76	2	0.51	0	0.00
Oxygen saturation decreased (酸素飽和度低下)	4	1.02	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
SARS-CoV-2 test positive (ＳＡＲＳ－ＣｏＶ－２検査陽性)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Blood pressure increased (血圧上昇)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Influenza A virus test positive (A型インフルエンザウイルス検査陽性)	1	0.26	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Liver function test increased (肝機能検査値上昇)	1	0.26	0	0.00	1	0.25	1	0.25	2	0.51	2	0.51
Lymphocyte count decreased (リンパ球数減少)	2	0.51	2	0.51	2	0.51	2	0.51	0	0.00	0	0.00
Protein urine present (尿中蛋白陽性)	1	0.26	1	0.26	1	0.25	0	0.00	2	0.51	0	0.00
Blood alkaline phosphatase increased (血中アルカリホスファターゼ増加)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Blood potassium increased (血中カリウム増加)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Heart rate increased (心拍数増加)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	1	0.26
Neutrophil count increased (好中球数増加)	2	0.51	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00
Red blood cell sedimentation rate increased (血沈亢進)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Weight increased (体重増加)	0	0.00	0	0.00	3	0.76	1	0.25	0	0.00	0	0.00
White blood cell count increased (白血球数増加)	2	0.51	2	0.51	1	0.25	0	0.00	0	0.00	0	0.00
Blood bilirubin increased (血中ビリルビン増加)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Blood potassium decreased (血中カリウム減少)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Carbohydrate antigen 19-9 increased (糖鎖抗原１９－９増加)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Faecal calprotectin increased (便中カルプロテクチン増加)	0	0.00	0	0.00	2	0.51	2	0.51	0	0.00	0	0.00
Forced vital capacity decreased (努力肺活量減少)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Haemoglobin decreased (ヘモグロビン減少)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hospital anxiety and depression scale abnormal (病院不安抑うつ尺度異常)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Interferon gamma release assay positive (インターフェロンγ応答測定陽性)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Mycobacterium tuberculosis complex test positive (結核菌群検査陽性)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Neutrophil count decreased (好中球数減少)	0	0.00	0	0.00	1	0.25	1	0.25	1	0.26	0	0.00
Oxygen consumption increased (酸素消費量増加)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Platelet count decreased (血小板数減少)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Platelet count increased (血小板数増加)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary function test decreased (肺機能検査値低下)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Transaminases increased (トランスアミナーゼ上昇)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
White blood cell count decreased (白血球数減少)	0	0.00	0	0.00	1	0.25	1	0.25	1	0.26	0	0.00
White blood cells urine positive (尿中白血球陽性)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Antineutrophil cytoplasmic antibody increased (抗好中球細胞質抗体増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
B-lymphocyte count decreased (Bリンパ球数減少)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Bacterial test positive (細菌検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Basophil count increased (好塩基球数増加)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Blood cholesterol increased (血中コレステロール増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood folate decreased (血中葉酸減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood magnesium decreased (血中マグネシウム減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood phosphorus decreased (血中リン減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood pressure diastolic increased (拡張期血圧上昇)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood pressure systolic increased (収縮期血圧上昇)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood testosterone decreased (血中テストステロン減少)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood thyroid stimulating hormone increased (血中甲状腺刺激ホルモン増加)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Blood triglycerides increased (血中トリグリセリド増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Blood urine present (尿中血陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Brain natriuretic peptide increased (脳性ナトリウム利尿ペプチド増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
CD4 lymphocytes decreased (ＣＤ４リンパ球減少)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Carcinoembryonic antigen increased (癌胎児性抗原増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Coagulation time prolonged (凝固時間延長)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Crystal urine present (尿中結晶陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ECG signs of myocardial ischaemia (心筋虚血の心電図所見)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ejection fraction decreased (駆出率減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Electrocardiogram PR shortened (心電図ＰＲ短縮)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Electrocardiogram T wave inversion (心電図Ｔ波逆転)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
False positive tuberculosis test (結核菌検査偽陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gamma-glutamyltransferase abnormal (γ－グルタミルトランスフェラーゼ異常)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Globulins increased (グロブリン増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Glucose urine present (尿中ブドウ糖陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Glycosylated haemoglobin increased (グリコヘモグロビン増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Haemoglobin increased (ヘモグロビン増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Heart rate decreased (心拍数減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Helicobacter test positive (ヘリコバクター検査陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hepatic enzyme decreased (肝酵素低下)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatitis B surface antigen positive (Ｂ型肝炎表面抗原陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hepatitis C antibody positive (Ｃ型肝炎抗体陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Human metapneumovirus test positive (ヒトメタニューモウイルス検査陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Imaging procedure abnormal (画像検査異常)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Intraocular pressure increased (眼圧上昇)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
KL-6 increased (ＫＬ－６増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lipids increased (脂質増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Low density lipoprotein increased (低比重リポ蛋白増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mean cell haemoglobin decreased (平均赤血球ヘモグロビン減少)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mean cell haemoglobin increased (平均赤血球ヘモグロビン増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mean cell volume increased (平均赤血球容積増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mycobacterium test positive (マイコバクテリウム検査陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
N-terminal prohormone brain natriuretic peptide increased (脳性ナトリウム利尿ペプチド前駆体N端フラグメント増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nitrite urine present (尿中亜硝酸塩陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Occult blood positive (便潜血陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pneumocystis test positive (ニューモシスチス検査陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Prostatic specific antigen increased (前立腺特異性抗原増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Prothrombin time prolonged (プロトロンビン時間延長)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Prothrombin time shortened (プロトロンビン時間短縮)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pseudomonas test positive (シュードモナス検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pulmonary arterial pressure increased (肺動脈圧上昇)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
QRS axis abnormal (ＱＲＳ軸異常)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Red blood cells urine positive (尿中赤血球陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Respiratory rate increased (呼吸数増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rheumatoid factor increased (リウマチ因子増加)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Serum ferritin decreased (血清フェリチン減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Staphylococcus test positive (ブドウ球菌検査陽性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Stool DNA test positive (便ＤＮＡ検査陽性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Streptococcus test positive (レンサ球菌検査陽性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
T-lymphocyte count decreased (Tリンパ球数減少)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Tumour marker increased (腫瘍マーカー上昇)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Urine output fluctuation (尿量変動)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vitamin B12 decreased (ビタミンＢ１２減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vitamin D decreased (ビタミンD減少)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Psychiatric disorders (精神障害)	82	20.92	15	3.83	90	22.90	21	5.34	88	22.51	20	5.12
Depression (うつ病)	47	11.99	6	1.53	41	10.43	10	2.54	43	11.00	13	3.32
Anxiety (不安)	38	9.69	4	1.02	41	10.43	5	1.27	43	11.00	9	2.30
Insomnia (不眠症)	11	2.81	1	0.26	11	2.80	4	1.02	9	2.30	2	0.51
Sleep disorder (睡眠障害)	3	0.77	1	0.26	3	0.76	0	0.00	4	1.02	0	0.00
Anxiety disorder (不安障害)	3	0.77	1	0.26	4	1.02	2	0.51	1	0.26	0	0.00
Suicidal ideation (自殺念慮)	2	0.51	2	0.51	1	0.25	0	0.00	3	0.77	1	0.26
Agitation (激越)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	1	0.26
Delirium (譫妄)	1	0.26	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Depressed mood (抑うつ気分)	1	0.26	1	0.26	1	0.25	1	0.25	2	0.51	0	0.00
Irritability (易刺激性)	2	0.51	1	0.26	0	0.00	0	0.00	1	0.26	1	0.26
Apathy (無感情)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Initial insomnia (初期不眠症)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Mixed anxiety and depressive disorder (混合性不安抑うつ障害)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Abnormal dreams (異常な夢)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Adjustment disorder with depressed mood (抑うつ気分を伴う適応障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Affect lability (感情不安定)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Anger (怒り)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Conversion disorder (転換性障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Disorientation (失見当識)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Euphoric mood (多幸気分)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Generalised anxiety disorder (全般性不安障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hallucination (幻覚)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Middle insomnia (中期不眠症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Negative thoughts (消極的思考)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Nervousness (神経過敏)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Panic attack (パニック発作)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Persistent depressive disorder (持続性抑うつ障害)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Premature ejaculation (早漏)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rapid eye movement sleep behaviour disorder (レム睡眠行動障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Restlessness (落ち着きのなさ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Stress (ストレス)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Suicide attempt (自殺企図)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Tearfulness (涙ぐむ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Nervous system disorders (神経系障害)	62	15.82	9	2.30	73	18.58	15	3.82	79	20.20	19	4.86
Headache (頭痛)	28	7.14	4	1.02	18	4.58	8	2.04	29	7.42	8	2.05
Dizziness (浮動性めまい)	12	3.06	3	0.77	17	4.33	2	0.51	18	4.60	4	1.02
Syncope (失神)	4	1.02	0	0.00	4	1.02	1	0.25	6	1.53	0	0.00
Tremor (振戦)	1	0.26	0	0.00	5	1.27	2	0.51	6	1.53	1	0.26
Paraesthesia (錯感覚)	2	0.51	0	0.00	4	1.02	0	0.00	3	0.77	0	0.00
Hypoaesthesia (感覚鈍麻)	3	0.77	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Lethargy (嗜眠)	2	0.51	0	0.00	3	0.76	0	0.00	2	0.51	2	0.51
Cerebrovascular accident (脳卒中)	3	0.77	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Dysgeusia (味覚不全)	2	0.51	0	0.00	1	0.25	1	0.25	2	0.51	1	0.26
Transient ischaemic attack (一過性脳虚血発作)	1	0.26	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Balance disorder (平衡障害)	0	0.00	0	0.00	4	1.02	0	0.00	0	0.00	0	0.00
Cognitive disorder (認知障害)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Neuralgia (神経痛)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Restless legs syndrome (下肢静止不能症候群)	0	0.00	0	0.00	2	0.51	0	0.00	2	0.51	1	0.26
Sciatica (坐骨神経痛)	0	0.00	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Cerebrovascular insufficiency (脳血管不全)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Dizziness postural (体位性めまい)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Migraine (片頭痛)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Neuropathy peripheral (末梢性ニューロパチー)	1	0.26	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Amnesia (健忘)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Carotid arteriosclerosis (頚動脈硬化症)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Carpal tunnel syndrome (手根管症候群)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cerebral haemorrhage (脳出血)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Loss of consciousness (意識消失)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Peroneal nerve palsy (腓骨神経麻痺)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Post herpetic neuralgia (ヘルペス後神経痛)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Somnolence (傾眠)	1	0.26	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Ageusia (味覚消失)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Bell's palsy (ベル麻痺)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Brain fog (ブレインフォグ)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Carotid artery dissection (頚動脈解離)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Carotid artery stenosis (頚動脈狭窄)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cerebral infarction (脳梗塞)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cerebral ischaemia (脳虚血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cubital tunnel syndrome (肘部管症候群)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dementia (認知症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Disturbance in attention (注意力障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Dizziness exertional (労作性めまい)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dystonia (ジストニア)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Epilepsy (てんかん)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor (本態性振戦)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Head discomfort (頭部不快感)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypercapnic coma (高炭酸ガス血性昏睡)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypertensive encephalopathy (高血圧性脳症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Lacunar infarction (ラクナ梗塞)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Memory impairment (記憶障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neuritis (神経炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Neurological symptom (神経学的症状)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Normal pressure hydrocephalus (正常圧水頭症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Occipital neuralgia (後頭神経痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Parkinson's disease (パーキンソン病)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Phantom limb syndrome (幻肢症候群)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Presyncope (失神寸前の状態)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Seizure (痙攣発作)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Spondylitic myelopathy (脊椎炎性脊髄症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Subarachnoid haemorrhage (くも膜下出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Taste disorder (味覚障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tension headache (緊張性頭痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Vagus nerve paralysis (迷走神経麻痺)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vertebral artery stenosis (椎骨動脈狭窄)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vertebrobasilar insufficiency (椎骨脳底動脈不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Metabolism and nutrition disorders (代謝および栄養障害)	67	17.09	17	4.34	72	18.32	15	3.82	61	15.60	19	4.86
Decreased appetite (食欲減退)	30	7.65	15	3.83	26	6.62	15	3.82	34	8.70	16	4.09
Hypokalaemia (低カリウム血症)	6	1.53	0	0.00	10	2.54	0	0.00	4	1.02	0	0.00
Hyponatraemia (低ナトリウム血症)	5	1.28	0	0.00	5	1.27	0	0.00	4	1.02	2	0.51
Hyperglycaemia (高血糖)	6	1.53	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Diabetes mellitus (糖尿病)	2	0.51	0	0.00	4	1.02	0	0.00	1	0.26	0	0.00
Hypoproteinaemia (低蛋白血症)	1	0.26	1	0.26	4	1.02	0	0.00	2	0.51	1	0.26
Hyperkalaemia (高カリウム血症)	6	1.53	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperlipidaemia (高脂血症)	0	0.00	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Dehydration (脱水)	1	0.26	1	0.26	2	0.51	0	0.00	2	0.51	1	0.26
Gout (痛風)	1	0.26	1	0.26	1	0.25	0	0.00	3	0.77	0	0.00
Hyperuricaemia (高尿酸血症)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Type 2 diabetes mellitus (２型糖尿病)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Vitamin D deficiency (ビタミンＤ欠乏)	0	0.00	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Diabetes mellitus inadequate control (コントロール不良の糖尿病)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Hypoalbuminaemia (低アルブミン血症)	1	0.26	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Hypophosphataemia (低リン血症)	2	0.51	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Dyslipidaemia (脂質異常症)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Hypercholesterolaemia (高コレステロール血症)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypoglycaemia (低血糖)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Iron deficiency (鉄欠乏)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Steroid diabetes (ステロイド糖尿病)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Vitamin B12 deficiency (ビタミンＢ１２欠乏)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Cachexia (悪液質)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fluid retention (体液貯留)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Folate deficiency (葉酸欠乏)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Malnutrition (栄養障害)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Abnormal weight gain (異常体重増加)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Food intolerance (食物不耐性)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperamylasaemia (高アミラーゼ血症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypernatraemia (高ナトリウム血症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hyperphagia (過食)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypervolaemia (血液量増加症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypocalcaemia (低カルシウム血症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hypovolaemia (血液量減少症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Impaired fasting glucose (空腹時血中ブドウ糖不良)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Increased appetite (食欲亢進)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Lactic acidosis (乳酸アシドーシス)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Magnesium deficiency (マグネシウム欠乏)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	54	13.78	12	3.06	51	12.98	9	2.29	44	11.25	8	2.05
Rash (発疹)	10	2.55	4	1.02	4	1.02	2	0.51	7	1.79	2	0.51
Eczema (湿疹)	8	2.04	1	0.26	9	2.29	2	0.51	3	0.77	1	0.26
Erythema (紅斑)	5	1.28	2	0.51	3	0.76	0	0.00	3	0.77	1	0.26
Pruritus (そう痒症)	4	1.02	2	0.51	4	1.02	0	0.00	3	0.77	2	0.51
Alopecia (脱毛症)	5	1.28	1	0.26	4	1.02	1	0.25	1	0.26	0	0.00
Dermatitis (皮膚炎)	2	0.51	0	0.00	4	1.02	0	0.00	1	0.26	1	0.26
Actinic keratosis (光線角化症)	2	0.51	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Skin lesion (皮膚病変)	3	0.77	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Night sweats (寝汗)	2	0.51	1	0.26	0	0.00	0	0.00	3	0.77	0	0.00
Urticaria (蕁麻疹)	1	0.26	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Dry skin (皮膚乾燥)	1	0.26	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Acne (ざ瘡)	0	0.00	0	0.00	2	0.51	1	0.25	1	0.26	0	0.00
Papule (丘疹)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	2	0.51
Rash macular (斑状皮疹)	1	0.26	1	0.26	1	0.25	0	0.00	1	0.26	1	0.26
Rosacea (酒さ)	0	0.00	0	0.00	2	0.51	1	0.25	1	0.26	0	0.00
Seborrhoeic dermatitis (脂漏性皮膚炎)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dermatitis allergic (アレルギー性皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Dermatitis contact (接触皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Ecchymosis (斑状出血)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Erythema multiforme (多形紅斑)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperkeratosis (過角化)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Photosensitivity reaction (光線過敏性反応)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Psoriasis (乾癬)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Skin exfoliation (皮膚剥脱)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin ulcer (皮膚潰瘍)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Xanthelasma (黄色板腫)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Cutaneous calcification (皮膚石灰化)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

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Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Decubitus ulcer (褥瘡性潰瘍)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Dermal cyst (皮膚嚢腫)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Dermatitis acneiform (ざ瘡様皮膚炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Dermatitis atopic (アトピー性皮膚炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Erythema annulare (環状紅斑)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Granulomatous dermatitis (肉芽腫性皮膚炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hyperhidrosis (多汗症)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Hypertrichosis (多毛症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypohidrosis (乏汗症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ingrowing nail (陥入爪)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ingrown hair (内方発育毛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intertrigo (間擦疹)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Leukoplakia (白斑症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lichen sclerosus (硬化性苔癬)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lipohypertrophy (脂肪肥大症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Macule (斑)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Miliaria (汗疹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nail deformation (爪変形)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Neurodermatitis (神経皮膚炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Onychoclasis (爪破損)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Polymorphic light eruption (多形日光疹)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Precancerous skin lesion (前癌性皮膚病変)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Purpura (紫斑)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Rash morbilliform (麻疹様発疹)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Rash pruritic (そう痒性皮疹)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Rhinophyma (鼻瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin discolouration (皮膚変色)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin discomfort (皮膚不快感)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Skin erosion (皮膚びらん)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Skin fissures (皮膚亀裂)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin hyperpigmentation (皮膚色素過剰)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin irritation (皮膚刺激)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin mass (皮膚腫瘤)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin reaction (皮膚反応)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Solar dermatitis (日光皮膚炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Telangiectasia (毛細血管拡張症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Urticaria papular (丘疹状蕁麻疹)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	47	11.99	2	0.51	49	12.47	4	1.02	39	9.97	2	0.51
Fall (転倒)	9	2.30	0	0.00	8	2.04	0	0.00	3	0.77	0	0.00
Contusion (挫傷)	4	1.02	0	0.00	4	1.02	0	0.00	9	2.30	0	0.00
Procedural pain (処置による疼痛)	4	1.02	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Spinal compression fracture (脊椎圧迫骨折)	4	1.02	0	0.00	2	0.51	0	0.00	3	0.77	0	0.00
Ligament sprain (靱帯捻挫)	4	1.02	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Medication error (投薬過誤)	1	0.26	0	0.00	4	1.02	4	1.02	1	0.26	1	0.26
Rib fracture (肋骨骨折)	0	0.00	0	0.00	2	0.51	0	0.00	4	1.02	0	0.00
Tooth fracture (歯牙破折)	2	0.51	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Bone contusion (骨挫傷)	2	0.51	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Limb injury (四肢損傷)	2	0.51	0	0.00	3	0.76	0	0.00	0	0.00	0	0.00
Foot fracture (足骨折)	0	0.00	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Overdose (過量投与)	2	0.51	1	0.26	1	0.25	0	0.00	1	0.26	1	0.26
Skin laceration (皮膚裂傷)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Immunisation reaction (免疫反応)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Joint injury (関節損傷)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Skin abrasion (皮膚擦過傷)	0	0.00	0	0.00	1	0.25	0	0.00	2	0.51	0	0.00
Animal bite (動物咬傷)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Ankle fracture (足関節部骨折)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Arthropod bite (節足動物咬傷)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Femur fracture (大腿骨骨折)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hand fracture (手骨折)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Head injury (頭部損傷)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Meniscus injury (半月板損傷)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Muscle rupture (筋断裂)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Muscle strain (肉離れ)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Radius fracture (橈骨骨折)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Road traffic accident (交通事故)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skull fracture (頭蓋骨骨折)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Thermal burn (熱傷)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Accident (事故)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Accident at home (家庭内事故)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Accident at work (労働災害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Accidental overdose (偶発的過量投与)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Animal scratch (動物による引っかき傷)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arthropod sting (節足動物刺傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Back injury (背部損傷)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Burns first degree (第１度熱傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Comminuted fracture (粉砕骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Concussion (脳振盪)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Confusion postoperative (術後錯乱)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Femoral neck fracture (大腿骨頸部骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Heat stroke (熱射病)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ligament rupture (靱帯断裂)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lumbar vertebral fracture (腰椎骨折)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Pelvic fracture (骨盤骨折)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Post procedural complication (処置後合併症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Post procedural erythema (処置後紅斑)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Post procedural haematoma (処置後血腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Postoperative wound complication (術後創合併症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Procedural dizziness (処置によるめまい)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Procedural pneumothorax (処置による気胸)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Respiratory fume inhalation disorder (フューム吸引性呼吸障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Respiratory tract procedural complication (呼吸器系処置合併症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Scratch (引っかき傷)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skin injury (皮膚損傷)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Skin wound (皮膚創傷)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Spinal column injury (脊柱損傷)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spinal fracture (脊椎骨折)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Stress fracture (ストレス骨折)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Subcutaneous haematoma (皮下血腫)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Subdural haematoma (硬膜下血腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tendon rupture (腱断裂)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Traumatic ulcer (外傷性潰瘍)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Wound complication (創合併症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiac disorders (心臓障害)	27	6.89	2	0.51	40	10.18	5	1.27	47	12.02	5	1.28

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Atrial fibrillation (心房細動)	1	0.26	0	0.00	7	1.78	0	0.00	10	2.56	0	0.00
Palpitations (動悸)	2	0.51	1	0.26	5	1.27	1	0.25	5	1.28	1	0.26
Coronary artery disease (冠動脈疾患)	2	0.51	0	0.00	4	1.02	0	0.00	2	0.51	0	0.00
Tachycardia (頻脈)	1	0.26	0	0.00	3	0.76	1	0.25	4	1.02	0	0.00
Cardiac failure (心不全)	3	0.77	1	0.26	1	0.25	0	0.00	2	0.51	0	0.00
Acute myocardial infarction (急性心筋梗塞)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Coronary artery stenosis (冠動脈狭窄)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	1	0.26
Sinus bradycardia (洞性徐脈)	1	0.26	1	0.26	1	0.25	0	0.00	3	0.77	0	0.00
Supraventricular extrasystoles (上室性期外収縮)	2	0.51	0	0.00	1	0.25	0	0.00	2	0.51	1	0.26
Angina unstable (不安定狭心症)	0	0.00	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Arteriosclerosis coronary artery (冠動脈硬化症)	0	0.00	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Myocardial infarction (心筋梗塞)	0	0.00	0	0.00	2	0.51	0	0.00	2	0.51	0	0.00
Myocardial ischaemia (心筋虚血)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	1	0.26
Ventricular extrasystoles (心室性期外収縮)	2	0.51	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Cardiac failure acute (急性心不全)	3	0.77	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sinus tachycardia (洞性頻脈)	0	0.00	0	0.00	3	0.76	2	0.51	0	0.00	0	0.00
Angina pectoris (狭心症)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Aortic valve incompetence (大動脈弁閉鎖不全症)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Arrhythmia (不整脈)	1	0.26	1	0.26	1	0.25	0	0.00	0	0.00	0	0.00
Atrial tachycardia (心房頻脈)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atrioventricular block first degree (第一度房室ブロック)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Bradycardia (徐脈)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bundle branch block right (右脚ブロック)	0	0.00	0	0.00	1	0.25	1	0.25	1	0.26	1	0.26
Cardiac failure congestive (うっ血性心不全)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cor pulmonale acute (急性肺性心)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Extrasystoles (期外収縮)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Left ventricular dysfunction (左室機能不全)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Pericardial effusion (心嚢液貯留)	1	0.26	1	0.26	0	0.00	0	0.00	1	0.26	0	0.00
Acute left ventricular failure (急性左室不全)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Aortic valve disease (大動脈弁疾患)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aortic valve sclerosis (大動脈弁硬化症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Atrial flutter (心房粗動)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Bifascicular block (二束ブロック)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Bundle branch block (脚ブロック)	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Bundle branch block left (左脚ブロック)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Cardiac amyloidosis (心アミロイドーシス)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cardiac arrest (心停止)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cardiac dysfunction (心機能障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cardiac failure chronic (慢性心不全)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cardio-respiratory arrest (心肺停止)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cardiogenic shock (心原性ショック)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cardiomyopathy (心筋症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cardiovascular disorder (心血管障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Conduction disorder (伝導障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cor pulmonale chronic (慢性肺性心)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Coronary artery occlusion (冠動脈閉塞)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Defect conduction intraventricular (心室内伝導障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypertensive heart disease (高血圧性心疾患)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Left atrial enlargement (左房拡大)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Mitral valve incompetence (僧帽弁閉鎖不全症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pericarditis (心膜炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Supraventricular tachycardia (上室性頻脈)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vascular disorders (血管障害)	30	7.65	2	0.51	30	7.63	2	0.51	31	7.93	4	1.02
Hypertension (高血圧)	14	3.57	0	0.00	14	3.56	2	0.51	18	4.60	2	0.51
Hypotension (低血圧)	4	1.02	0	0.00	3	0.76	0	0.00	3	0.77	0	0.00
Vasculitis (血管炎)	1	0.26	0	0.00	3	0.76	0	0.00	1	0.26	1	0.26
Deep vein thrombosis (深部静脈血栓症)	2	0.51	0	0.00	1	0.25	0	0.00	1	0.26	1	0.26
Haematoma (血腫)	3	0.77	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hot flush (ほてり)	1	0.26	1	0.26	1	0.25	0	0.00	1	0.26	0	0.00
Orthostatic hypotension (起立性低血圧)	1	0.26	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Peripheral venous disease (末梢静脈疾患)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cyanosis (チアノーゼ)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Raynaud's phenomenon (レイノー現象)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Varicose vein (静脈瘤)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Aortic arteriosclerosis (大動脈硬化症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Aortic dilatation (大動脈拡張)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Aortic dissection (大動脈解離)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Aortic thrombosis (大動脈血栓症)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Arteriosclerosis (動脈硬化症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Flushing (潮紅)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypertensive crisis (高血圧クリーゼ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Peripheral arterial occlusive disease (末梢動脈閉塞性疾患)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Peripheral artery aneurysm (末梢動脈瘤)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Phlebitis superficial (表在性静脈炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Phlebolith (静脈結石)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Subclavian artery thrombosis (鎖骨下動脈血栓症)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Thrombophlebitis (血栓性静脈炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vena cava thrombosis (大静脈血栓症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Renal and urinary disorders (腎および尿路障害)	26	6.63	2	0.51	19	4.83	3	0.76	21	5.37	3	0.77
Haematuria (血尿)	6	1.53	1	0.26	2	0.51	0	0.00	3	0.77	1	0.26
Dysuria (排尿困難)	4	1.02	0	0.00	2	0.51	0	0.00	3	0.77	1	0.26
Nephrolithiasis (腎結石症)	2	0.51	0	0.00	1	0.25	0	0.00	4	1.02	0	0.00
Pollakiuria (頻尿)	3	0.77	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Micturition urgency (尿意切迫)	1	0.26	0	0.00	3	0.76	3	0.76	0	0.00	0	0.00
Proteinuria (蛋白尿)	2	0.51	1	0.26	0	0.00	0	0.00	2	0.51	1	0.26
Acute kidney injury (急性腎障害)	1	0.26	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Calculus urinary (尿路結石)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Renal cyst (腎嚢胞)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Glycosuria (糖尿)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Renal colic (腎仙痛)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Renal failure (腎不全)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Renal impairment (腎機能障害)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urinary incontinence (尿失禁)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Urinary retention (尿閉)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Urine odour abnormal (尿臭異常)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Albuminuria (アルブミン尿)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Anuria (無尿)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Bladder discomfort (膀胱不快感)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chronic kidney disease (慢性腎臓病)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Diabetic nephropathy (糖尿病性腎症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Focal segmental glomerulosclerosis (巣状分節性糸球体硬化症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Glomerulonephritis (糸球体腎炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hyperuricosuria (高尿酸尿症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Leukocyturia (白血球尿)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nephropathy (腎症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nocturia (夜間頻尿)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Renal injury (腎損傷)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Renal pain (腎臓痛)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Subacute kidney injury (亜急性腎障害)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urinary tract obstruction (尿路閉塞)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urine flow decreased (尿流量減少)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Eye disorders (眼障害)	11	2.81	0	0.00	12	3.05	0	0.00	22	5.63	3	0.77
Cataract (白内障)	4	1.02	0	0.00	2	0.51	0	0.00	7	1.79	0	0.00
Vision blurred (霧視)	3	0.77	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Conjunctival haemorrhage (結膜出血)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Dry eye (ドライアイ)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Retinal detachment (網膜剥離)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Visual impairment (視力障害)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Blepharitis (眼瞼炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cataract cortical (皮質白内障)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cataract subcapsular (嚢下白内障)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Central serous chorioretinopathy (中心性漿液性脈絡網膜症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Chalazion (霰粒腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Conjunctivitis allergic (アレルギー性結膜炎)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Conjunctivochalasis (結膜弛緩症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Corneal oedema (角膜浮腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dry age-related macular degeneration (乾性加齢黄斑変性)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Epiretinal membrane (網膜上膜)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Eye pain (眼痛)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eye pruritus (眼そう痒症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Foreign body sensation in eyes (眼の異物感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Lacrimation increased (流涙増加)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lagophthalmos (兎眼)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Macular hole (黄斑円孔)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Macular rupture (黄斑破裂)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Ocular discomfort (眼部不快感)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ocular hyperaemia (眼充血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Ocular hypertension (高眼圧症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Optic nerve sheath haemorrhage (視神経鞘出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Optic neuropathy (視神経症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Photopsia (光視症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Retinal haemorrhage (網膜出血)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vitreous degeneration (硝子体変性)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vitreous detachment (硝子体剥離)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vitreous floaters (硝子体浮遊物)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）)	10	2.55	0	0.00	17	4.33	0	0.00	16	4.09	0	0.00
Basal cell carcinoma (基底細胞癌)	1	0.26	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00
Squamous cell carcinoma of skin (皮膚有棘細胞癌)	0	0.00	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Lung neoplasm malignant (肺の悪性新生物)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Non-small cell lung cancer (非小細胞肺癌)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Skin papilloma (皮膚乳頭腫)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Small cell lung cancer (小細胞肺癌)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Adenosquamous cell carcinoma (腺扁平上皮癌)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Benign anorectal neoplasm (肛門直腸の良性新生物)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Benign lung neoplasm (肺の良性新生物)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Bowen's disease (ボーエン病)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Brain neoplasm malignant (脳の悪性新生物)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Colon cancer (結腸癌)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Colon neoplasm (結腸新生物)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Colorectal adenoma (結腸直腸腺腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Colorectal cancer (結腸直腸癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dysplastic naevus (異形成母斑)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eyelid seborrhoeic keratosis (眼瞼脂漏性角化症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Fibrous histiocytoma (線維性組織球腫)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Gastric cancer (胃癌)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Haemangioma of skin (皮膚血管腫)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hepatocellular carcinoma (肝細胞癌)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Keratoacanthoma (ケラトアカントーマ)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Large intestine benign neoplasm (大腸の良性新生物)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myelodysplastic syndrome (骨髄異形成症候群)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Neuroma (神経腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Papillary thyroid cancer (甲状腺乳頭癌)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Prostate cancer (前立腺癌)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Seborrhoeic keratosis (脂漏性角化症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Skin cancer (皮膚癌)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Small intestine carcinoma (小腸癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Squamous cell carcinoma (扁平上皮癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Squamous cell carcinoma of lung (肺扁平上皮癌)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Squamous cell carcinoma of the cervix (子宮頚部扁平上皮癌)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Uterine leiomyoma (子宮平滑筋腫)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Ear and labyrinth disorders (耳および迷路障害)	7	1.79	1	0.26	17	4.33	1	0.25	16	4.09	1	0.26
Vertigo (回転性めまい)	3	0.77	1	0.26	10	2.54	0	0.00	8	2.05	0	0.00
Tinnitus (耳鳴)	2	0.51	0	0.00	3	0.76	1	0.25	1	0.26	1	0.26
Hypoacusis (聴力低下)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Cerumen impaction (耳垢栓塞)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Ear pain (耳痛)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Excessive cerumen production (耳垢分泌過多)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Chondrodermatitis nodularis chronica helicis (耳介慢性結節性軟骨膜炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Deafness neurosensory (感音性難聴)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Ear discomfort (耳不快感)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Ear pruritus (耳そう痒症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Meniere's disease (メニエール病)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Otorrhoea (耳漏)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Tympanic membrane perforation (鼓膜穿孔)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Vertigo positional (頭位性回転性めまい)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hepatobiliary disorders (肝胆道系障害)	15	3.83	3	0.77	8	2.04	1	0.25	16	4.09	2	0.51
Hepatic function abnormal (肝機能異常)	7	1.79	2	0.51	1	0.25	1	0.25	3	0.77	1	0.26
Cholelithiasis (胆石症)	2	0.51	0	0.00	0	0.00	0	0.00	5	1.28	1	0.26

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Hepatic steatosis (脂肪肝)	1	0.26	0	0.00	1	0.25	0	0.00	3	0.77	0	0.00
Cholecystitis (胆嚢炎)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hepatic failure (肝不全)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hypertransaminasaemia (高トランスアミナーゼ血症)	1	0.26	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Bile duct stone (胆管結石)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Drug-induced liver injury (薬物性肝障害)	1	0.26	1	0.26	1	0.25	0	0.00	0	0.00	0	0.00
Liver disorder (肝障害)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Liver injury (肝損傷)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cholangitis (胆管炎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cholangitis acute (急性胆管炎)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Cholestasis (胆汁うっ滞)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congestive hepatopathy (うっ血性肝障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Gallbladder polyp (胆嚢ポリープ)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatic cirrhosis (肝硬変)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hepatic cytolysis (肝細胞融解)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hepatobiliary disease (肝胆道系疾患)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hyperplastic cholecystopathy (過形成性胆嚢症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Suspected drug-induced liver injury (薬物性肝障害の疑い)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Blood and lymphatic system disorders (血液およびリンパ系障害)	14	3.57	2	0.51	11	2.80	1	0.25	12	3.07	1	0.26
Anaemia (貧血)	6	1.53	1	0.26	6	1.53	0	0.00	9	2.30	1	0.26
Iron deficiency anaemia (鉄欠乏性貧血)	0	0.00	0	0.00	1	0.25	1	0.25	1	0.26	0	0.00
Leukocytosis (白血球増加症)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lymphadenopathy (リンパ節症)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Macrocytosis (大赤血球症)	2	0.51	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Thrombocytopenia (血小板減少症)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Autoimmune haemolytic anaemia (自己免疫性溶血性貧血)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Eosinophilia (好酸球増加症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypercoagulation (凝固亢進)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Increased tendency to bruise (内出血発生の増加傾向)	1	0.26	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00
Neutropenia (好中球減少症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Polycythaemia (赤血球増加症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Splenomegaly (脾腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Reproductive system and breast disorders (生殖系および乳房障害)	11	2.81	0	0.00	13	3.31	1	0.25	13	3.32	2	0.51
Benign prostatic hyperplasia (良性前立腺肥大症)	3	0.77	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00
Gynaecomastia (女性化乳房)	0	0.00	0	0.00	3	0.76	0	0.00	1	0.26	0	0.00
Balanoposthitis (亀頭包皮炎)	2	0.51	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Erectile dysfunction (勃起不全)	2	0.51	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Breast swelling (乳房腫脹)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Ejaculation failure (射精不能)	1	0.26	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Prostatitis (前立腺炎)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Prostatomegaly (前立腺腫大)	1	0.26	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
Adenomyosis (腺筋症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Adnexa uteri cyst (子宮付属器嚢胞)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Adnexa uteri mass (子宮付属器腫瘤)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Amenorrhoea (無月経)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Breast hyperplasia (乳房過形成)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Breast mass (乳房腫瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Breast tenderness (乳房圧痛)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Dysmenorrhoea (月経困難症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Endometriosis (子宮内膜症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Fibrocystic breast disease (線維嚢胞性乳腺疾患)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Genital haemorrhage (性器出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nipple disorder (乳頭障害)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Nipple swelling (乳頭腫脹)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Ovarian mass (卵巣腫瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Uterine enlargement (子宮肥大)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Vaginal haemorrhage (膣出血)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	1	0.26
Endocrine disorders (内分泌障害)	4	1.02	0	0.00	3	0.76	0	0.00	2	0.51	0	0.00
Hypothyroidism (甲状腺機能低下症)	0	0.00	0	0.00	2	0.51	0	0.00	0	0.00	0	0.00
Adrenal mass (副腎腫瘤)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cushingoid (クッシング様症状)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hyperthyroidism (甲状腺機能亢進症)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Inappropriate antidiuretic hormone secretion (抗利尿ホルモン不適合分泌)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Secondary adrenocortical insufficiency (続発性副腎皮質機能不全)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Thyroid cyst (甲状腺嚢腫)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Thyroid mass (甲状腺腫瘤)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Immune system disorders (免疫系障害)	2	0.51	0	0.00	4	1.02	0	0.00	3	0.77	0	0.00
Seasonal allergy (季節性アレルギー)	1	0.26	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Allergy to arthropod bite (節足動物咬傷アレルギー)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Anaphylactoid reaction (アナフィラキシー様反応)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Autoimmune disorder (自己免疫障害)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Cell-mediated immune deficiency (細胞性免疫不全症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Food allergy (食物アレルギー)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Hypersensitivity (過敏症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Sarcoidosis (サルコイドーシス)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害)	3	0.77	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Atrial septal defect (心房中隔欠損症)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Birth mark (あざ)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dolichocolon (過長結腸)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Hydrocele (陰嚢水瘤)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Phimosis (包茎)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Porokeratosis (汗孔角化症)	1	0.26	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Social circumstances (社会環境)	0	0.00	0	0.00	2	0.51	0	0.00	1	0.26	0	0.00
Menopause (閉経)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Personal relationship issue (人間関係の問題)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00
Pollution (汚染)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Sick relative (病気の近親者)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Product issues (製品の問題)	0	0.00	0	0.00	1	0.25	0	0.00	1	0.26	0	0.00
Device loosening (医療機器のゆるみ)	0	0.00	0	0.00	1	0.25	0	0.00	0	0.00	0	0.00
Device occlusion (医療機器閉塞)	0	0.00	0	0.00	0	0.00	0	0.00	1	0.26	0	0.00

Table 15.3.99: 3 Frequency of patients with all-cause AEs and drug-related AEs by treament, primary system organ class and preferred term (original and Japanese terms) - TS

Primary System Organ Class/ Preferred Term	Placebo				Nera 9mg				Nera 18mg			
	All-cause		Drug-related		All-cause		Drug-related		All-cause		Drug-related	
	N	%	N	%	N	%	N	%	N	%	N	%
Surgical and medical procedures (外科および内科処置)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00
Tooth extraction (抜歯)	0	0.00	0	0.00	0	0.00	0	0.00	2	0.51	0	0.00

15.4.2 Listings of deaths - other serious adverse events - adverse events of special interest and other significant adverse events

Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	62	69	8	Grade 4	No	NoChg	Yes	Rcver	LIFE THR	non-fatal MACE	
Acute myocardial infarction (急性心筋梗塞)																
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	145	160	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Atrial fibrillation (心房細動)																
Cardiac disorders (心臓障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	468			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP	not MACE	
Bradycardia (徐脈)																
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/F	438	438	1	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP		
Cardiac arrest (心停止)																
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	165	169	5	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Cardiac failure (心不全)																

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LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,REQ/PROL HSP=Requires or Prolongs Hospitalization,
CONG AB=Congenital Anomaly or Birth Defect,NA=Not Applicable,Withdr=Drug Withdrawn.MedDRA version used for reporting: 27.1

Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	208	298	91	Grade 4	No	Withdr	No	UNK	LIFE THR/REQ/PROL HSP		
Cardiac failure (心不全)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	362			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	150			Grade 1	Yes	NA	No	Nrec	OTHER		
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	145	160	16	Grade 2	No	NoChg	Yes	Rcver	OTHER	not MACE	
Cardiac failure acute (急性心不全)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	237	238	2	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	238			Grade 1	No	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害) Cardiac failure acute (急性心不全)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	174	183	10	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Cardiac disorders (心臓障害) Cardiac failure congestive (うっ血性心不全)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	330			Grade 1	No	NoChg	No	Nrec	REQ/PROL HSP		
Cardiac disorders (心臓障害) Cor pulmonale acute (急性肺性心)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	306			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Cardiac disorders (心臓障害) Coronary artery disease (冠動脈疾患)	Off-treatment	[redacted]	None	Other fibrotic patterns	7[redacted]/F	55	66	12	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP	not MACE	
	Off-treatment	[redacted]	None	Other fibrotic patterns	7[redacted]/F	126	128	3	Grade 3	No	NA	No	Seq	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臟障害) Coronary artery disease (冠動脈疾患)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	135			Grade 3	No	NoChg	No	UNK	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	263	264	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	284	285	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders (心臟障害) Coronary artery stenosis (冠動脈狭窄)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	213	216	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders (心臟障害) Supraventricular tachycardia (上室性頻脈)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	550			Grade 3	No	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害) Porokeratosis (汗孔角化症)	Placebo	[redacted]	None	Other fibrotic patterns	[redacted]/F	421			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Endocrine disorders (内分泌障害) Inappropriate antidiuretic hormone secretion (抗利尿ホルモン不適合分泌)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	238			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Eye disorders (眼障害) Cataract (白内障)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	488	490	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders (眼障害) Cataract subcapsular (嚢下白内障)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	58	126	69	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Eye disorders (眼障害) Retinal detachment (網膜剥離)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	335			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Gastrointestinal disorders (胃腸障害) Colitis (大腸炎)	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	262	301	40	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Diarrhoea (下痢)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	434	436	3	Grade 3	Yes	NoChg	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Gastritis erosive (びらん性胃炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	259	307	49	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Inguinal hernia (鼠径ヘルニア)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	[redacted]/M	220	223	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害) Obstructive pancreatitis (閉塞性膵炎)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	63	69	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Pancreatitis (膵炎)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/M	37			Grade 1	Yes	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	123	144	22	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Pancreatitis acute (急性膵炎)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	470	488	19	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	290	298	9	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Chest pain (胸痛)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	348	359	12	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	570	587	18	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	401	417	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/F	346	349	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	12	27	16	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	435			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	158	178	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	223	240	18	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	185	222	38	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	148	173	26	Grade 4	Yes	Withdr	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	20			Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	3[redacted]/F	36			Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	574			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	37	49	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	405[a]	434		Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	182	189	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	174	179	6	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	196	207	12	Grade 2	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	84	92	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	449	458	10	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	424	430	7	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	242	333	92	Grade 2	No	Withdr	No	Nrec	OTHER		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	431	431	1	Grade 5	No	NoChg	No	Fatal	FATAL		

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	529	558	30	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/F	187	200	14	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	277	309	33	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	253	269	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	347	363	17	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	97	102	6	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	102			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	257	258	2	Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	281	305	25	Grade 4	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/M	41	113	73	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	190	193	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	216	220	5	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		

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General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	113	116	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	52	101	50	Grade 4	No	NoChg	Yes	Seq	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	143	150	8	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	239	363	125	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	380			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	135			Grade 3	Yes	NoChg	Yes	UNK	REQ/PROL HSP		

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General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	108	115	8	Grade 5	No	NA	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	276	301	26	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	19	25	7	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	111	140	30	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	372	376	5	Grade 3	No	NA	No	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	179	183	5	Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		

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General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	183	183	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	139			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	258	258	1	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	16	21	6	Grade 4	Yes	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	21	21	1	Grade 5	Yes	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease

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General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	392	415	24	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined	Undetermined
Condition aggravated (状態悪化)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	351	351	1	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR	Respiratory	Underlying interstitial lung disease
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	140	164	25	Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	400	400	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined	Undetermined
Death (死亡)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	274	274	1	Grade 5	No	NA	No	Fatal	FATAL	Undetermined	Undetermined

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Disease progression (疾患進行)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	369	401	33	Grade 5	No	Withdr	Yes	Fatal	FATAL	Non-cardiovascular/non-respiratory	Other non-cv/non-respiratory causes
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Fatigue (疲労)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	98			Grade 4	Yes	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Oedema peripheral (末梢性浮腫)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	301	306	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Pyrexia (発熱)	Placebo	[redacted]	None	Other fibrotic patterns	3[redacted]/F	274	279	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Hepatobiliary disorders (肝胆道系障害) Cholangitis (胆管炎)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	595	604	10	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	639	649	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders (肝胆道系障害) Cholecystitis (胆嚢炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	70	73	4	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	391	392	2	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders (肝胆道系障害) Cholelithiasis (胆石症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	70	73	4	Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Hepatobiliary disorders (肝胆道系障害) Drug-induced liver injury (薬物性肝障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	86	107	22	Grade 3	Yes	NoChg	No	Rcver	OTHER		
Hepatobiliary disorders (肝胆道系障害) Hepatic failure (肝不全)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	426	446	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/F	428	434	7	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Immune system disorders (免疫系障害) Sarcoidosis (サルコイドーシス)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	156			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Aspergillus infection (アスペルギルス感染)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	296			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Bacteraemia (菌血症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	21	38	18	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	402			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Bronchitis (気管支炎)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/F	191	194	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) COVID-19 (ＣＯＶＩＤ－１９)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/M	284	294	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	110	127	18	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	241	244	4	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
COVID-19 (ＣＯＶＩＤ－１９)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	198	204	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	230	249	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	97	107	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	187	206	20	Grade 2	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	115	121	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	3[redacted]/F	134	141	8	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	21	38	18	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Diverticulitis (憩室炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	374	378	5	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/M	314	331	18	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastroenteritis (胃腸炎)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	13	15	3	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	297	341	45	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatitis E (E型肝炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	337	371	35	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Infection (感染)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	45	73	29	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	188	195	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Influenza (インフルエンザ)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	128	135	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	298	336	39	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Lower respiratory tract infection (下気道感染)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	366	373	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Lower respiratory tract infection (下気道感染)																
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	152	164	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Meningitis aseptic (無菌性髄膜炎)																
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	452	465	14	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Non-cardiovascular/non-respiratory	Infection (including sepsis)
Meningitis viral (ウイルス性髄膜炎)																
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	564	581	18	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Nasopharyngitis (上咽頭炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Peritonsillar abscess (扁桃周囲膿瘍)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	70	74	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	393	400	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumocystis jirovecii pneumonia (ニューモシスチス・イロベチイ肺炎)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	201			Grade 3	No	NoChg	Yes	UNK	OTHER		
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/M	284	293	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	430	445	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	3[redacted]/F	61	69	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	8[redacted]/F	184	203	20	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	8[redacted]/F	300	308	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	363	367	5	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	41	58	18	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	130	153	24	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Treatment: Placebo

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Infections and infestations (感染症および寄生虫症)																
Pneumonia (肺炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	338	344	7	Grade 3	Yes	NoChg	Yes	Rcver	OTHER		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	415	419	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	174	219	46	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	148	173	26	Grade 4	Yes	Withdr	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	92	98	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/M	93	104	12	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	62	69	8	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	448			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	267	277	11	Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	86	112	27	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	230	238	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	64	80	17	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	359	367	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	347	363	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/M	41			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	215	220	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	241	247	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	131	140	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	121	122	2	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Residual effect	[redacted]	None	Other fibrotic patterns	6[redacted]/F	277	277	1	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Pneumonia
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	410			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	140			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia aspiration (誤嚥性肺炎)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	63	72	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia bacterial (細菌性肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	284	298	15	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	109	120	12	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Pneumonia bacterial (細菌性肺炎)																
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	568	587	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	257			Grade 4	No	NoChg	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	76	88	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	337	347	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia fungal (真菌性肺炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	574			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia pneumococcal (肺炎球菌性肺炎)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	531			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pulmonary tuberculosis (肺結核)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	399			Grade 3	Yes	Withdr	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Respiratory syncytial virus infection (ＲＳウイルス感染)	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	127	139	13	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Respiratory tract infection (気道感染)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	496			Grade 2	No	NA	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Sepsis (敗血症)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	595	604	10	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP/OTHER		
Infections and infestations (感染症および寄生虫症) Upper respiratory tract infection (上気道感染)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	97	125	29	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	178	185	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Placebo

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Infections and infestations (感染症および寄生虫症) Urinary tract infection (尿路感染)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	173	177	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Viral infection (ウイルス感染)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	10	20	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Concussion (脳振盪)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	545	547	3	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Contusion (挫傷)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	466	483	18	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Femur fracture (大腿骨骨折)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	22	37	16	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Ligament rupture (靱帯断裂)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	346	350	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Overdose (過量投与)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	90	129	40	Grade 3	No	NoChg	No	Rcver	OTHER		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Pelvic fracture (骨盤骨折)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	226	434	209	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Post procedural complication (処置後合併症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	121			Grade 3	No	Withdr	No	UNK	OTHER		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Road traffic accident (交通事故)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	545	545	1	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Skin laceration (皮膚裂傷)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	545	547	3	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Spinal compression fracture (脊椎圧迫骨折)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	81	114	34	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Investigations (臨床検査) Human metapneumovirus test positive (ヒトメタニューモウイルス検査陽性)	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/F	346	349	4	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Investigations (臨床検査) Mycobacterium tuberculosis complex test positive (結核菌群検査陽性)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	444			Grade 3	Yes	NA	Yes	Nrec	OTHER		
Investigations (臨床検査) Oxygen saturation decreased (酸素飽和度低下)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	98[a]	147		Grade 3	No	NA	No	Rcver	OTHER		

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Investigations (臨床検査) Streptococcus test positive (レンサ球菌検査陽性)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	[redacted]/F	239	363	125	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders (代謝および栄養障害) Decreased appetite (食欲減退)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/F	301	309	9	Grade 3	Yes	NA	No	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders (代謝および栄養障害) Dehydration (脱水)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/F	301	309	9	Grade 3	Yes	NA	No	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders (代謝および栄養障害) Diabetes mellitus inadequate control (コントロール不良の糖尿病)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	8	9	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		

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Metabolism and nutrition disorders (代謝および栄養障害) Steroid diabetes (ステロイド糖尿病)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	414			Grade 1	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Antisynthetase syndrome (抗合成酵素症候群)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/M	99	104	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Dermatomyositis (皮膚筋炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	183			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	3[redacted]/F	36			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Facet joint syndrome (椎間関節症候群)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	310	315	6	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Idiopathic inflammatory myopathy (特発性炎症性ミオパチー)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	308			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Jaw cyst (顎骨嚢胞)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	316	319	4	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Muscular weakness (筋力低下)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	107			Grade 4	No	Withdr	Yes	UNK	LIFE THR/REQ /PROL HSP/OTHER		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Osteolysis (骨溶解)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	121			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Osteonecrosis (骨壊死)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	15	16	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Scleroderma (強皮症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	57			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	253			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Systemic scleroderma (全身性強皮症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	201			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	122			Grade 1	No	NoChg	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	277	322	46	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Basal cell carcinoma (基底細胞癌)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Bowen's disease (ボーエン病)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	277	321	45	Grade 2	No	NoChg	No	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Brain neoplasm malignant (脳の悪性新生物)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	32			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Colon cancer (結腸癌)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	177			Grade 3	No	Withdr	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Neuroma (神経腫)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/M	473	477	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Papillary thyroid cancer (甲状腺乳頭癌)	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/M	594			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Squamous cell carcinoma of lung (肺扁平上皮癌)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	457			Grade 2	No	Withdr	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Carotid artery stenosis (頚動脈狭窄)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	68	68	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Nervous system disorders (神経系障害) Carpal tunnel syndrome (手根管症候群)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	253	255	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Nervous system disorders (神経系障害) Cerebrovascular accident (脳卒中)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	599			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	40	68	29	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	527	540	14	Grade 2	No	NA	Yes	Rcver	OTHER	non-fatal MACE	
Nervous system disorders (神経系障害) Dementia (認知症)	Placebo	[redacted]	None	Other fibrotic patterns	8[redacted]/M	6			Grade 1	No	NA	No	UNK	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Epilepsy (てんかん)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	455			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Nervous system disorders (神経系障害) Headache (頭痛)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	149	164	16	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Nervous system disorders (神経系障害) Loss of consciousness (意識消失)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	114			Grade 4	Yes	NA	Yes	UNK	LIFE THR/REQ/PROL HSP		
Nervous system disorders (神経系障害) Transient ischaemic attack (一過性脳虚血発作)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	152	152	1	Grade 2	No	NoChg	Yes	Seq	OTHER	not MACE	
Psychiatric disorders (精神障害) Anxiety (不安)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	183			Grade 3	No	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Psychiatric disorders (精神障害) Anxiety (不安)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	365			Grade 3	No	NoChg	No	Nrec	OTHER		
Psychiatric disorders (精神障害) Delirium (譫妄)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/M	48			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Psychiatric disorders (精神障害) Depression (うつ病)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	365			Grade 3	No	Withdr	No	Nrec	OTHER		
Psychiatric disorders (精神障害) Disorientation (失見当識)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489			Grade 4	No	NA	No	UNK	LIFE THR/REQ /PROL HSP		
Psychiatric disorders (精神障害) Suicidal ideation (自殺念慮)	Placebo	[redacted]	Pirfenidone	UIP or UIP-like fibrotic pattern	6[redacted]/M	86	127	42	Grade 1	Yes	NoChg	No	Rcver	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	170	170	1	Grade 1	Yes	NoChg	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Renal and urinary disorders (腎および尿路障害)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	267			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Acute kidney injury (急性腎障害)																
Renal and urinary disorders (腎および尿路障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	195	454	260	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Glomerulonephritis (糸球体腎炎)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	329			Grade 1	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Acute respiratory failure (急性呼吸不全)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	8[redacted]/F	373			Grade 4	Yes	NoChg	No	Nrec	LIFE THR		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	174	176	3	Grade 2	No	NoChg	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Acute respiratory failure (急性呼吸不全)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	22	25	4	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Alveolar proteinosis (肺胞蛋白症)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/M	67			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Bronchiectasis (気管支拡張症)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/F	191	194	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Choking (息詰まり)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	36	36	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Other respiratory causes

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Chronic obstructive pulmonary disease (慢性閉塞性肺疾患)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489			Grade 4	No	NA	Yes	UNK	LIFE THR		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Dyspnoea (呼吸困難)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	188	365	178	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	328	334	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	30	37	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	264			Grade 2	No	Withdr	Yes	Nrec	REQ/PROL HSP		

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	438	458	21	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
Dyspnoea (呼吸困難)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	350	374	25	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	98			Grade 4	Yes	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	406			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/F	152			Grade 1	No	NoChg	No	Nrec	REQ/PROL HSP		
Dyspnoea exertional (労作性呼吸困難)																

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489			Grade 4	No	NA	No	UNK	LIFE THR/REQ/PROL HSP		
Hypercapnia (高炭酸ガス血症)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	212			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Hypersensitivity pneumonitis (過敏性肺臓炎)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	98			Grade 4	Yes	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP		
Hypoxia (低酸素症)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	141	168	28	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Interstitial lung disease (間質性肺疾患)																

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Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	365			Grade 2	No	NoChg	No	Nrec	OTHER		
Interstitial lung disease (間質性肺疾患)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	105	130	26	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	62	69	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	190			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	568	572	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	113	250	138	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/OTHER	Respiratory	Underlying interstitial lung disease
Interstitial lung disease (間質性肺疾患)	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/M	478			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	None	Other fibrotic patterns	4[redacted]/F	372	372	1	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	620	620	1	Grade 5	No	NoChg	No	Fatal	FATAL		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	238			Grade 2	No	NoChg	No	Nrec	OTHER		
Pneumomediastinum (気縦隔症)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)																
Pneumomediastinum (気縦隔症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	125	190	66	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)																
Pneumothorax (気胸)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	227			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	322	327	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	58	85	28	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	5[redacted]/M	273			Grade 1	No	NoChg	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	261	293	33	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Pneumothorax (気胸)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	181	267	87	Grade 1	No	NoChg	No	Rcver	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	281	309	29	Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	309	323	15	Grade 2	No	NoChg	No	Nrec	REQ/PROL HSP/OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	323	341	19	Grade 1	No	NoChg	No	Rcver	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	362	365	4	Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	365			Grade 2	No	Withdr	No	Nrec	REQ/PROL HSP/OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/M	46			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Pneumothorax (気胸)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	121	121	1	Grade 1	No	NoChg	No	Rcver	OTHER		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	119			Grade 1	No	NA	No	UNK	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	290			Grade 2	No	NoChg	No	Nrec	OTHER		
Pulmonary arterial hypertension (肺動脈性肺高血圧症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	33			Grade 3	No	NoChg	No	UNK	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	110	112	3	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Pulmonary arterial hypertension (肺動脈性肺高血圧症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	164			Grade 2	Yes	NoChg	Yes	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	37	137	101	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pulmonary embolism (肺塞栓症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	372	372	1	Grade 5	No	NA	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	109			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Pulmonary fibrosis (肺線維症)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	320			Grade 1	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	186			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	None	Other fibrotic patterns	8[redacted]/M	177			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Residual effect	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	398	398	1	Grade 5	No	NA	No	Fatal	FATAL		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	403			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Pulmonary hypertension (肺高血圧症)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	198			Grade 3	No	NA	No	Nrec	REQ/PROL HSP		
Pulmonary hypertension (肺高血圧症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	453			Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	315			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	273			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	8[redacted]/F	17			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	243	245	3	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary hypertension (肺高血圧症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	366			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	231			Grade 1	No	NoChg	No	Nrec	OTHER		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	254			Grade 3	No	NoChg	No	UNK	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary mass (肺腫瘤)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	421			Grade 1	No	NoChg	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	230			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Pulmonary oedema (肺水腫)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489			Grade 4	No	NA	No	UNK	LIFE THR/REQ/PROL HSP		
Respiratory distress (呼吸窮迫)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/M	284	294	11	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Respiratory failure (呼吸不全)																
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	146	151	6	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	127	159	33	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Respiratory failure (呼吸不全)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	201	227	27	Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	98	118	21	Grade 5	Yes	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	406	426	21	Grade 5	No	NoChg	No	Fatal	FATAL/REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	199			Grade 3	No	NA	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Respiratory failure (呼吸不全)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	150	173	24	Grade 2	Yes	NA	Yes	Rcver	OTHER		
	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489	492	4	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP		
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害) Psoriasis (乾癬)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	125	135	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders (血管障害) Aortic thrombosis (大動脈血栓症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	398			Grade 2	Yes	NoChg	Yes	Nrec	OTHER	not MACE	
Vascular disorders (血管障害) Deep vein thrombosis (深部静脈血栓症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	14[a]	398		Grade 2	No	NoChg	Yes	Seq	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Vascular disorders (血管障害) Deep vein thrombosis (深部静脈血栓症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	38			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Vascular disorders (血管障害) Hypertension (高血圧)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	81	82	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders (血管障害) Subclavian artery thrombosis (鎖骨下動脈血栓症)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	398			Grade 2	Yes	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Blood and lymphatic system disorders (血液およびリンパ系障害) Anaemia (貧血)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	418	430	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders (心臓障害) Acute left ventricular failure (急性左室不全)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	14	18	5	Grade 3	Yes	NA	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders (心臓障害) Acute myocardial infarction (急性心筋梗塞)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	57	57	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Cardiac disorders (心臓障害) Angina unstable (不安定狭心症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	534			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP	not MACE	

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害) Arteriosclerosis coronary artery (冠動脈硬化症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	534			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP	not MACE	
Cardiac disorders (心臓障害) Atrial fibrillation (心房細動)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	357	363	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	306	308	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	84	86	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders (心臓障害) Atrial flutter (心房粗動)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	154			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害) Cardiac failure (心不全)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	204	214	11	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Cardiac disorders (心臓障害) Cardiac failure chronic (慢性心不全)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	75	93	19	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders (心臓障害) Cardio-respiratory arrest (心肺停止)	Residual effect	[redacted]	None	Other fibrotic patterns	6[redacted]/F	304	304	1	Grade 5	No	NA	No	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
Cardiac disorders (心臓障害) Cardiogenic shock (心原性ショック)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	47	51	5	Grade 5	No	NA	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Cardiovascular procedures
Cardiac disorders (心臓障害) Conduction disorder (伝導障害)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	173	184	12	Grade 4	No	NA	Yes	Seq	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	301			Grade 1	No	NoChg	No	Nrec	OTHER		
Cor pulmonale acute (急性肺性心)																
Cardiac disorders (心臓障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	171	176	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Coronary artery disease (冠動脈疾患)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	359	360	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	44			Grade 4	No	NA	Yes	UNK	LIFE THR/REQ/PROL HSP		
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	287	335	49	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Coronary artery occlusion (冠動脈閉塞)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害) Coronary artery stenosis (冠動脈狭窄)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	544			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders (心臓障害) Myocardial infarction (心筋梗塞)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	5[redacted]/M	123	129	7	Grade 4	No	NoChg	Yes	Seq	LIFE THR/REQ/PROL HSP	non-fatal MACE	
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	287	295	9	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP	non-fatal MACE	
Cardiac disorders (心臓障害) Tachycardia (頻脈)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	338			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害) Atrial septal defect (心房中隔欠損症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	2[redacted]/F	401	402	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Ear and labyrinth disorders (耳および迷路障害) Deafness neurosensory (感音性難聴)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	235			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Ear and labyrinth disorders (耳および迷路障害) Vertigo (回転性めまい)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	337	338	2	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Ear and labyrinth disorders (耳および迷路障害) Vertigo positional (頭位性回転性めまい)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	19	42	24	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders (眼障害) Central serous chorioretinopathy (中心性漿液性脈絡網膜症)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	236			Grade 1	No	NoChg	No	Nrec	OTHER		
Eye disorders (眼障害) Dry age-related macular degeneration (乾性加齢黄斑変性)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	422			Grade 1	No	NoChg	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害) Colitis (大腸炎)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	502	508	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Dyspepsia (消化不良)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	437	445	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Gastrointestinal haemorrhage (胃腸出血)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	109	115	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Non-cardiovascular/non-respiratory	Gastrointestinal causes
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	266	267	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Inguinal hernia (鼠径ヘルニア)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	120	176	57	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害) Large intestine polyp (大腸ポリープ)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	576	578	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	298	309	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Oesophageal varices haemorrhage (食道静脈瘤出血)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	299	301	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Pancreatic failure (膵不全)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	417			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Gastrointestinal disorders (胃腸障害) Peptic ulcer (消化性潰瘍)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	109			Grade 3	No	NA	Yes	UNK	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害) Rectal haemorrhage (直腸出血)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	160			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Rectal polyp (直腸ポリープ)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	298	309	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrointestinal disorders (胃腸障害) Subileus (亜イレウス)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	143	149	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Chest pain (胸痛)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	70	71	2	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	465	465	1	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP	not MACE	
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	117			Grade 3	No	NoChg	Yes	UNK	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	82	117	36	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	181	194	14	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	51	101	51	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	365	400	36	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	148	203	56	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	4	19	16	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	34			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	297	307	11	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	297	303	7	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	4[redacted]/M	212	224	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	511	521	11	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	340			Grade 2	No	NA	Yes	Nrec	REQ/PROL HSP		
Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	4[redacted]/F	148			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	53	80	28	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	344	351	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	282	288	7	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	330	346	17	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	262	276	15	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	319			Grade 4	No	NoChg	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	255	316	62	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	186	269	84	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	62			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	462	474	13	Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	428	437	10	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	464			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	303	305	3	Grade 4	No	Withdr	Yes	UNK	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	218	238	21	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	501	510	10	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	479	484	6	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	372	375	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	209	225	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	254	278	25	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	102	112	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	107	121	15	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	156			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	212			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	321			Grade 2	No	NoChg	No	Nrec	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	455			Grade 2	No	NA	No	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	Other fibrotic patterns	4[redacted]/M	56	68	13	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	281			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	511	512	2	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	305	305	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Death (死亡)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	23	23	1	Grade 5	No	NA	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Sudden cardiac death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Fatigue (疲労)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	359[a]	424		Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) General physical health deterioration (全身健康状態悪化)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	440			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Hepatobiliary disorders (肝胆道系障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	43			Grade 4	No	NA	No	UNK	LIFE THR/DISABL/REQ/PROL HSP		
Congestive hepatopathy (うっ血性肝障害)																
Hepatobiliary disorders (肝胆道系障害)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	1			Grade 3	No	NoChg	No	Nrec	OTHER		
Drug-induced liver injury (薬物性肝障害)																
Hepatobiliary disorders (肝胆道系障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	410	441	32	Grade 2	No	NA	Yes	Rcver	OTHER		
Hepatic failure (肝不全)																
Immune system disorders (免疫系障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	435	535	101	Grade 1	No	NoChg	No	Rcver	OTHER		
Cell-mediated immune deficiency (細胞性免疫不全症)																
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	83	84	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Appendicitis (虫垂炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/F	108	112	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Bronchitis (気管支炎)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	173	176	4	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	434			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Bronchopulmonary aspergillosis (気管支肺アスペルギルス症)																
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	418	430	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
COVID-19 (ＣＯＶＩＤ－１９)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	528	535	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) COVID-19 (ＣＯＶＩＤ－１９)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	408	415	8	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	45	51	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	266	273	8	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Cellulitis (蜂巣炎)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	145	154	10	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Haemophilus infection (ヘモフィルス感染)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	143	147	5	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Influenza (インフルエンザ)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	140	166	27	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	88	96	9	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Lower respiratory tract infection (下気道感染)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	242	252	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	97	119	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	6[redacted]/F	57	62	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	433	442	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	181	194	14	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	530	547	18	Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	418	430	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	462	472	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	367	373	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	339	349	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	330	354	25	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	146	204	59	Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	266	282	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	204	214	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	612	619	8	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	84	102	19	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	357			Grade 1	No	NA	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	189	196	8	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	499	512	14	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	48	58	11	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	309			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	464			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	344	359	16	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	217	224	8	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	493	514	22	Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	228	232	5	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	588			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	407			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	254	265	12	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	113	117	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/F	224	229	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/F	338	345	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	322	325	4	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP/OTHER		
Pneumonia (肺炎)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	250	251	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	134	176	43	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	85	91	7	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	407	436	30	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	528	530	3	Grade 4	No	NA	No	UNK	LIFE THR/REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	281			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	261	286	26	Grade 4	No	NA	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia bacterial (細菌性肺炎)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	446	460	15	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia influenzal (インフルエンザ性肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	45	49	5	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	513	521	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	521	521	1	Grade 5	No	NoChg	Yes	Fatal	FATAL		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia necrotising (壊死性肺炎)	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	421			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Infections and infestations (感染症および寄生虫症) Respiratory syncytial virus infection (ＲＳウイルス感染)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	400			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Respiratory tract infection (気道感染)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	511			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	45	55	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	217	230	14	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Respiratory tract infection (気道感染)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	367	377	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Sepsis (敗血症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	237	247	11	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	407	436	30	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Septic shock (敗血症性ショック)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	527	530	4	Grade 5	No	Withdr		Fatal	FATAL	Non-cardiovascular/non-respiratory	Infection (including sepsis)
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	113	117	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Septic shock (敗血症性ショック)	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	150	155	6	Grade 5	No	NA	Yes	Fatal	FATAL	Non-cardiovascular/non-respiratory	Malignancy (new or worsening)
Infections and infestations (感染症および寄生虫症) Soft tissue infection (軟部組織感染)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	3[redacted]/M	280	295	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Upper respiratory tract infection (上気道感染)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	234	266	33	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	147	166	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	330	350	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Urinary tract infection (尿路感染)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	209	225	17	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Fall (転倒)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	417	430	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Femur fracture (大腿骨骨折)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	197	206	10	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Lumbar vertebral fracture (腰椎骨折)																

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Procedural pneumothorax (処置による気胸)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	84	89	6	Grade 1	No	NoChg	No	Rcver	OTHER		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Rib fracture (肋骨骨折)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	303	309	7	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	309	330	22	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Skull fracture (頭蓋骨骨折)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	72	128	57	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Spinal compression fracture (脊椎圧迫骨折)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	147	262	116	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations (臨床検査) C-reactive protein increased (Ｃ－反応性蛋白増加)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	295	306	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations (臨床検査) Heart rate increased (心拍数増加)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	56	253	198	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		
Metabolism and nutrition disorders (代謝および栄養障害) Hyponatraemia (低ナトリウム血症)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	97	139	43	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Metabolism and nutrition disorders (代謝および栄養障害) Hypovolaemia (血液量減少症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	418	430	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Metabolism and nutrition disorders (代謝および栄養障害) Lactic acidosis (乳酸アシドーシス)	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	407	410	4	Grade 1	No	NoChg	No	Rcver	OTHER		
Metabolism and nutrition disorders (代謝および栄養障害) Malnutrition (栄養障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	223	232	10	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Back pain (背部痛)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	6	53	48	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Intervertebral disc protrusion (椎間板突出)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	203	213	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Rheumatoid arthritis (関節リウマチ)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	451[a]	495		Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Sjogren's syndrome (シェーグレン症候群)	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	410			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Spinal stenosis (脊柱管狭窄症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	432	435	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Systemic scleroderma (全身性強皮症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	227	230	4	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Adenosquamous cell carcinoma (腺扁平上皮癌)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	448	448	1	Grade 1	No	Withdr	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Basal cell carcinoma (基底細胞癌)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	346	430	85	Grade 3	No	NA	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	75	233	159	Grade 1	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	432	432	1	Grade 3	No	NoChg	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Benign anorectal neoplasm (肛門直腸の良性新生物)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	176	176	1	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Colon neoplasm (結腸新生物)	Residual effect	[redacted]	None	Other fibrotic patterns	才/F	145			Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ /PROL HSP/OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Gastric cancer (胃癌)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	才/F	402			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Hepatocellular carcinoma (肝細胞癌)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	才/M	34	53	20	Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ /PROL HSP/OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Lung neoplasm malignant (肺の悪性新生物)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	275			Grade 3	No	Withdr	No	UNK	REQ/PROL HSP		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Myelodysplastic syndrome (骨髄異形成症候群)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	[redacted]/M	149			Grade 2	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Non-small cell lung cancer (非小細胞肺癌)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	30	68	39	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Prostate cancer (前立腺癌)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	166			Grade 3	No	Withdr	Yes	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Skin cancer (皮膚癌)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	286[a]			Grade 2	No	NoChg	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Squamous cell carcinoma of skin (皮膚有棘細胞癌)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	255	280	26	Grade 1	No	NoChg	Yes	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Carotid artery dissection (頚動脈解離)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	160			Grade 4	No	NoChg	Yes	UNK	LIFE THR	not MACE	
Nervous system disorders (神経系障害) Cerebral haemorrhage (脳出血)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	72	128	57	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ /PROL HSP	not MACE	
Nervous system disorders (神経系障害) Cerebral infarction (脳梗塞)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	247	257	11	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Nervous system disorders (神経系障害) Cerebrovascular accident (脳卒中)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	215	216	2	Grade 4	No	NoChg	Yes	Seq	LIFE THR/REQ /PROL HSP	non-fatal MACE	
Nervous system disorders (神経系障害) Hypercapnic coma (高炭酸ガス血性昏睡)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	158			Grade 4	No	NoChg	Yes	Nrec	LIFE THR/REQ /PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Hypertensive encephalopathy (高血圧性脳症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	235	251	17	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Nervous system disorders (神経系障害) Lacunar infarction (ラクナ梗塞)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	495			Grade 2	No	NoChg	Yes	Nrec	OTHER	not MACE	
Nervous system disorders (神経系障害) Spondylitic myelopathy (脊椎炎性脊髄症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	242	324	83	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	407	476	70	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Nervous system disorders (神経系障害) Syncope (失神)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	318	318	1	Grade 4	No	NoChg	No	Seq	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Transient ischaemic attack (一過性脳虚血発作)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	114	114	1	Grade 3	No	NoChg	Yes	Rcver	OTHER	not MACE	
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	320	320	1	Grade 2	No	NA	Yes	Rcver	REQ/PROL HSP/OTHER	not MACE	
Nervous system disorders (神経系障害) Vagus nerve paralysis (迷走神経麻痺)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	160			Grade 2	No	NoChg	No	Nrec	OTHER		
Nervous system disorders (神経系障害) Vertebral artery stenosis (椎骨動脈狭窄)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	206	215	10	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP	not MACE	
Product issues (製品の問題) Device loosening (医療機器のゆるみ)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	44	283	240	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Psychiatric disorders (精神障害) Anxiety (不安)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	[redacted]/M	275	277	3	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		
Psychiatric disorders (精神障害) Delirium (譫妄)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/F	330	344	15	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Psychiatric disorders (精神障害) Depression (うつ病)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	255	290	36	Grade 3	No	NoChg	No	Nrec	OTHER		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	370			Grade 1	No	NoChg	Yes	Nrec	OTHER		
Psychiatric disorders (精神障害) Suicidal ideation (自殺念慮)	Off-treatment	[redacted]	None	Other fibrotic patterns	[redacted]/F	274	311	38	Grade 1	No	NoChg	No	Rcver	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Psychiatric disorders (精神障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	260	286	27	Grade 4	Yes	Withdr	No	Rcver	LIFE THR/REQ/PROL HSP		
Suicide attempt (自殺企図)																
Renal and urinary disorders (腎および尿路障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	337	341	5	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Acute kidney injury (急性腎障害)																
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	114			Grade 3	No	NA	No	UNK	REQ/PROL HSP		
Renal and urinary disorders (腎および尿路障害)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	115			Grade 3	No	NA	No	UNK	REQ/PROL HSP		
Anuria (無尿)																
Renal and urinary disorders (腎および尿路障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	229	230	2	Grade 1	No	NoChg	No	Rcver	REQ/PROL HSP		
Nephrolithiasis (腎結石症)																

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Reproductive system and breast disorders (生殖系および乳房障害) Adnexa uteri mass (子宮付属器腫瘤)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	355			Grade 3	No	NoChg	No	Nrec	OTHER		
Reproductive system and breast disorders (生殖系および乳房障害) Benign prostatic hyperplasia (良性前立腺肥大症)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	1	4	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	320	322	3	Grade 2	No	NA	Yes	Rcver	REQ/PROL HSP		
Reproductive system and breast disorders (生殖系および乳房障害) Prostatitis (前立腺炎)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	160	188	29	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Acute respiratory distress syndrome (急性呼吸窮迫症候群)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	284	290	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Acute respiratory failure (急性呼吸不全)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	121	147	27	Grade 3	No	NoChg	Yes	Rcver	OTHER		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	343			Grade 2	No	NA	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	254	263	10	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	368	375	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Asthma (喘息)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	340			Grade 2	No	NA	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Chronic obstructive pulmonary disease (慢性閉塞性肺疾患)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	445	456	12	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Chronic respiratory failure (慢性呼吸不全)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	349			Grade 3	No	NoChg	No	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Cough (咳嗽)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	237	246	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	206	212	7	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Dyspnoea (呼吸困難)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	257			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	423	430	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	31	50	20	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	183			Grade 2	No	NoChg	No	UNK	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	275	277	3	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	132	189	58	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hypersensitivity pneumonitis (過敏性肺臓炎)																
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	250	261	12	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	367			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	423	430	8	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hypoxia (低酸素症)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	116			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Interstitial lung disease (間質性肺疾患)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	28	33	6	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	610	614	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	183	309	127	Grade 1	No	NoChg	No	Rcver	OTHER		
Pneumomediastinum (気縦隔症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	233	261	29	Grade 1	No	NoChg	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	24	39	16	Grade 2	No	NoChg	No	Rcver	OTHER		
Pneumothorax (気胸)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	419	446	28	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	44	57	14	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	16	24	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	110	132	23	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	132	144	13	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	148	167	20	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Pneumothorax (気胸)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	167	173	7	Grade 2	No	NoChg	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	185	214	30	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	214	221	8	Grade 2	No	NoChg	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	568	572	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	127			Grade 1	No	NoChg	No	Nrec	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	454	475	22	Grade 1	No	NoChg	No	Rcver	OTHER		
Pneumothorax (気胸)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	322	323	2	Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	323	331	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	331	390	60	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	418	419	2	Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	546	551	6	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	551			Grade 1	Yes	NoChg	No	Nrec	OTHER		
Pneumothorax (気胸)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	156	168	13	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	446	457	12	Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	457	533	77	Grade 1	No	NoChg	No	Rcver	OTHER		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	168	302	135	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	421	435	15	Grade 2	No	NoChg	Yes	Rcver	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	434			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Pulmonary embolism (肺塞栓症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	73	260	188	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	498			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	87	271	185	Grade 2	No	NoChg	Yes	Rcver	OTHER		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	421			Grade 3	No	NoChg	Yes	Nrec	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	422			Grade 2	No	NoChg	Yes	UNK	OTHER		
Pulmonary fibrosis (肺線維症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	313			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	376			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/M	253			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Pulmonary hypertension (肺高血圧症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	252			Grade 2	No	NoChg	Yes	Nrec	OTHER		

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Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	109	131	23	Grade 1	No	NoChg	No	Nrec	OTHER		
Pulmonary hypertension (肺高血圧症)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	131			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	401			Grade 1	No	NoChg	No	Nrec	OTHER		
	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	147			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	107			Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	421			Grade 1	No	NoChg	No	Nrec	OTHER		

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System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary mass (肺腫瘤)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	447	451	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary oedema (肺水腫)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	112			Grade 3	No	NA	Yes	UNK	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Respiratory acidosis (呼吸性アシドーシス)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	158			Grade 4	No	NoChg	No	Nrec	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	19	21	3	Grade 2	No	Withdr	No	Nrec	REQ/PROL HSP		
Respiratory failure (呼吸不全)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	21	21	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	327	327	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Pneumonia
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	14	18	5	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	284	284	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Vascular disorders (血管障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	160	220	61	Grade 5	No	NoChg	Yes	Fatal	FATAL	Cardiovascular (fatal MACE)	Other cardiovascular causes
Aortic dissection (大動脈解離)																
Vascular disorders (血管障害)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/F	136			Grade 3	No	NA	Yes	Rcver	OTHER		
Deep vein thrombosis (深部静脈血栓症)																
Vascular disorders (血管障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	313	317	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hypotension (低血圧)																
	Off-treatment	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	407	409	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders (血管障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	278			Grade 2	No	Withdr	Yes	Nrec	OTHER	Vasculitis	
Vasculitis (血管炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Vascular disorders (血管障害) Vasculitis (血管炎)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	93	104	12	Grade 1	No	NoChg	No	Rcver	OTHER	not Vasculitis	
Vascular disorders (血管障害) Vena cava thrombosis (大静脈血栓症)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	245	259	15	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Blood and lymphatic system disorders (血液およびリンパ系障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	43	57	15	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Anaemia (貧血)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	64			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	95	110	16	Grade 4	No	NoChg	Yes	Rcver	LIFE THR	non-fatal MACE	
Acute myocardial infarction (急性心筋梗塞)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	257	263	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	555			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	non-fatal MACE	

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	473	478	6	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Angina pectoris (狭心症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	253	302	50	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	113	117	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Angina unstable (不安定狭心症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	288			Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	282	284	3	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Cardiovascular (fatal MACE)	Cardiovascular procedures

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	121	121	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
Arteriosclerosis coronary artery (冠動脈硬化症)																
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	286	289	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Atrial fibrillation (心房細動)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	140	143	4	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	94	126	33	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	241	248	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	395			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	not MACE	
Atrial fibrillation (心房細動)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	562			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP	non-fatal MACE	
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	60	65	6	Grade 1	No	NoChg	Yes	Rcver	OTHER		
Cardiac failure (心不全)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	244	282	39	Grade 4	No	NoChg	Yes	Seq	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	Other fibrotic patterns	8[redacted]/M	210	215	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	65	72	8	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP	not MACE	
Cardiac failure congestive (うっ血性心不全)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	245			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Cor pulmonale chronic (慢性肺性心)																
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	337	366	30	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP/OTHER		
Coronary artery disease (冠動脈疾患)																
Cardiac disorders (心臓障害)	Interruption (residual effect)	[redacted]	Ninted anib	UIP or UIP-like fibrotic pattern	7[redacted]/M	43	43	1	Grade 4	No	NoChg	No	Seq	LIFE THR	not MACE	
Myocardial infarction (心筋梗塞)																
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	492			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Cardiac disorders (心臓障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	245			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Pericardial effusion (心嚢液貯留)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Eye disorders (眼障害)																
Cataract (白内障)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	[redacted]/F	427	432	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders (眼障害)																
Cataract cortical (皮質白内障)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	151	151	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Eye disorders (眼障害)																
Conjunctivochalasis (結膜弛緩症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/F	519	521	3	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Eye disorders (眼障害)																
Macular hole (黄斑円孔)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	151	196	46	Grade 1	No	NoChg	No	Rcver	OTHER		
Eye disorders (眼障害)																
Macular rupture (黄斑破裂)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	151			Grade 1	No	NoChg	No	Nrec	OTHER		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Eye disorders (眼障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	151	196	46	Grade 1	No	NoChg	No	Rcver	OTHER		
Macular rupture (黄斑破裂)																
Eye disorders (眼障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	27	78	52	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Retinal detachment (網膜剥離)																
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	172	173	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Abdominal pain lower (下腹部痛)																
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	297	302	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Diverticulum intestinal (腸憩室)																
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	170	179	10	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Enteritis (小腸炎)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	103	132	30	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastric antral vascular ectasia (胃前庭部毛細血管拡張症)																
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	170	173	4	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
Gastritis (胃炎)																
Gastrointestinal disorders (胃腸障害)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	122	131	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Gastrooesophageal reflux disease (胃食道逆流性疾患)																
Gastrointestinal disorders (胃腸障害)	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	379	383	5	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		
Inguinal hernia (鼠径ヘルニア)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Gastrointestinal disorders (胃腸障害) Intestinal obstruction (腸閉塞)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	145	151	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Asthenia (無力症)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	117	121	5	Grade 3	Yes	NA	Yes	Rcver	REQ/PROL HSP		
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	111	139	29	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	378	435	58	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	121	138	18	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	511			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Condition aggravated (状態悪化)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	35	43	9	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	351	406	56	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	47	50	4	Grade 2	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	46	58	13	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	215	248	34	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Underlying interstitial lung disease
Condition aggravated (状態悪化)	Nera 18mg bid	[redacted]	Pirfenidone	Other fibrotic patterns	8[redacted]/M	28	55	28	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Pirfenidone	Other fibrotic patterns	8[redacted]/M	181	187	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	512			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	295	324	30	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	138	164	27	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	439	456	18	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	302	333	32	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	398	414	17	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	455	477	23	Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	613			Grade 4	No	Withdr	No	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	450	455	6	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	128	134	7	Grade 4	No	NoChg	No	Rcver	LIFE THR/REQ/PROL HSP		
Condition aggravated (状態悪化)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	39			Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	178	179	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	574			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	19	168	150	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	50	52	3	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	52	54	3	Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ /PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	54	54	1	Grade 5	No	NA	Yes	Fatal	FATAL	Respiratory	Other respiratory causes
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Disease progression (疾患進行)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	183			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	81	81	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Hepatobiliary disorders (肝胆道系障害) Bile duct stone (胆管結石)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	203	211	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders (肝胆道系障害) Cholangitis acute (急性胆管炎)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	203	211	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders (肝胆道系障害) Cholecystitis (胆嚢炎)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	359	367	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hepatobiliary disorders (肝胆道系障害) Cholelithiasis (胆石症)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	8[redacted]/F	32	32	1	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	438	447	10	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Hepatobiliary disorders (肝胆道系障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	43	49	7	Grade 3	No	NoChg	No	Rcver	OTHER		
Suspected drug-induced liver injury (薬物性肝障害の疑い)																
Immune system disorders (免疫系障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	513	515	3	Grade 2	No	NoChg	No	Rcver	OTHER		
Anaphylactoid reaction (アナフィラキシー様反応)																
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	420	462	43	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
Bacterial infection (細菌感染)																
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	503	526	24	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Bronchiolitis (細気管支炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Bronchitis (気管支炎)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	555	570	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Bronchitis bacterial (細菌性気管支炎)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	185	190	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Bronchopulmonary aspergillosis (気管支肺アスペルギルス症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/M	205			Grade 1	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	[redacted]/F	170	201	32	Grade 3	No	NA	Yes	Nrec	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	272	276	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
COVID-19 (ＣＯＶＩＤ－１９)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	22	44	23	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	108	127	20	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	392	394	3	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	8[redacted]/M	344	348	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
COVID-19 pneumonia (ＣＯＶＩＤ－１９肺炎)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	99	105	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
COVID-19 pneumonia (ＣＯＶＩＤ－１９肺炎)																
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	60	65	6	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	185	190	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Citrobacter infection (シトロバクター感染)																
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	623			Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Influenza (インフルエンザ)																
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	19	25	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Respiratory	Pneumonia

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	47	86	40	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Influenza (インフルエンザ)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	59	65	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	38	60	23	Grade 2	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	156	202	47	Grade 4	Yes	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Lower respiratory tract infection (下気道感染)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	475			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	188	200	13	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
Lower respiratory tract infection (下気道感染)																
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	474	493	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	556[a]			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Medical device site infection (医療機器使用部位感染)																
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	488	510	23	Grade 1	Yes	NoChg	No	Nrec	OTHER		
Osteomyelitis (骨髄炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Osteomyelitis (骨髄炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/F	510	565	56	Grade 2	Yes	NoChg	Yes	Rcver	OTHER		
Infections and infestations (感染症および寄生虫症) Pneumocystis jirovecii pneumonia (ニューモシスチス・イロベチイ肺炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	280	303	24	Grade 3	Yes	Withdr	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	[redacted]/F	6	13	8	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	[redacted]/M	358	406	49	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	25	34	10	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Pneumonia (肺炎)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	242	252	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	160	179	20	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	372	374	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	236	241	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	287	302	16	Grade 3	No	NA	Yes	Seq	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	217	245	29	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	387	402	16	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	197	260	64	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	54	95	42	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	34	43	10	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	406	419	14	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	79	83	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	362	380	19	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	493	504	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	90	94	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	78	90	13	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	48	52	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumonia (肺炎)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	270	278	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	375	398	24	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	184	200	17	Grade 3	No	Withdr		Nrec	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	53	59	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	127	133	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	239	255	17	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	154	164	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Off-treatment	[redacted]	None	Other fibrotic patterns	4[redacted]/F	226	236	11	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	Other fibrotic patterns	8[redacted]/F	138	152	15	Grade 3	Yes	NA	Yes	Rcver	REQ/PROL HSP		
	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/M	272	276	5	Grade 4	No	NA	Yes	Nrec	LIFE THR/REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia aspiration (誤嚥性肺炎)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	192	214	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pneumonia bacterial (細菌性肺炎)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	248	295	48	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia bacterial (細菌性肺炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	245	250	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	433	446	14	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pulmonary sepsis (肺敗血症)	Interruption (residual effect)	[redacted]	Ninted anib	UIP or UIP-like fibrotic pattern	7[redacted]/M	125	159	35	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Pyelonephritis (腎盂腎炎)	Nera 18mg bid	[redacted]	Ninted anib	Other fibrotic patterns	8[redacted]/F	311	315	5	Grade 4	No	NoChg	Yes	Rcver	LIFE THR/REQ/PROL HSP		

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Treatment: Nera 18mg bid

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Infections and infestations (感染症および寄生虫症) Respiratory tract infection (気道感染)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	189	197	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Sepsis (敗血症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	314			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
	Residual effect	[redacted]	None	Other fibrotic patterns	8[redacted]/F	138	152	15	Grade 1	No	NA	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Serratia infection (セラチア感染)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	185	190	6	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Infections and infestations (感染症および寄生虫症) Upper respiratory tract infection (上気道感染)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	125	135	11	Grade 2	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Infections and infestations (感染症および寄生虫症)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	245	255	11	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Urinary tract infection (尿路感染)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	3[redacted]/F	75	75	1	Grade 5	No	NA	No	Fatal	FATAL	Non-cardiovascular/non-respiratory	Trauma
Accident (事故)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	363			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Comminuted fracture (粉砕骨折)																
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	79	119	41	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Femoral neck fracture (大腿骨頚部骨折)																

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Treatment: Nera 18mg bid

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Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Overdose (過量投与)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	84	127	44	Grade 3	Yes	NoChg	No	Rcver	OTHER		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Rib fracture (肋骨骨折)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	363			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Skull fracture (頭蓋骨骨折)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	147	161	15	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Spinal compression fracture (脊椎圧迫骨折)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	340	347	8	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		

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Treatment: Nera 18mg bid

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Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	135	160	26	Grade 3	No	NA	Yes	Rcver	REQ/PROL HSP		
Spinal compression fracture (脊椎圧迫骨折)																
	Off-treatment	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/F	163	192	30	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	489	497	9	Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER	not MACE	
Subdural haematoma (硬膜下血腫)																
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	497	565	69	Grade 2	No	NoChg	No	Rcver	OTHER	not MACE	

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Investigations (臨床検査) ECG signs of myocardial ischaemia (心筋虚血の心電図所見)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/F	463	463	1	Grade 4	No	NA	No	Rcver	LIFE THR/REQ /PROL HSP	not MACE	
Investigations (臨床検査) Influenza A virus test positive (A型インフルエンザウイルス検査陽性)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	195	204	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Investigations (臨床検査) Mycobacterium tuberculosis complex test positive (結核菌群検査陽性)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	370			Grade 2	No	NoChg	No	Nrec	OTHER		
Investigations (臨床検査) Respiratory rate increased (呼吸数増加)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	282	288	7	Grade 3	No	NA	No	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Metabolism and nutrition disorders (代謝および栄養障害)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	138	145	8	Grade 3	Yes	NoChg	Yes	Rcver	REQ/PROL HSP		
Dehydration (脱水)																
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	297	317	21	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Arthritis (関節炎)																
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	116	120	5	Grade 2	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Back pain (背部痛)																
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	294	453	160	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Intervertebral disc protrusion (椎間板突出)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	75			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Osteonecrosis (骨壊死)																
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	303			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	41	57	17	Grade 3	Yes	NoChg	No	Rcver	REQ/PROL HSP		
Osteoporotic fracture (骨粗鬆症性骨折)																
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	156			Grade 3	No	NoChg	Yes	Nrec	OTHER		
Polymyositis (多発性筋炎)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Rheumatoid arthritis (関節リウマチ)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	3[redacted]/F	156	158	3	Grade 3	Yes	NoChg	Yes	Seq	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Scleroderma (強皮症)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	2	5	4	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	184	188	5	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害) Spinal stenosis (脊柱管狭窄症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	404	407	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	385			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Basal cell carcinoma (基底細胞癌)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	54	61	8	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	353	353	1	Grade 3	No	Withdr	Yes	Rcver	OTHER		
Colorectal cancer (結腸直腸癌)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Keratoacanthoma (ケラトアカントーマ)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	230	230	1	Grade 3	No	Withdr	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Lung neoplasm malignant (肺の悪性新生物)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	477			Grade 1	No	NoChg	No	Nrec	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Non-small cell lung cancer (非小細胞肺癌)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	351	523	173	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Small cell lung cancer (小細胞肺癌)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/M	394	402	9	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	120			Grade 3	No	Withdr	Yes	Nrec	REQ/PROL HSP/OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Small intestine carcinoma (小腸癌)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	207	247	41	Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	247	262	16	Grade 3	No	Withdr	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Squamous cell carcinoma (扁平上皮癌)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	269	493	225	Grade 1	No	Withdr	Yes	Rcver	OTHER		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Squamous cell carcinoma of skin (皮膚有棘細胞癌)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	235[a]	279		Grade 2	No	Withdr	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/F	23	23	1	Grade 2	No	Withdr	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	302	342	41	Grade 1	No	Withdr	Yes	Rcver	OTHER		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	182			Grade 3	No	Withdr	Yes	UNK	REQ/PROL HSP/OTHER		
Squamous cell carcinoma of the cervix (子宮頚部扁平上皮癌)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	171	207	37	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	non-fatal MACE	
Cerebral haemorrhage (脳出血)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	258	323	66	Grade 2	No	NoChg	No	Rcver	OTHER	not MACE	
Cerebral ischaemia (脳虚血)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	5[redacted]/M	111			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP	non-fatal MACE	
Cerebrovascular accident (脳卒中)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	188	198	11	Grade 2	No	NoChg	Yes	Seq	REQ/PROL HSP	not MACE	
Cerebrovascular insufficiency (脳血管不全)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	423	425	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Cubital tunnel syndrome (肘部管症候群)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	147	161	15	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP		
Loss of consciousness (意識消失)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	129	130	2	Grade 3	No	NA	No	Rcver	REQ/PROL HSP		
Migraine (片頭痛)																
Nervous system disorders (神経系障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	3[redacted]/M	389			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Neurological symptom (神経学的症状)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害) Seizure (痙攣発作)	Interruption (residual effect)	[redacted]	Nintedanib	Other fibrotic patterns	3[redacted]/M	228	259	32	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
Nervous system disorders (神経系障害) Subarachnoid haemorrhage (くも膜下出血)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	147	161	15	Grade 3	No	NoChg	No	Seq	REQ/PROL HSP	not MACE	
Nervous system disorders (神経系障害) Syncope (失神)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	7[redacted]/F	307	315	9	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	317	317	1	Grade 3	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	231	235	5	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Nervous system disorders (神経系障害)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	330	357	28	Grade 3	No	NoChg	Yes	Rcver	DISABL/ REQ/PROL HSP	not MACE	
Transient ischaemic attack (一過性脳虚血発作)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	215	240	26	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP	not MACE	
Nervous system disorders (神経系障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	85	89	5	Grade 3	Yes	NA	Yes	Seq	REQ/PROL HSP	non-fatal MACE	
Vertebrobasilar insufficiency (椎骨脳底動脈不全)																
Psychiatric disorders (精神障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	36	76	41	Grade 3	Yes	NoChg	No	Rcver	OTHER		
Anxiety (不安)																
Psychiatric disorders (精神障害)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	298	298	1	Grade 1	No	NA	No	Rcver	OTHER		
Delirium (譫妄)																

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Psychiatric disorders (精神障害) Delirium (譫妄)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	176	234	59	Grade 1	No	NA	Yes	Rcver	OTHER		
Psychiatric disorders (精神障害) Suicidal ideation (自殺念慮)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	8	8	1	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	533	533	1	Grade 3	Yes	Withdr	No	Rcver	OTHER		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	43	127	85	Grade 1	No	Withdr	No	Rcver	OTHER		
Renal and urinary disorders (腎および尿路障害) Haematuria (血尿)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	216	218	3	Grade 3	No	NA	No	Rcver	REQ/PROL HSP		
Renal and urinary disorders (腎および尿路障害) Nephrolithiasis (腎結石症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	341	344	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Renal and urinary disorders (腎および尿路障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	114	136	23	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Renal colic (腎仙痛)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	6[redacted]/F	377	386	10	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Acute respiratory failure (急性呼吸不全)																
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	53	56	4	Grade 1	No	NoChg	Yes	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	60	65	6	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	289			Grade 4	No	Withdr	Yes	Nrec	LIFE THR/REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	250	252	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Dyspnoea (呼吸困難)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	364			Grade 3	No	NoChg	No	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	363	369	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Haemothorax (血胸)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	368	368	1	Grade 5	No	NA	No	Fatal	FATAL	Respiratory	Underlying interstitial lung disease
Interstitial lung disease (間質性肺疾患)	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/F	372	392	21	Grade 3	Yes	NA	Yes	Rcver	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	8[redacted]/M	442			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP/OTHER		
Pleural effusion (胸水)																
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	365	526	162	Grade 1	No	NoChg	No	Rcver	OTHER		
Pneumomediastinum (気縦隔症)																
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	7[redacted]/M	43	116	74	Grade 2	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	138	143	6	Grade 2	No	NoChg	No	Nrec	OTHER		
	Nera 18mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	143	309	167	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	449	456	8	Grade 2	No	NoChg	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	491	501	11	Grade 2	No	NoChg	No	Rcver	OTHER		
Pneumomediastinum (気縦隔症)																
	Off-treatment	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	250	260	11	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	343	351	9	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Pneumothorax (気胸)																
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	127	141	15	Grade 1	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	183	526	344	Grade 1	No	NoChg	No	Rcver	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	547	552	6	Grade 1	No	NoChg	No	Rcver	OTHER		
Pneumothorax (気胸)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	189	245	57	Grade 3	No	NA	Yes	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	363	369	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	245			Grade 2	No	NoChg	Yes	Nrec	OTHER		
Pulmonary arterial hypertension (肺動脈性肺高血圧症)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary embolism (肺塞栓症)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	294			Grade 2	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	562	565	4	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary hypertension (肺高血圧症)	Interruption (residual effect)	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	26	79	54	Grade 2	No	NoChg	No	Rcver	OTHER		
	Interruption (residual effect)	[redacted]	None	Other fibrotic patterns	6[redacted]/F	377			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	293			Grade 2	No	NoChg	No	Nrec	OTHER		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/F	80			Grade 1	No	NoChg	No	Nrec	OTHER		
Pulmonary hypertension (肺高血圧症)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/F	481	482	2	Grade 2	No	NoChg	No	Rcver	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	140	343	204	Grade 2	No	NoChg	No	Rcver	OTHER		
	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	173			Grade 1	No	NoChg	No	Nrec	OTHER		
	Off-treatment	[redacted]	None	Other fibrotic patterns	6[redacted]/M	527			Grade 3	No	NoChg	Yes	Nrec	OTHER		
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	291			Grade 1	No	NA	No	Nrec	OTHER		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	296			Grade 3	No	NA	Yes	UNK	OTHER		
Pulmonary hypertension (肺高血圧症)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	461			Grade 3	No	NA	Yes	UNK	OTHER		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Interruption (residual effect)	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	358	396	39	Grade 4	No	NoChg	No	Rcver	LIFE THR		
Respiratory failure (呼吸不全)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	287	302	16	Grade 3	No	NA	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/M	251	349	99	Grade 2	No	NoChg	No	Rcver	OTHER		

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	54	57	4	Grade 3	No	NoChg	No	Rcver	REQ/PROL HSP/OTHER		
Respiratory failure (呼吸不全)																
	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	65	72	8	Grade 3	No	NoChg	Yes	Seq	REQ/PROL HSP		
	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/F	335			Grade 3	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	250	252	3	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Sinus congestion (副鼻腔うっ血)																

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Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Vocal cord leukoplakia (声帯白斑症)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	5[redacted]/M	214			Grade 1	No	NoChg	Yes	Nrec	REQ/PROL HSP		
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Wheezing (喘鳴)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	7	21	15	Grade 2	No	NoChg	Yes	Seq	REQ/PROL HSP		
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害) Neurodermatitis (神経皮膚炎)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	369			Grade 3	Yes	NoChg	Yes	Nrec	REQ/PROL HSP		
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害) Papule (丘疹)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	369			Grade 3	Yes	NoChg	Yes	Nrec	REQ/PROL HSP		

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Listing 15.4.2: 1 Patients with serious adverse events by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Outcome	Adj Cause of Death
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	192	198	7	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Skin ulcer (皮膚潰瘍)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	5[redacted]/F	328	339	12	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Vascular disorders (血管障害)	Nera 18mg bid	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	45	126	82	Grade 3	Yes	NoChg	Yes	Rcver	OTHER		
Deep vein thrombosis (深部静脈血栓症)																
Vascular disorders (血管障害)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	262	263	2	Grade 3	No	NoChg	Yes	Rcver	REQ/PROL HSP		
Hypertension (高血圧)																
Vascular disorders (血管障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/F	146	182	37	Grade 2	No	NoChg	Yes	Rcver	OTHER		
Hypertensive crisis (高血圧クリーゼ)																

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Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Cardiac disorders (心臓障害)	Placebo	[redacted]	None	Other fibrotic patterns	4[redacted]/F	438	438	1	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	
Cardiac arrest (心停止)															
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	12	27	16	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Underlying interstitial lung disease
Condition aggravated (状態悪化)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	431	431	1	Grade 5	No	NoChg	No	Fatal	FATAL	
	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/M	41	113	73	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	108	115	8	Grade 5	No	NA	Yes	Fatal	FATAL/LIFE THR/REQ/PROL HSP	Underlying interstitial lung disease

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	183	183	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	258	258	1	Grade 5	No	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	21	21	1	Grade 5	Yes	NA	No	Fatal	FATAL	Underlying interstitial lung disease
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	392	415	24	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	351	351	1	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR	Underlying interstitial lung disease
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Death (死亡)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	400	400	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Undetermined
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	274	274	1	Grade 5	No	NA	No	Fatal	FATAL	Undetermined
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Disease progression (疾患進行)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	369	401	33	Grade 5	No	Withdr	Yes	Fatal	FATAL	Other non-cv/ non-respiratory causes

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) COVID-19 (ＣＯＶＩＤ－１９)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	198	204	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Infections and infestations (感染症および寄生虫症) Infection (感染)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/F	45	73	29	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Infections and infestations (感染症および寄生虫症) Meningitis viral (ウイルス性髄膜炎)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	452	465	14	Grade 5	No	Withdr	No	Fatal	FATAL/REQ/PROL HSP	Infection (including sepsis)
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	121	122	2	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
	Residual effect	[redacted]	None	Other fibrotic patterns	6[redacted]/F	277	277	1	Grade 5	No	NA	Yes	Fatal	FATAL	Pneumonia

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia bacterial (細菌性肺炎)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	8[redacted]/M	109	120	12	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Choking (息詰まり)	Placebo	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	36	36	1	Grade 5	No	NA	No	Fatal	FATAL	Other respiratory causes
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Dyspnoea (呼吸困難)	Placebo	[redacted]	None	Other fibrotic patterns	7[redacted]/F	328	334	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Dyspnoea (呼吸困難)	Placebo	[redacted]	None	Other fibrotic patterns	6[redacted]/F	350	374	25	Grade 5	No	NA	Yes	Fatal	FATAL	Underlying interstitial lung disease
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Interstitial lung disease (間質性肺疾患)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	113	250	138	Grade 5	No	Withdr	Yes	Fatal	FATAL/LIFE THR/OTHER	Underlying interstitial lung disease
	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	6[redacted]/M	620	620	1	Grade 5	No	NoChg	No	Fatal	FATAL	
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Pulmonary embolism (肺塞栓症)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	372	372	1	Grade 5	No	NA	Yes	Fatal	FATAL	Sudden cardiac death

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Placebo

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Residual effect	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	398	398	1	Grade 5	No	NA	No	Fatal	FATAL	
Pulmonary fibrosis (肺線維症)															
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Placebo	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	98	118	21	Grade 5	Yes	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Respiratory failure (呼吸不全)	Placebo	[redacted]	Nintedanib	Other fibrotic patterns	7[redacted]/M	406	426	21	Grade 5	No	NoChg	No	Fatal	FATAL/REQ/PROL HSP	
	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	489	492	4	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
Cardiac disorders (心臓障害)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/F	57	57	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Acute myocardial infarction (急性心筋梗塞)															
Cardiac disorders (心臓障害)	Residual effect	[redacted]	None	Other fibrotic patterns	6[redacted]/F	304	304	1	Grade 5	No	NA	No	Fatal	FATAL	Sudden cardiac death
Cardio-respiratory arrest (心肺停止)															
Cardiac disorders (心臓障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	47	51	5	Grade 5	No	NA	Yes	Fatal	FATAL	Cardiovascular procedures
Cardiogenic shock (心原性ショック)															
Gastrointestinal disorders (胃腸障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	109	115	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Gastrointestinal causes
Gastrointestinal haemorrhage (胃腸出血)															

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	8[redacted]/F	148	203	56	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
	Nera 9mg bid	[redacted]	None	Other fibrotic patterns	6[redacted]/M	330	346	17	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/F	479	484	6	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	511	512	2	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Pneumonia

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Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Condition aggravated (状態悪化)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	5[redacted]/M	305	305	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
General disorders and administration site conditions (一般・全身障害および投与部位の状態) Death (死亡)	Nera 9mg bid	[redacted]	Nintedanib	Other fibrotic patterns	6[redacted]/M	23	23	1	Grade 5	No	NA	Yes	Fatal	FATAL	Sudden cardiac death
Infections and infestations (感染症および寄生虫症) Influenza (インフルエンザ)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	140	166	27	Grade 5	No	NA	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Infections and infestations (感染症および寄生虫症) Pneumonia (肺炎)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	499	512	14	Grade 5	No	NoChg	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia

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Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Pneumonia influenzal (インフルエンザ性肺炎)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	521	521	1	Grade 5	No	NoChg	Yes	Fatal	FATAL	
Infections and infestations (感染症および寄生虫症) Septic shock (敗血症性ショック)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	527	530	4	Grade 5	No	Withdr		Fatal	FATAL	Infection (including sepsis)
	Residual effect	[redacted]	None	Other fibrotic patterns	7[redacted]/F	150	155	6	Grade 5	No	NA	Yes	Fatal	FATAL	Malignancy (new or worsening)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害) Respiratory failure (呼吸不全)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	21	21	1	Grade 5	No	NA	No	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 9mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Dura-tion	Inten-sity-(CTCAE)	Drug Rel.	Action Taken	The-rapy	Out-come	Serious	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 9mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	327	327	1	Grade 5	No	NA	No	Fatal	FATAL	Pneumonia
Respiratory failure (呼吸不全)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	284	284	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
Vascular disorders (血管障害)	Nera 9mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	4[redacted]/M	160	220	61	Grade 5	No	NoChg	Yes	Fatal	FATAL	Other cardiovascular causes
Aortic dissection (大動脈解離)															

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MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Cardiac disorders (心臓障害)	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/F	282	284	3	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Cardiovascular procedures
Angina unstable (不安定狭心症)															
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	8[redacted]/M	215	248	34	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Underlying interstitial lung disease
Condition aggravated (状態悪化)															
	Residual effect	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	54	54	1	Grade 5	No	NA	Yes	Fatal	FATAL	Other respiratory causes
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	Residual effect	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	81	81	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
Disease progression (疾患進行)															

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Seq=Recovered or Resolved with Sequelae, UNK=Unknown. LIFE THR=Is Life Threatening, DISABL=Persist or Signif Disability/Incapacity,
REQ/PROL HSP=Requires or Prolongs Hospitalization, CONG AB=Congenital Anomaly or Birth Defect, NA=Not Applicable,Withdr=Drug Withdrawn.
MedDRA definition:HLGT Anxiety disorders and symptoms (primary SOC allocation only)

Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity- (CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Infections and infestations (感染症および寄生虫症) Influenza (インフルエンザ)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	7[redacted]/M	19	25	7	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	Pneumonia
Injury, poisoning and procedural complications (傷害、中毒および処置合併症) Accident (事故)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	3[redacted]/F	75	75	1	Grade 5	No	NA	No	Fatal	FATAL	Trauma
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (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）) Non-small cell lung cancer (非小細胞肺癌)	Nera 18mg bid	[redacted]	None	UIP or UIP-like fibrotic pattern	6[redacted]/M	351	523	173	Grade 5	No	Withdr	Yes	Fatal	FATAL/REQ/PROL HSP	

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Listing 15.4.2: 8 Patients with adverse events leading to death by treatment, primary system organ class and preferred term - TS

Treatment: Nera 18mg bid

System organ class/ Preferred term	Actual TRT at onset of AE	Patient	Anti-fibrotic treatment at baseline	Baseline HRCT Pattern	Age/ Sex	Start Day [1]	Stop Day [1]	Duration	Intensity-(CTCAE)	Drug Rel.	Action Taken	Therapy	Outcome	Serious	Adj Cause of Death
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	Nera 18mg bid	[redacted]	Nintedanib	UIP or UIP-like fibrotic pattern	7[redacted]/M	368	368	1	Grade 5	No	NA	No	Fatal	FATAL	Underlying interstitial lung disease
Interstitial lung disease (間質性肺疾患)															

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