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略号一覧表

略号又は略称	名称及び内容
[redacted]	[redacted]
AUC	血漿中濃度-時間曲線下面積（area under the curve）
AUC_{0-t}	0 時間から定量限界を超えた最終定量可能 t 時間までの血漿中濃度-時間曲線下面積（area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the lower limit of quantification）
$AUC_{0-\infty}$	0 時間から無限大時間までの血漿中濃度-時間曲線下面積（area under the plasma concentration-time curve from time zero to infinity）
AUC_{72h}	0 時間から 72 時間までの血漿中濃度-時間曲線下面積（area under the plasma concentration-time curve from time zero to 72 hours）
BCS	生物薬剤学分類（biopharmaceutical classification system）
CI	信頼区間（confidence interval）
C_{last}	最終定量可能時間における血漿中濃度（last quantifiable plasma concentration）
CL/F	経口クリアランス（oral clearance）
C_{max}	最高血漿中濃度（maximum plasma concentration）
COVID-19	新型コロナウイルス感染症（coronavirus disease 2019）
CSR	治験総括報告書（clinical study report）
CV	変動係数（coefficient of variation）
CVw	被験者内変動係数（intraparticipant [within-participant] coefficient of variation）
EDTA	エチレンジアミン四酢酸（ethylenediaminetetraacetic acid）
ERA	エンドセリン受容体拮抗薬（endothelin receptor antagonist）
ET	エンドセリン（endothelin）
[redacted]	[redacted]
FDC	マシテンタン 10 mg／タダラフィル 40 mg 配合剤（fixed dose combination）
FDC-2	マシテンタン 10 mg／タダラフィル 40 mg フィルムコーティング錠製剤-2（fixed dose combination formulation 2）
LC-MS/MS	液体クロマトグラフィー－タンデム質量分析（liquid chromatography with tandem mass spectrometry）
LLOQ	定量下限（lower limit of quantification）
MS	質量分析（mass spectrometry）
PAH	肺動脈性肺高血圧症（pulmonary arterial hypertension）
PDE5	ホスホジエステラーゼ 5（phosphodiesterase type 5）
PK	薬物動態（pharmacokinetic[s]）
SD	標準偏差（standard deviation）
$t_{1/2}$	消失半減期（elimination half-life）
t_{max}	最高血漿中濃度到達時間（time to the reach maximum plasma concentration）
Vd_z/F	分布容積（volume of distribution）
WHO	世界保健機関（World Health Organization）
λ_z	消失速度定数（elimination rate constant）

2.7.1　生物薬剤学試験及び関連する分析法

2.7.1.1　背景及び概観

本項では，ACT-064992D（すなわちマシテンタン 10 mg／タダラフィル 40 mg 配合剤，以下本配合剤）の製剤開発を要約するとともに，血漿中マシテンタン，その活性代謝物 ACT-132577/JNJ-68212820（以下 ACT-132577），及びタダラフィルを測定するために開発した生体試料分析法を示す。また，マシテンタンとタダラフィルを本配合剤として投与したとき，及び各単味製剤として併用投与したときのマシテンタンとタダラフィルの生物学的同等性と，本配合剤投与時のマシテンタン及びタダラフィルの PK に対する食事の影響を評価した生物薬剤学試験から得られた所見を要約する。

経口投与可能な強力な ET_A 及び ET_B 受容体拮抗薬であるマシテンタン（オプスミット®錠），及び PDE5 阻害薬であるタダラフィル（アドシルカ®錠）は，PAH（WHO グループ 1）の治療薬である。PAH 治療の 1 つとして，ERA 及び PDE5 阻害薬の併用療法が用いられている。

マシテンタンの用法・用量は，食事の有無によらず，通常，成人に対して 1 日 1 回 10 mg の経口投与である。マシテンタンと同様，食事の有無によらず 1 日 1 回経口投与可能なタダラフィル 40 mg を，マシテンタン 10 mg との配合剤に含む PDE5 阻害薬として選択した。なお，マシテンタン及びタダラフィルの薬物動態学的薬物間相互作用は想定されない【2.7.2.3.3】。

2.7.1.1.1　製剤開発

2.7.1.1.1.1　BCS 分類

マシテンタン及びタダラフィル原薬はいずれも水溶性が低く，膜透過性が高いことから，BCS クラス 2 の化合物に分類される。

2.7.1.1.1.2　製剤開発の概要及び根拠

製剤開発過程の包括的な概要を 3.2.P.2.2.1 項に，全試験を通じて使用された製剤の概要を表 2.7.1-付録-1 に示す。市販予定製剤であるマシテンタン 10 mg／タダラフィル 40 mg フィルムコーティング錠製剤-2（FDC-2）の組成を 3.2.P.2.2.1 項の Table 1 に示す。

(1) 臨床製剤の開発

本配合剤は，マシテンタン及びタダラフィルの両単剤の市販用製剤に含まれる添加剤を最大限活用する方針で製剤開発を実施した。異なる組み合わせの添加剤，マシテンタン及びタダラフィル原薬を含む複数の製剤を検討した結果，臨床試験製剤及び市販予定製剤として FDC-2 が選択され，製剤番号 [redacted] が割り当てられた。その後に実施された，生物学的同等性試験 67896062PAH1006 試験，及び本配合剤の安全性及び有効性を評価する第 III 相試験 AC-077A301 試験では FDC-2 を使用した。

(2) 臨床試験用製剤，[redacted]及び申請製剤間の処方変更

67896062PAH1006 試験及び第 III 相試験 AC-077A301 試験で使用した FDC-2 は，[redacted]市販予定製剤と同一製剤である。

2.7.1.1.2　生物薬剤学試験

2.7.1.1.2.1　概観及び根拠

生物薬剤学試験の概観は表 2.7.1-付録-2 に示す。詳細は，2.7.1.2，全ての臨床試験の一覧表（5.2 項），概要（2.7.6 項），及び治験総括報告書（5.3 項）に示す。

67896062PAH1006 試験では，マシテンタン及びタダラフィルを FDC-2（マシテンタン 10 mg／タダラフィル 40 mg フィルムコーティング錠，試験製剤）として投与したときと，マシテンタン及びタダラフィルの各単味製剤（マシテンタン 10mg 錠 1 錠及びタダラフィル 20mg 錠 2 錠，標準製剤）を併用投与したときのタダラフィルの生物学的同等性を評価した（2.7.1.2.1）。

67896062PAH1006 試験で使用されたマシテンタン 10mg 錠及びタダラフィル 20mg 錠は，国内外での各市販用製剤と同一であった。また，67896062PAH1006 試験は FDC-2 を投与したとき及び各単味製剤を併用投与したときのタダラフィルの生物学的同等性を評価することが目的であったが，マシテンタンの生物学的同等性も適切に評価可能な試験デザインであった。2.7.1.2.1 に 67896062PAH1006 試験の詳細を記載した。また，67896062PAH1006 試験では，FDC-2 投与における，マシテンタン及びタダラフィルの PK に対する食事の影響も評価した。

2.7.1.1.3　分析法

2.7.1.1.3.1　緒言

未変化体及び代謝物の血漿中濃度分析法の要約を表 2.7.1-付録-3 に示す。各分析法のバリデーションパラメータは，表 2.7.1-付録-4 及び表 2.7.1-付録-5 に示した。各臨床試験で用いた分析法の概要は，表 2.7.1-付録-6 に示した。

2.7.1.1.3.2　血漿中マシテンタン及びその活性代謝物 ACT-132577 の測定

マシテンタン及び ACT-132577 の血漿中濃度を定量するための LC-MS/MS 法は，[redacted] 社（[redacted]，Switzerland）及び [redacted] 社（[redacted]，[redacted]The Netherlands）で開発された。

[redacted] 社でヒト血漿試料中のマシテンタン及び代謝物を定量する LC-MS/MS 法が開発された後（5.3.1.4.1/BA-13.225），この分析法に関する追加のバリデーションデータが，BA-14.033 試験で得られた（5.3.1.4.2/BA-14.033）。さらに，[redacted] 社でヒト血漿試料中のマシテンタン及び代謝物を定量するための分析法を開発した（5.3.1.4.4/BA13063）。この分析法は，BA-14.033 試験とクロスバリデーションされ，67896062PAH1006 試験から得られた PK 試料の測定に用いた（5.3.1.4.4/BA13063）。

2.7.1.1.3.3　血漿中タダラフィルの測定

タダラフィルの血漿中濃度を定量するため，[redacted] 社（[redacted]Germany）及び [redacted] 社で LC-MS/MS 法が開発された。

[redacted] 社で，ヒト血漿試料中のタダラフィルを定量する LC-MS/MS 法を開発した（5.3.1.4.3/316B14_Val）。さらに，[redacted] 社でヒト血漿試料中のタダラフィルを定量するための分析法を開発した（5.3.1.4.5/BA13320）。この分析法を用いて，67896062PAH1006 試験から得られた PK 試料を測定した（5.3.1.4.5/BA13320）。

2.7.1.2　個々の試験結果の要約

2.7.1.2.1　67896062PAH1006 試験（評価資料 5.3.1.2/67896062PAH1006）

67896062PAH1006 試験は，外国人健康成人被験者を対象とした，2 つのグループから成る単施設，非盲検，単回投与，ランダム化，2 期クロスオーバー第 I 相試験であった。グループ 1 ではマシテンタン及びタダラフィルを本配合剤として投与，又は各単味製剤として併用投与したときのタダラフィルの生物学的同等性の評価を，グループ 2 では本配合剤投与時の PK への食事の影響の評価を，それぞれ主要目的とした。以下に，67896062PAH1006 試験の詳細を記載する。

試験の目的：

グループ 1（生物学的同等性グループ）

主要目的

- 健康成人被験者を対象に，空腹時に本配合剤（マシテンタン 10 mg／タダラフィル 40 mg フィルムコーティング錠）を単回投与したとき又はマシテンタン 10 mg 錠 1 錠及びタダラフィル 20 mg 錠 2 錠（各単味製剤）を単回併用投与したときの，タダラフィルの生物学的同等性を，タダラフィルの主要な PK パラメータ（C_{max}，AUC_{0-t}，及び $AUC_{0-\infty}$）に基づき検証する。

副次目的

- 健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤又は各単味製剤として単回併用投与したときの，タダラフィルの副次 PK パラメータ（t_{max}，C_{last}，AUC_{72h}，$t_{1/2}$，λ_z，CL/F，及び Vd_z/F）並びにマシテンタンの主要及び副次 PK パラメータを評価する。
- 健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤又は各単味製剤として単回併用投与したときの安全性及び忍容性を評価する。

グループ 2（食事の影響グループ）

主要目的

- 健康成人被験者を対象に，本配合剤を単回投与したときの，マシテンタン及びタダラフィルの主要 PK パラメータに対する食事の影響を評価する。

副次目的

- 健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときの，マシテンタン及びタダラフィルの副次 PK パラメータを評価する。
- 健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときの，安全性及び忍容性を評価する。

被験者数及び試験デザイン：本試験は，単施設，非盲検，単回投与，ランダム化，2 期クロスオーバー第 I 相試験であった。健康成人被験者計 62 例（グループ 1：46 例，グループ 2：16 例）を組み入れ，下記のとおり投与した。

- グループ 1（46 例）
  - Treatment A：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として単回経口投与した（試験製剤）
  - Treatment B：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を各単味製剤として単回経口投与した（標準製剤）
- グループ 2（16 例）
  - Treatment C：マシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として高脂肪食摂取直後に単回経口投与した
  - Treatment D：マシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として空腹時に単回経口投与した

グループ 1 では Treatment A 及び B（A-B 又は B-A），グループ 2 では Treatment C 及び D（C-D 又は D-C）の 2 つの投与順序のいずれかに無作為に割り付けた。マシテンタン，ACT-132577，及びタダラフィルの血漿中濃度は，投与後 216 時間まで測定し，各投与期の間には 10 日間以上の休薬期間を設けた。

Treatment 間における $AUC_{0-\infty}$，AUC_{0-t} 及び C_{max} の幾何平均比の 90% CI が生物学的同等性基準である 80%から 125%の範囲内にある場合，Treatment 間の生物学的同等性が示されたとした。

COVID-19 の感染拡大の影響により，治験実施医療機関が閉鎖されたため，20[redacted]年[redacted]月[redacted]日に本試験を中断した。この中断により，申請者はカナダ保健省の生物学的同等性ガイダンス（Health Canada Guidance Document 2018）に従って試験デザインを二段階のアダプティブデザインに変更し，グループ 1（生物学的同等性グループ）の中間解析を実施した（5.3.1.2 項 67896062PAH1006-Interim，Protocol Amendment）。中間解析の結果，第一段階の分散推定値及び $\alpha = 0.05$ を用いて算出した生物学的同等性を結論付ける検出力は 80%以上であり，かつ，生物学的同等性の基準を満たしたため，第一段階で終了した。グループ 2 は，COVID-19 感染拡大の影響により一時的に中断した後，再開し完了した。

結果：

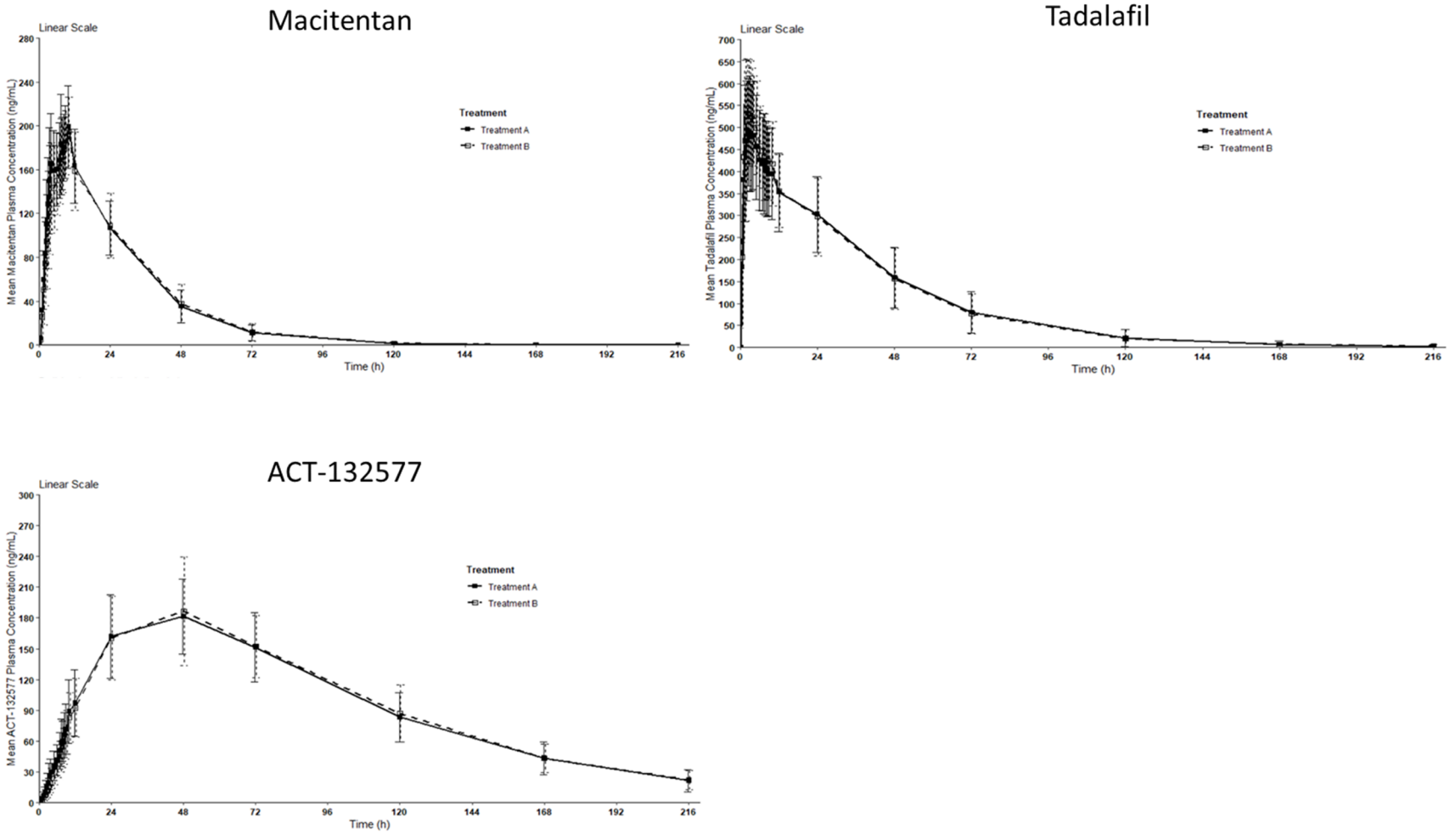
<u>グループ 1（生物学的同等性グループ）</u>

46 例の健康被験者が組み入れられ，33 例が試験を完了した。なお，13 例の未完了例のうち 10 例は，COVID-19 感染拡大の影響により，第 1 期での投与後に試験継続が困難となり試験を中止した。両投与期間を完了した 33 例から，評価可能な主要 PK パラメータ（試験を早期に中止した 1 例から，信頼性の高いデータが得られたため C_{max} については 34 例となった。）を算出し，生物学的同等性を判定した。

試験製剤（Treatment A：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として単回経口投与）を単回経口投与したときのマシテンタン，ATC-132577 及びタダラフィルの平均血漿中濃度－時間プロファイルは，標準製剤（Treatment B：空腹時にマシテンタン 10 mg 及び

タダラフィル 40 mg を各単味製剤として単回経口投与）と同様であり（図 2.7.1-1），PK パラメータは同程度であった（表 2.7.1-1）。

図 2.7.1-1 グループ 1（生物学的同等性グループ）におけるマシテンタン，タダラフィル及び ACT-132577 の平均血漿中濃度ー時間推移（PK 解析集団）



Note: Treatment A=FDC-2 of macitentan and tadalafil (test). Treatment B=free combination of macitentan and tadalafil (reference).
参照:5.3.1.2/67896062PAH1006/Fig2; Fig3; Fig4

表 2.7.1-1 グループ 1（生物学的同等性グループ）のマシテンタン，タダラフィル及び ACT-132577 の PK パラメータ（PK 解析集団）

Parameter	Means (SD); t_{max}: Median (Range)					
	Macitentan		Tadalafil		ACT-132577	
	Treatment A FDC-2	Treatment B Free Combination	Treatment A FDC-2	Treatment B Free Combination	Treatment A FDC-2	Treatment B Free Combination
N	34	34	34	34	34	34
C_{max}, ng/mL	210 (39.7)	206 (32.6)	545 (143)	610 (120)	187 (36.4)	191 (51.2)
AUC_{0-t}, ng.h/mL	5846 (1378), (n=33) [a]	5804 (1504), (n=33) [a]	20593 (7376), (n=33) [a]	20769 (7062), (n=33) [a]	20930 (4982), (n=33) [a]	20832 (4525), (n=33) [a]
$AUC_{0-\infty}$, ng.h/mL	5934 (1384), (n=33) [a]	5903 (1490), (n=33) [a]	20733 (7511), (n=33) [a]	20913 (7174), (n=33) [a]	22638 (5688), (n=33) [a]	22500 (5222), (n=33) [a]
t_{max}, h	10.0 (2.48-10.2)	10.0 (3.55-12.0)	3.00 (1.00-24.0)	2.50 (1.00-7.00)	48.0 (24.0-72.0)	48.0 (24.0-72.0)
$t_{1/2}$, h	13.9 (2.87), (n=33) [a]	14.6 (2.67), (n=33) [a]	22.8 (7.76), (n=33) [a]	22.7 (7.26), (n=33) [a]	50.7 (9.99), (n=33) [a]	49.4 (6.92), (n=33) [a]

[a] R^2adj less than 0.90 or % $AUC_{0-\infty}$_ex more than 20.00% or parameter not estimated due to missing concentration or parameter not evaluable in 1 of the periods or participant participated only in 1 period.
Note: Treatment A=FDC-2 of macitentan and tadalafil (test). Treatment B=free combination of macitentan and tadalafil (reference).
Note: Participants with evaluable PK parameters and completed Periods 1 and 2 are included.
参照：5.3.1.2/67896062PAH1006/Tab4; Tab10; Tab12

生物学的同等性の評価のため，評価可能な主要な PK パラメータをもつ両投与期間を完了した被験者を対象に統計解析を実施した結果，タダラフィル及びマシテンタンの主要 PK パラメータの幾何平均比（試験製剤／標準製剤）の 90% CI はいずれも生物学的同等性の基準である 80%～125%の範囲内であった（表 2.7.1-2）。

事後解析にてタダラフィル及びマシテンタンの各 PK パラメータの検出力を算出したところ，いずれの PK パラメータの検出力も 80%超であった（タダラフィル：80.9%～99.9%超，マシテンタン：99.9%超）（表 2.7.1-3）。

67896062PAH1006 試験は，本配合剤投与時及び各単味製剤の併用投与時におけるタダラフィルの生物学的同等性を検証することを目的とした試験であり，マシテンタンの生物学的同等性を示すことは目的に設定していなかった。しかしながら，以下の理由から 67896062PAH1006 試験の試験デザインは，マシテンタンの生物学的同等性を検討するものとしても適切であった。

- 被験者数の妥当性：67896062PAH1006 試験の生物学的同等性パートの予定被験者数は，タダラフィルの主要な PK パラメータの CVw を 20%と仮定して設定された。本配合剤投与時及び各単味製剤の併用投与時におけるマシテンタンの生物学的同等性を評価するために先行して実施した生物学的同等性試験のマシテンタンの各 PK パラメータの CVw は約 8%～15%であったことから，CVw 20%を仮定して設定された被験者数はマシテンタンの生物学的同等性を評価するのに十分な統計学的検出力を有しており，妥当であったと考える。また，事後解析でのマシテンタンの各 PK パラメータの検出力は 80%超であり（表 2.7.1-3），十分な検出力があることが示されたことから，67896062PAH1006 試験の結果に基づき，マシテンタンについても本配合剤と各単味製剤の生物学的同等性を評価可能と考えた。以上より，生物学的同等性パートの予定被験者数及び実際に組み入れられた被験者数

は，本配合剤と各単味製剤のマシテンタンの生物学的同等性を評価するのに適切であったと考える。

・ 血漿中濃度評価時点の妥当性：67896062PAH1006 試験のマシテンタン及びタダラフィルの血漿中濃度評価時点は，投与前，投与後 30 分，1，1.5，2，2.5，3，3.5，4，5，6，7，7.5，8，8.5，9，10，12，24，48，72，120，168 及び 216 時間であり，本配合剤投与時及び各単味製剤の併用投与時におけるマシテンタンの生物学的同等性を評価するために先行して実施した生物学的同等性試験で設定した時点と同様であった。血漿中濃度評価時点は先行して実施した生物学的同等性試験のマシテンタンの $t_{1/2}$ の平均値（約 14～16 時間）及び t_{max} の中央値（投与後 9.0 時間）に基づいて，投与直前に 1 点，C_{max} に達するまでに 1 点，C_{max} 付近に 2 点，消失過程に 3 点の計 7 点以上の血漿中濃度評価時点が設定された。実際に，67896062PAH1006 試験では，Treatment A 及び Treatment B のマシテンタンの $t_{1/2}$ の平均値はそれぞれ 13.9 時間及び 14.6 時間，t_{max} の中央値はどちらも 10.0 時間であり（表 2.7.1-1），先行して実施した生物学的同等性試験と大きく異ならず，既報とも同程度であった（2014 年 5 月 26 日申請　オプスミット錠 10mg CTD5.3.3.1.5）。また，消失半減期の 5 倍以上である投与後 216 時間まで血漿中濃度を評価しており，PK 解析対象の全ての被験者で $AUC_{0-\infty}$ の外挿率が 20%未満であった。よって，設定された血漿中濃度評価時点は，後発医薬品の生物学的同等性試験ガイドライン II 1.5）b の要件を全て満たしており，マシテンタンの C_{max} 及び消失相を十分に捉えていたと考えた。さらに，各製剤の投与の間に少なくとも 10 日の休薬期間を設けており，消失半減期の 5 倍以上の時間を確保したことから，生物学的同等性試験の設定として適切だったと考えた。実際に，両投与期で全ての被験者の投与前血漿中濃度は検出限界未満であった。

以上より，67896062PAH1006 試験は，本配合剤投与時と各単味製剤の併用投与時のタダラフィル及びマシテンタンの生物学的同等性を評価するのに適切な試験であったと判断した。また，タダラフィル及びマシテンタンの主要 PK パラメータの幾何平均比（試験製剤／標準製剤）の 90% CI はいずれも生物学的同等性の基準内であり，事後解析での検出力は 80%超であったことから，本配合剤投与と各単味製剤併用投与におけるタダラフィル及びマシテンタンは生物学的に同等であると結論づけた。

表 2.7.1-2 グループ 1（生物学的同等性グループ）におけるタダラフィル及びマシテンタンの幾何平均比及び 90% CI（PK 解析集団）

		Geometric Means		Ratio of Geometric Means (%)		P-value		
Parameter	N	Treatment B Free Combination	Treatment A FDC-2	(Treatment A/B)	90% CI (%)	Period	Sequence	Intraparticipant CV (%)
Tadalafil								
C_{max}, ng/mL	34	598	528	88.30	82.68-94.31	0.2640	0.6014	16.1
AUC_{0-t}, ng.h/mL	33	19579	19359	98.87	94.33-103.64	0.1376	0.5465	11.3
$AUC_{0-\infty}$, ng.h/mL	33	19702	19471	98.82	94.27-103.60	0.1295	0.5437	11.3
Macitentan								
C_{max}, ng/mL	34	203	206	101.49	96.95-106.25	0.6424	0.0670	11.2
AUC_{0-t}, ng.h/mL	33	5631	5685	100.96	96.99-105.09	0.1813	0.9160	9.6
$AUC_{0-\infty}$, ng.h/mL	33	5736	5774	100.66	96.77-104.70	0.1543	0.8984	9.5

Note: Analysis done on log-transformed data and the results were back-transformed using antilogarithm.
Note: Participants who completed both treatment periods and had PK parameters estimated are included in the analysis.
Note: Treatment A: Single oral dose of fixed dose combination of macitentan/tadalafil (10/40 mg) under fasting conditions (test).
Note: Treatment B: Single oral dose of a free combination of 10 mg macitentan and 2 × 20 mg Canadian-sourced tadalafil under fasting conditions (reference).
Note: Intraparticipant CV(%)=100* (sqrt(exp(MSE)-1).
参照： 5.3.1.2/67896062PAH1006/Tab6; Tab14; Group 1_TABPK08; Group 1_TABPK23

表 2.7.1-3 グループ 1（生物学的同等性グループ）における健康成人に本配合剤（Treatment A）又は各単味製剤（Treatment B）を空腹時経口投与したときのタダラフィル及びマシテンタンの各 PK パラメータの統計学的検出力に対する事後解析（PK 解析集団）

Parameter	N Treatment B Free Combination, Treatment A FDC-2	Geometric Mean Ratio	CV	Power (%)
Tadalafil				
Completers				
C_{max}, ng/mL	34, 34	0.8830	0.161	80.9
AUC_{0-t}, ng.h/mL	33, 33	0.9887	0.113	>99.9
$AUC_{0-\infty}$, ng.h/mL	33, 33	0.9882	0.113	>99.9
Sensitivity				
C_{max}, ng/mL	39, 40	0.8902	0.165	89.0
AUC_{0-t}, ng.h/mL	38, 40	0.9858	0.113	>99.9
$AUC_{0-\infty}$, ng.h/mL	38, 40	0.9853	0.114	>99.9
Macitentan				
Completers				
C_{max}, ng/mL	34, 34	1.0149	0.112	>99.9
AUC_{0-t}, ng.h/mL	33, 33	1.0096	0.096	>99.9
$AUC_{0-\infty}$, ng.h/mL	33, 33	1.0066	0.095	>99.9
Sensitivity				
C_{max}, ng/mL	39, 40	1.0266	0.114	>99.9
AUC_{0-t}, ng.h/mL	38, 40	1.0115	0.096	>99.9
$AUC_{0-\infty}$, ng.h/mL	38, 40	1.0085	0.095	>99.9

Note: Participants who have completed both treatment periods and have PK parameter estimated are included in the analysis for the completers.
Note: Participants who had PK parameters in any of the periods are included in the sensitivity analysis, excluding those who had AUC extrapolated greater than 20.00% or a parameter not estimated due to a missing concentration.
Note: Treatment A: Single oral dose of fixed dose combination of macitentan/tadalafil (10/40 mg) under fasting conditions (test).
Note: Treatment B: Single oral dose of a free combination of 10 mg macitentan and 2 × 20 mg Canadian-sourced tadalafil under fasting conditions (reference).
参照： 5.3.1.2/67896062PAH1006-Final/Tab7; Tab9; Tab15; Tab17

グループ 2（食事の影響グループ）

本配合剤を，高脂肪食摂取後に単回経口投与したとき（Treatment C）のマシテンタン及びタダラフィルの平均血漿中濃度－時間推移は，空腹時に単回経口投与したとき（Treatment D）と比較して投与後 24 時間まで高値傾向であり，24 時間後は同様であった（図 2.7.1-2，表 2.7.1-4）。ACT-132577 の平均血漿中濃度－時間推移は Treatment C と Treatment D で同様であった。

マシテンタン

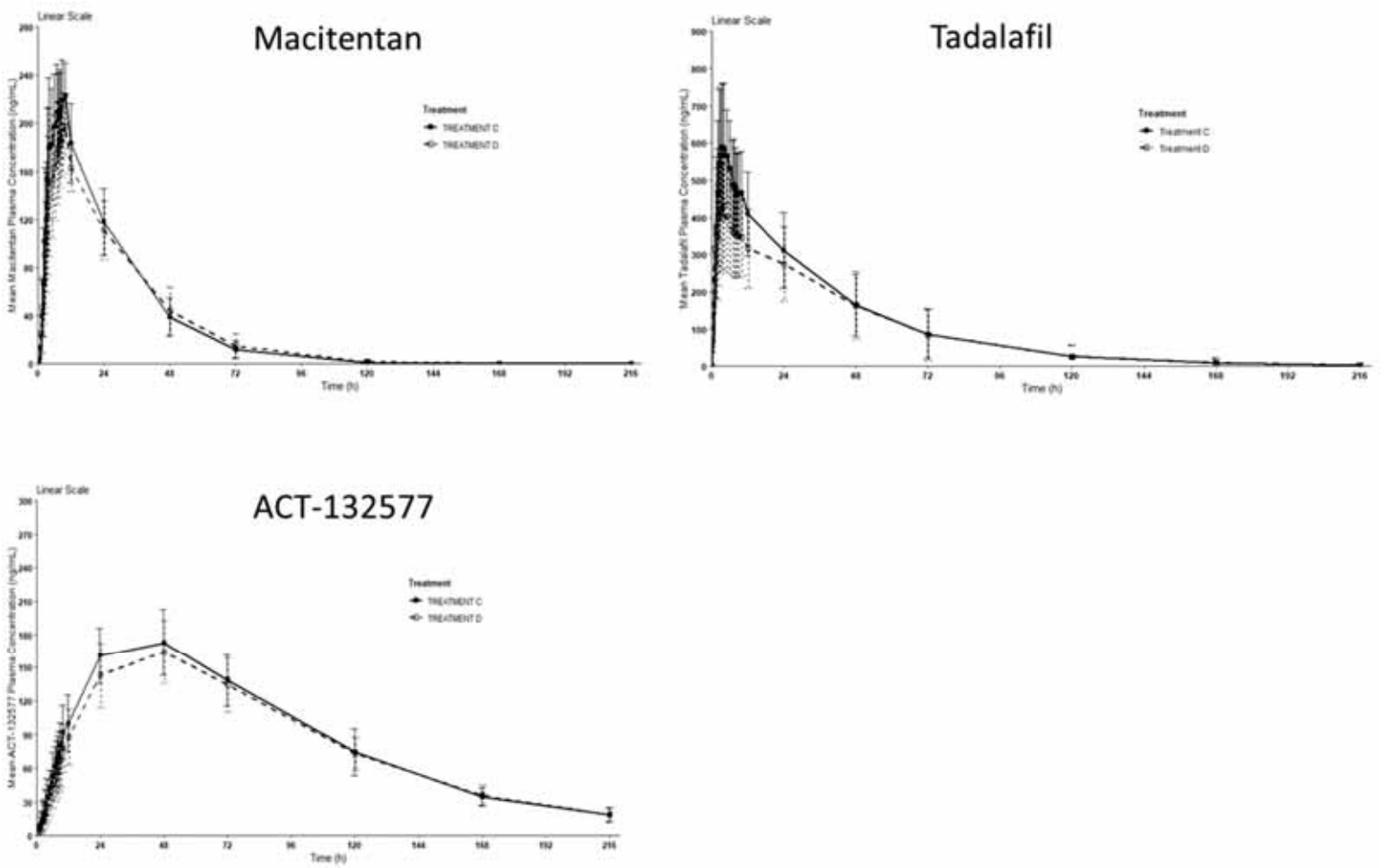
高脂肪食摂取後に本配合剤を単回経口投与したときのマシテンタン及び ACT-132577 の主要 PK パラメータは，空腹時と比較してマシテンタンの C_{max} を除いて全て生物学的同等性基準の範囲内であった。マシテンタンの C_{max} の幾何平均比及び 90% CI は 1.16 及び 1.07～1.26 と生物学的同等性基準とほぼ同程度であることから，この差に臨床的意義はないと考えた（表 2.7.1-5）。

タダラフィル

空腹時投与に対する高脂肪食摂取後のタダラフィルの C_{max} の幾何平均比及び 90% CI は 1.45 及び 1.29～1.63 であった。AUC（AUC_{0-t} 及び $AUC_{0-\infty}$）の幾何平均比及び 90% CI は，1.11 及び 1.04～1.19 であり，生物学的同等性基準の範囲内であった（表 2.7.1-5）。

以上より，健康成人被験者に空腹時及び高脂肪食摂取後に本配合剤を投与した食事の影響試験では，マシテンタンの PK に対する食事の影響は認められなかった。タダラフィルの C_{max} は，空腹時と比較して高脂肪食摂取後では 45%増加したが，AUC は変化しなかった。

図 2.7.1-2 グループ 2（食事の影響グループ）におけるマシテンタン，タダラフィル，及び ACT-132577 の平均血漿中濃度-時間推移（PK 解析集団）



Note: Treatment C=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fed conditions (test). Treatment D=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fasting conditions (reference).

参照： 5.3.1.2/67896062PAH1006-Final/Fig5; Fig6; Fig7

表 2.7.1-4 グループ 2（食事の影響グループ）におけるマシテンタン，タダラフィル，及び ACT-132577 の PK パラメータ（PK 解析集団）

	Means (SD); t_{max}: Median (Range)					
	Macitentan		Tadalafil		ACT-132577	
Parameter	Treatment C FDC-2 Under Fed Conditions	Treatment D FDC-2 Under Fasted Conditions	Treatment C FDC-2 Under Fed Conditions	Treatment D FDC-2 Under Fasted Conditions	Treatment C FDC-2 Under Fed Conditions	Treatment D FDC-2 Under Fasted Conditions
N	15	15	15	15	15	15
C_{max}, ng/mL	241 (22.8)	208 (31.4)	677 (127)	475 (162)	176 (27.8)	165 (29.3)
AUC_{0-t}, ng.h/mL	6431 (1377)	6224 (1550)	22330 (9697)	19731 (10439)	18934 (3148)	18095 (3061)
$AUC_{0-\infty}$, ng.h/mL	6539 (1380)	6338 (1532)	22503 (9969)	19875 (10667)	20329 (3566)	19499 (3546)
t_{max}, h	9.00 (4.00-10.0)	10.0 (4.00-10.0)	4.00 (1.50-10.0)	2.50 (1.50-12.0)	48.0 (24.0-48.1)	48.0 (24.0-48.0)
$t_{1/2}$, h	14.1 (2.50)	15.5 (2.68)	24.5 (7.29)	23.4 (6.64)	49.4 (6.02)	49.7 (7.63)

Note: Treatment C=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fed conditions (test). Treatment D=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fasting conditions (reference).

参照：5.3.1.2/67896062PAH1006-Final/Tab18; Tab21; Tab24

表 2.7.1-5 グループ 2（食事の影響グループ）におけるマシテンタン，ACT-132577，及びタダラフィルの幾何平均比及び 90% CI（PK 解析集団）

		Geometric Means				P-value		
Parameter	N	Treatment D FDC-2 Under Fasted Conditions	Treatment C FDC-2 Under Fed Conditions	Ratio of Geometric Means (%) (Treatment C/D)	90% CI (%)	Period	Sequence	Intraparticipant CV (%)
Macitentan								
C_{max}, ng/mL	15	207	240	116.10	107.12-125.83	0.2695	0.3839	12.4
AUC_{0-t}, ng.h/mL	15	6090	6230	102.32	97.90-106.94	0.8388	0.3341	6.6
$AUC_{0-\infty}$, ng.h/mL	15	6200	6330	102.13	97.85-106.61	0.8083	0.3193	6.4
ACT-132577								
C_{max}, ng/mL	15	162	173	107.25	102.08-112.69	0.0095	0.1468	7.4
AUC_{0-t}, ng.h/mL	15	17800	18600	104.50	99.60-109.63	0.0115	0.1472	7.2
$AUC_{0-\infty}$, ng.h/mL	15	19200	19900	103.98	99.21-108.99	0.0048	0.1476	7.0
Tadalafil								
C_{max}, ng/mL	15	454	659	144.97	128.96-162.97	0.1429	0.2775	17.7
AUC_{0-t}, ng.h/mL	15	18300	20400	111.07	103.93-118.71	0.8148	0.5736	9.9
$AUC_{0-\infty}$, ng.h/mL	15	18400	20500	111.04	103.92-118.65	0.8136	0.5807	9.9

Note: Analysis done on log-transformed data and the results were back-transformed using antilogarithm.
Note: Participants who completed both treatment periods and had PK parameters estimated are included in the analysis.
Note: Treatment C=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fed conditions (test). Treatment D=single FDC-2 film-coated tablet of macitentan/tadalafil 10/40 mg under fasting conditions (reference).
Note: Intraparticipant CV(%)=100* (sqrt(exp(MSE)-1).
参照：5.3.1.2/67896062PAH1006/Tab19; Tab22; Tab25; Group 2_TABPK09; Group 2_TABPK16; Group 2_TABPK23

2.7.1.3　全試験を通しての結果の比較と解析

2.7.1.3.1　生物学的同等性

67896062PAH1006 試験のグループ 1 では，マシテンタン 10 mg 及びタダラフィル 40 mg を配合剤（試験製剤）として投与したとき，又は各単味製剤（標準製剤）を併用投与したときのマシテンタンとタダラフィルの生物学的同等性を評価した。その結果，配合剤と各単味製剤におけるマシテンタン及びタダラフィルの生物学的同等性が示された。67896062PAH1006 試験で用いた配合剤（試験製剤）FDC-2 は，市販開始後に利用予定の製造施設で製造された製剤であり，本配合剤の安全性及び有効性を評価した第 III 相 AC-077A301 試験で使用された製剤[redacted]と同一製剤である。

2.7.1.3.2　食事の影響

67896062PAH1006 試験のグループ 2 では，本配合剤（マシテンタン 10 mg／タダラフィル 40 mg フィルムコーティング錠）の食事の影響を評価した。その結果，高脂肪食摂取後に本配合剤を投与したときには，空腹時と比べてマシテンタンの AUC は同程度であり，C_{max} の幾何平均比の 90% CI は 80%～125%から外れたがその差は 1%未満であった。したがって，食事はマシテンタンの PK に臨床的意義のある影響を及ぼさないと考えられた。タダラフィルの C_{max} の幾何平均値は空腹時と比較して高脂肪食摂取後で 45%増加したが，AUC は同程度であった。以下の理由より，食事はタダラフィルに臨床的意義のある影響を及ぼさないと考えた。

- 空腹時のタダラフィルの C_{max} の被験者間変動は 34.0%であり，空腹時と高脂肪食摂取後の C_{max} の個別値の分布はほとんど重なっていた。
- 有効性と関連があると考えられているタダラフィルの AUC は食事の影響を受けなかった（Ferguson-Sells 2022）。
- 67896062PAH1006 試験の結果から，食後投与と空腹時投与で安全性プロファイルは同様であった。
- AC-077A301 試験では，食事条件を設定せず本配合剤を投与したが，本配合剤群で認められた有害事象は，PAH 患者で既に確認されている合併症，並びにマシテンタン及びタダラフィルの各単剤療法で報告されている安全性プロファイルと同様であり，臨床的に管理可能であった【2.7.6.2】。

したがって，本配合剤は食事の有無にかかわらず服用できると考えた。

2.7.1.4　付録

表 2.7.1-付録-1 全試験を通じて使用された製剤の概要

Formulation Number	Strength		Description	Batch Number	Study Number
[redacted]	Macitentan/tadalafil (10/40 mg)		Tablet	[redacted]	67896062PAH1006, AC-077A301
[redacted]	Macitentan (OPSUMIT)	10 mg	Tablet	[redacted]	67896062PAH1006
Reference product	Tadalafil (ADCIRCA)	20 mg	Tablet	[redacted]	67896062PAH1006
[redacted]	Macitentan/tadalafil (10/40 mg)		Tablet	[redacted]	AC-077A301
[redacted]	Macitentan/tadalafil (10/40 mg)		Tablet	[redacted]	AC-077A301
[redacted]	Macitentan (OPSUMIT)	10 mg	Tablet	[redacted]	AC-077A301
Reference product	Tadalafil (ADCIRCA)	20 mg	Tablet	[redacted]	AC-077A301

[a] The FDC-2 formulation is identical to the commercial proposed macitentan/tadalafil 10/40 mg FDC [redacted] formulation.

参照: 3.2.P.2.2.1; 3.2.P.5.4; 5.3.1.2/67896062PAH1006

表 2.7.1-付録-2 生物薬剤学試験の概観

Study ID	Objective(s)	Participants	Dose	Route	Formulation	Section in Module 2.7.1	Location of Report
67896062PAH1006	To demonstrate bioequivalence of tadalafil given as FDC of macitentan/tadalafil and as free combination of macitentan and Canadian-sourced tadalafil. To evaluate the effect of food on the primary PK parameters of macitentan and tadalafil administered as an FDC.	62 (healthy) Age at screening: 18-55 years	Group 1: • Treatment A: 10/40 mg, macitentan/tadalafil FDC-2 (1 film-coated tablet), fasting conditions • Treatment B: 10 mg macitentan (1 film-coated tablet) plus 40 mg Canadian-sourced tadalafil (2 film-coated tablets of 20 mg), fasting conditions Group 2: • Treatment C: 10/40 mg, macitentan/tadalafil FDC-2 (1 film-coated tablet), fed conditions • Treatment D: 10/40 mg, macitentan/tadalafil FDC-2 (1 film-coated tablet), fasting conditions	Oral	FDC-2	2.1	5.3.1.2/67896062PAH1006

参照：5.3.1.2/67896062PAH1006

表 2.7.1-付録-3 バリデートされた分析法の概要

Laboratory, Report Number	Year Start Validation	Matrix, Anticoagulant	Extraction Procedure	Chromatography	Mass Spectrometry Conditions	Remarks
Quantification of Macitentan and ACT-132577						
[redacted] (Switzerland), BA-13.225	20[redacted]	Plasma, EDTA	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] The Netherlands), BA13063	20[redacted]	Plasma, EDTA				
Quantification of Tadalafil						

Laboratory, Report Number	Year Start Validation	Matrix, Anticoagulant	Extraction Procedure	Chromatography	Mass Spectrometry Conditions	Remarks
[redacted] 316B14_Val	20[redacted]	Plasma, EDTA	[redacted]	[redacted]		[redacted]
[redacted] ([redacted] The Netherlands), BA13320	20[redacted]	Plasma, EDTA	[redacted]	[redacted]		[redacted]

参照：5.3.1.4.1/BA-13.225; 5.3.1.4.4/BA13063; 5.3.1.4.3/316B14_Val; 5.3.1.4.5/BA13320

表 2.7.1-付録-4 分析法：マシテンタン及び ACT-132577 の生体内試料分析法のバリデーションパラメータ

BA-13.225 ([redacted]) [5.3.1.4.1/BA-13.225]	Macitentan	ACT-132577
Matrix	plasma	plasma
Validated concentration range	1-2000 ng/mL	1-2000 ng/mL
Inter-run accuracy (%)	[redacted]	
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (10/50 [a] x dilution) (%)		
Intra-run precision (10/50 [a] x dilution) (%CV)		
Incurred sample reproducibility		
Selectivity (including hemolyzed and hyperlipidemic plasma)		
Matrix effect		
Stability in plasma		
Processed sample stability		
Stability in stock solution		

BA13063 ([redacted]) [5.3.1.4.4/BA13063]	Macitentan	ACT-132577
Matrix	plasma	plasma
Validated concentration range	1-2000 ng/mL	1-2000 ng/mL
Inter-run accuracy (%)	[redacted]	
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (10 x dilution) (%)		
Intra-run precision (10 x dilution) (%CV)		
Incurred sample reproducibility		
Selectivity (including hemolyzed and hyperlipidemic plasma)		
Matrix effect		
Stability in blood		

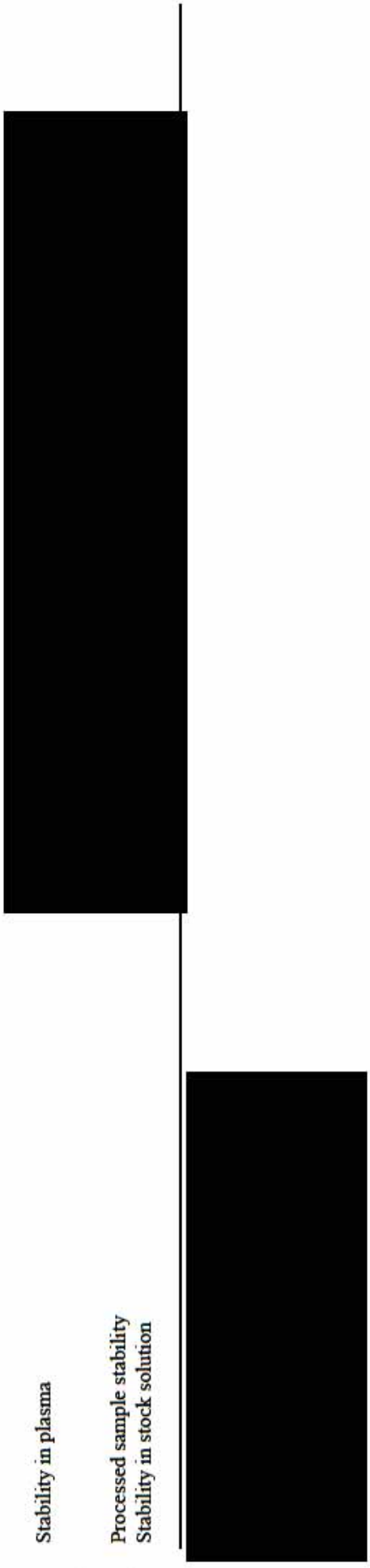

Stability in plasma
Processed sample stability
Stability in stock solution

表 2.7.1-付録-5 分析法：タダラフィルの生体内試料分析法のバリデーションパラメータ

316B14-Val ([redacted]) [5.3.1.4.3/316B14-Val]	Tadalafil (Original Assay)	Tadalafil (Supplement 2)	Tadalafil (Supplement 4)	Tadalafil (Supplement 5)
Matrix	plasma	plasma	plasma	plasma
Validated concentration range	0.5-800 ng/mL	0.5-800 ng/mL	0.5-800 ng/mL	0.5-1000 ng/mL
Inter-run accuracy (%) Inter-run precision (%CV) Intra-run accuracy (%) Intra-run precision (%CV) Intra-run accuracy (10 x dilution) (%) Intra-run precision (10 x dilution) (%CV) Incurred sample reproducibility Selectivity (including hemolyzed and hyperlipidemic plasma) Matrix effect Stability in plasma Processed sample stability in autosampler Reinjection stability Stability in stock solution	[redacted]			

BA13320 ([redacted] [5.3.1.4.5/BA13320]	Tadalafil
Matrix	plasma
Validated concentration range	0.5-1000 ng/mL
Inter-run accuracy (%)	[redacted]
Inter-run precision (%CV)	
Intra-run accuracy (%)	
Intra-run precision (%CV)	
Intra-run accuracy (2 x dilution) (%)	
Intra-run precision (2 x dilution) (%CV)	
Incurred sample reproducibility	
Selectivity (including hemolyzed and hyperlipidemic plasma)	
Matrix effect	
Stability in blood	
Stability in plasma	
Processed sample stability	
Stability in stock solution	

[redacted]

表 2.7.1-付録-6 各臨床試験で用いた分析法の概要

Study ID (Location)	Matrix	Analyte	Concentration Range (LLOQ is Lower end of the Concentration Range)	Method	Method Validation Report (Location)	Bioanalytical Study Number
67896062PAH1006	Plasma	Macitentan and ACT-132577	1.00-2000 ng/mL	LC-MS/MS	BA13063 [5.3.1.4.4/BA13063]	JJP19866-19866X-B (included in CSR)
	Plasma	Tadalafil	0.500-1000 ng/mL	LC-MS/MS	BA13320 [5.3.1.4.5/BA13320]	JJP19866-19866X-A (included in CSR)

参照：5.3.1.2 /67896062PAH1006

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略号一覧表

略号又は略称	名称及び内容
AUC	血漿中濃度-時間曲線下面積（area under the plasma concentration-time curve）
AUC_{∞}	0 時間から無限大時間までの血漿中濃度-時間曲線下面積（area under the plasma concentration-time curve from time zero to infinity）
C_{max}	最高血漿中濃度（maximum plasma concentration）
CYP	チトクローム P450（cytochrome P450）
CYP3A4	チトクローム P450 3A4（cytochrome P450 isozyme 3A4）
ET	エンドセリン（endothelin）
ERA	エンドセリン受容体拮抗薬（endothelin receptor antagonist）
MATE	多剤・毒性化合物排出タンパク質（multidrug and toxin extrusion transporter）
MDR-1	多剤耐性タンパク質 1（multidrug resistance protein 1）
OATP	有機アニオン輸送ポリペプチド（organic anion transporting polypeptide）
PAH	肺動脈性肺高血圧症（pulmonary arterial hypertension）
PDE5	ホスホジエステラーゼ 5（phosphodiesterase type 5）
P-gp	P-糖タンパク質（P-glycoprotein）
PK	薬物動態（pharmacokinetic[s]）
WHO	世界保健機関（World Health Organization）

2.7.2 臨床薬理試験

2.7.2.1 背景及び概観

経口投与可能な強力な ET_A 及び ET_B 受容体拮抗薬であるマシテンタン（オプスミット®錠），及び経口投与可能な PDE5 阻害薬であるタダラフィル（アドシルカ®錠）は PAH（WHO グループ I）の治療薬である。PAH 治療の 1 つとして，ERA 及び PDE5 阻害薬の併用投与が用いられている。マシテンタン及びタダラフィルを含む配合剤は PAH 患者の服薬遵守を高め，投薬過誤のリスクを低減する可能性がある。

本項では，ACT-064992D（すなわちマシテンタン 10 mg／タダラフィル 40 mg 配合剤，以下本配合剤）投与での，マシテンタン及びタダラフィルの薬物動態学的薬物間相互作用の可能性について包括的に記述した。

2.7.2.1.1 ヒト生体試料を用いた試験

ヒト生体試料を用いたマシテンタン及びタダラフィルの臨床薬理に関連する試験について，本配合剤の開発のために新たに実施したものはない。

2.7.2.1.2 臨床薬理試験

本配合剤の PK は，本配合剤と各単味製剤間の生物学的同等性，及び本配合剤の PK に対する食事の影響を評価した健康成人対象の第 I 相臨床試験（67896062PAH1006 試験）で検討した。この試験の要約は【2.7.1.2.1】項に示した。

2.7.2.2 個々の試験結果の要約

生物学的同等性及び食事の影響を評価した第 I 相臨床試験の要約は，【2.7.1.2.1】項に示した。その他の臨床薬理試験は実施していない。

2.7.2.3 全試験を通しての結果の比較と解析

2.7.2.3.1 民族的要因の影響

マシテンタン及びタダラフィルの主代謝酵素である CYP3A4 の遺伝子多型や代謝能には，明らかな民族差は報告されておらず，CYP3A4 の典型的な基質であるミダゾラムの薬物動態に CYP3A4 の遺伝子多型による民族差は認められないことが報告されている（Myrand SP 2008; van Dyk M 2018）。よって，マシテンタン及びタダラフィルの PK に薬物代謝酵素の遺伝子多型による民族差が生じる可能性は低いと考えた。実際に，日本人健康成人及び外国人健康成人にマシテンタン 10 mg を単回，及び反復投与したときのマシテンタン及びその活性代謝物 ACT-132577/JNJ-68212820（以下 ACT-132577）の PK は類似しており（2014 年 5 月 26 日申請　オプスミット錠 10mg　CTD　2.7.2.3.1.1.2; 2.7.2.3.1.1.3），大きな国内外差はみられていない。

また，外国人 PAH 患者及び日本人 PAH 患者でマシテンタン 1 日 1 回 10 mg の有効性が認められ，安全性も許容可能と判断したことから（2014 年 5 月 26 日申請　オプスミット錠 10mg　CTD 1.8.3.2），マシテンタンの成人 PAH 患者の治療における日本の承認用法用量は，海外と同様に 1 日 1 回 10 mg である。タダラフィルについても，成人 PAH 患者の治療における日本での承認用

法用量は，通常 1 日 1 回 40 mg であり，米国及び欧州を含め世界的に承認されている用法用量と同一である。

これらのことから，民族は本配合剤の用法用量の設定に影響を与えうる臨床的に意義のある要因ではないと考えた。

2.7.2.3.2　食事の影響

本配合剤投与時のマシテンタン及びタダラフィルの PK に対する食事の影響は【2.7.1.3.2】項に記載した。食事はマシテンタン及びタダラフィルの PK に対して臨床的に意義のある影響を及ぼさないと考えられたため，本配合剤は食事の有無に関わらず服用できる。

2.7.2.3.3　薬物動態学的薬物間相互作用

本項では，マシテンタンとタダラフィル間の薬物動態学的薬物間相互作用の可能性について記載した。なお，マシテンタン 10 mg 及びタダラフィル 40 mg の薬物間相互作用を直接評価する臨床試験は実施していない。

(1) マシテンタンの PK に対するタダラフィルの影響

マシテンタンは主に CYP3A4 によって代謝される。CYP3A4 基質であるミダゾラム又はロバスタチンとタダラフィル 10 mg 又は 20 mg を 1 日 1 回併用投与したとき，タダラフィルはこれらの薬剤の曝露量（AUC）に有意な影響はなかった（Ring 2005）。また，CYP2C9 及び CYP3A4 の基質であるボセンタンとタダラフィル 40 mg を 1 日 1 回併用投与したとき，ボセンタンの曝露量（AUC 及び C_{max}）に臨床的に意義のある影響はなかった（Wrishko 2008）。マシテンタン 10 mg を単独投与した時の PK と本剤を投与した時の PK の試験間比較を行った。マシテンタン 10 mg を単独投与した時の PK として，外国人健康成人にマシテンタン 10 mg 錠を空腹時単回投与した AC-055-108 試験（108 試験，2014 年 5 月 26 日申請　オプスミット錠 10mg　CTD　5.3.1.2.1）及び AC-055-109 試験（109 試験，2014 年 5 月 26 日申請　オプスミット錠 10mg　CTD 5.3.3.1.5），マシテンタン 10 mg をタダラフィル 40 mg と併用投与した時の PK として，外国人健康成人に本剤を空腹時単回投与した 67896062PAH1006 試験【2.7.1.2.1】から得られた結果を比較した。マシテンタンについて，C_{max} の平均値は 108 試験，109 試験，67896062PAH1006 試験グループ 1（Treatment A）及びグループ 2（Treatment D）でそれぞれ 153，228，210 及び 208 ng/mL，AUC_{∞}の平均値は 4955，6942，5934 及び 6338 ng· h/mL であり，本剤投与時の C_{max} 及び AUC_{∞}の平均値はマシテンタン 10 mg 錠投与時と同程度であった。また，C_{max} 及び AUC_{∞}の範囲はいずれもおおむね重なっていた。ACT-132577 についても，C_{max} の平均値は，108 試験，109 試験，67896062PAH1006 試験グループ 1 及びグループ 2 でそれぞれ 159，243，187 及び 165 ng/mL，AUC_{∞}の平均値は 17923，27653，22638 及び 19499 ng· h/mL であり，本剤投与時の C_{max} 及び AUC_{∞}の平均値はマシテンタン 10 mg 錠投与時と同程度であり，C_{max} 及び AUC_{∞}の範囲はいずれもおおむね重なっていた。これらのことは，タダラフィル 40 mg の 1 日 1 回投与は，CYP3A4 を介してマシテンタンの PK に臨床的意義のある影響を及ぼさないことを示唆している。

また，マシテンタンは P-gp の基質ではなく，マシテンタン及び ACT-132577 は OATP1B1 及び 1B3 の基質ではない。タダラフィルは in vitro において，P-gp（MDR-1）の阻害作用，及び

OATP1B1 及び 1B3 の弱い阻害作用を持つが（Margelidon-Cozzolino 2017;Weiss 2013），タダラフィルは P-gp の基質であるジゴキシンの PK に有意な影響を与えないことが報告されている（Schwartz 2010）。よって，これらのトランスポーターを介した薬物動態学的薬物間相互作用は想定されない。

以上より，マシテンタン及びタダラフィルの併用投与において，タダラフィルはマシテンタンの PK に対し臨床的に意義のある影響を与えないと考えた。

(2) タダラフィルの PK に対するマシテンタンの影響

タダラフィルは主に CYP3A4 により代謝される。また，臨床薬物相互作用試験において，強力な CYP3A4 阻害薬によりタダラフィルの AUC が 2 倍以上から 5 倍未満増加する中等度の感度の CYP3A4 基質である（FDA 2020）。タダラフィルの PK に対するマシテンタンの影響を検討した臨床薬物相互作用試験は実施していないが，より感度の高い CYP3A4 基質であるシルデナフィルとの臨床薬物相互作用試験を実施した（2014 年 5 月 26 日申請　オプスミット錠 10mg　CTD 5.3.3.4.2）。シルデナフィルは主に CYP3A4 により代謝され，強力な CYP3A4 阻害薬によりシルデナフィルの AUC が 5 倍以上増加する（FDA 2020）。臨床薬物相互作用試験において，マシテンタン 10 mg 1 日 1 回投与がシルデナフィル 20 mg の PK に及ぼす影響を評価したところ，シルデナフィルの PK に臨床的に意義のある影響はなかった（Sidharta 2014）。加えて，CYP3A4 基質であるエチニルエストラジオール（35 µg）及びノルエチンドロン（1 mg）を含有する避妊薬とマシテンタン 10 mg を併用投与したところ，エチニルエストラジオール及びノルエチンドロンの PK にマシテンタン 10 mg 1 日 1 回投与は影響を及ぼさないことが示されている（Hurst 2016）。マシテンタン 10 mg は，タダラフィルより感度の高い CYP3A4 基質であるシルデナフィルの PK に臨床的意義のある影響を及ぼさず，エチニルエストラジオール及びノルエチンドロンの PK にも影響を及ぼさなかったことから，マシテンタン 10 mg は CYP3A4 を介してタダラフィルの PK に臨床的に意義のある影響を及ぼさないと考えた。

さらに，マシテンタンは P-gp の阻害剤ではなく，臨床用量では，ACT-132577 も P-gp を阻害しない。また，臨床用量では，マシテンタン及び ACT-132577 は，下記のとおりその他のトランスポーターに対しても作用しない。

- OATP1B1 及び 1B3 の基質や阻害剤ではない。
- 取り込みトランスポーターである有機カチオントランスポーター1 及び 2，有機アニオントランスポーター1 及び 3，並びに薬物排出ポンプである乳癌耐性タンパク質，MATE-1 及び MATE2-K を阻害しない。
- 肝臓の胆汁酸塩排出ポンプ及びナトリウム依存性タウロコール酸共輸送ポリペプチドと相互作用しない。

以上の 2 つの臨床相互作用試験の結果（Sidharta 2014;Hurst 2016）及び非臨床のデータ（2.4 項 CJNJ-68150420 非臨床に関する概括評価）から，マシテンタンはタダラフィルの PK に対して臨床的に意義のある影響を与えないと考えた。

2.7.2.3.4 結論

- PAH 患者の治療のためのマシテンタン及びタダラフィルの既承認用法用量は，通常，日本及び海外で同一であり，民族は本配合剤の用法用量の設定に影響を与えうる臨床的に意義のある要因ではないと考えた。このことから，本配合剤の開発においても，日本人と外国人で同一の用法用量を選択することは妥当とし，配合剤の含有用量として，マシテンタン 10 mg 及びタダラフィル 40 mg を選択した。
- マシテンタン及びタダラフィルは CYP3A4 により主に代謝される。臨床薬物間相互作用試験の結果より，マシテンタン及びタダラフィルは臨床用量で CYP3A4 を阻害又は誘導しないと考えた。また，マシテンタン及びタダラフィル間でトランスポーターを介した相互作用は想定されない。これらのことから，マシテンタン及びタダラフィル間の薬物動態学的薬物間相互作用は想定されない。

2.7.2.4 特別な試験

該当する試験はない。

2.7.2.5 付録

なし。

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略号一覧表

略号又は略称	名称及び内容
6MWD	6-minute walk distance（6 分間歩行距離）
ANCOVA	analysis of covariance（共分散分析）
CEC	clinical event committee（イベント評価委員会）
CI	confidence interval（信頼区間）
CL	confidence limit（信頼限界）
CO	cardiac output（心拍出量）
EDBT	end of double-blind treatment（二重盲検投与期間終了）
EOLT	end of open-label treatment（オープンラベル投与期間終了）
ERA	endothelin receptor antagonist（エンドセリン受容体拮抗薬）
FAS	Full analysis set
M/M	morbidity/mortality
mRAP	mean right atrial pressure（平均右房圧）
mPAP	mean pulmonary arterial pressure（平均肺動脈圧）
NT-proBNP	N-terminal pro-brain natriuretic peptide（BNP 前駆体の N 端側フラグメント）
PAH	pulmonary arterial hypertension（肺動脈性肺高血圧症）
PAH-SYMPACT®	pulmonary arterial hypertension – symptoms and impact questionnaire（肺動脈性肺高血圧症－症状及び影響に関する質問票）
PDE5i	phosphodiesterase type 5 inhibitor（ホスホジエステラーゼ 5 阻害薬）
PK	pharmacokinetics（薬物動態）
PVR	pulmonary vascular resistance（肺血管抵抗）
PVRi	pulmonary vascular resistance index（肺血管抵抗係数）
SD	standard deviation （標準偏差）
SVI	stroke volume index （1 回拍出係数）
SVO_2	mixed venous oxygen saturation（混合静脈血酸素飽和度）
WHO FC	World Health Organization functional class（世界保健機関機能分類）

2.7.3 臨床的有効性

2.7.3.1 背景及び概観

マシテンタン／タダラフィル配合錠（ACT-064992D，以下，本配合剤）は，1 錠中にマシテンタン／タダラフィルとして 10 mg/40 mg を含有する配合剤である。

PAH 患者に対する本配合剤の臨床的有効性は，国際共同第 III 相試験である AC-077A301（以下，A DUE 試験）の二重盲検投与期（クリニカルカットオフ日：2022 年 8 月 23 日）の成績を用いて評価した。また，二重盲検投与期＋オープンラベル投与期（クリニカルカットオフ日：2022 年 12 月 31 日）の成績を参考的位置付けとして提示した。A DUE 試験の概略を表 2.7.3-1 に示す。

表 2.7.3-1 有効性の評価に用いた臨床試験

試験番号／実施時期	実施国・地域 実施医療機関数*	試験デザイン 対象患者 主要評価項目	用法・用量 治験薬投与期間	有効性解析対象 被験者数
AC-077A301 2019 年 10 月 15 日～クリニカルカットオフ日：2022 年 8 月 23 日（二重盲検投与期），2022 年 12 月 31 日（オープンラベル投与期） 試験継続中	日本，欧州，米国，カナダ等，全 16 カ国／地域 76 施設	オープンラベル投与期を有する，ランダム化，二重盲検，実薬対照，トリプルダミー，国際共同，多施設共同第 III 相試験 PAH 患者 EDBT 時の PVR 変化比	二重盲検投与期： 本配合剤，マシテンタン 10 mg，又はタダラフィル 40 mg を 1 日 1 回投与 16 週 オープンラベル投与期： 本配合剤を 1 日 1 回投与 24 カ月	186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例），うち日本人 8 例（本配合剤群 6 例，マシテンタン単剤投与群 1 例，タダラフィル単剤投与群 1 例）

*被験者が組み入れられた国，治験実施医療機関

以降，A DUE 試験の試験デザイン，有効性の評価項目，及び統計解析手法について記載する。

2.7.3.1.1 試験デザイン

A DUE 試験は，PAH 患者を対象に，マシテンタン 10 mg 単剤投与（マシテンタン単剤投与）群及びタダラフィル 40 mg 単剤投与（タダラフィル単剤投与）群それぞれに対する本配合剤群の有効性及び安全性を評価することを目的とした，オープンラベル投与期を有する，前向き，ランダム化，二重盲検，実薬対照，トリプルダミー，多施設共同，国際共同第 III 相試験である。

A DUE 試験の試験デザインを図 2.7.3-1 に示す。試験期間は，スクリーニング期，二重盲検投与期，オープンラベル投与期及び安全性フォローアップ期から構成された。同意取得後，スクリーニング期間中に被験者の適格性を評価した。適格となった被験者をベースライン時の PAH 治療（前治療；未治療，ERA 既治療，又は PDE5i 既治療）を割付け因子とし，本配合剤群，マシテンタン単剤投与群，又はタダラフィル単剤投与群のいずれかに以下の比でランダムに割り付け，二重盲検下で治験薬を 16 週間投与した。

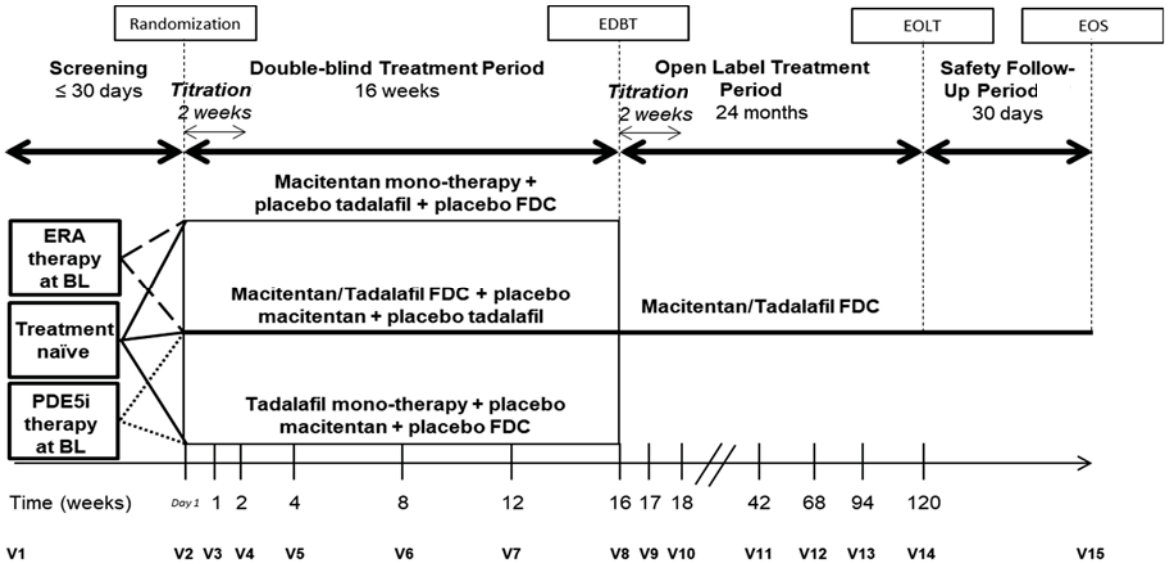
- 未治療

本配合剤群：マシテンタン単剤投与群：タダラフィル単剤投与群＝2：1：1

- ERA 既治療
  本配合剤群：マシテンタン単剤投与群＝2：1
- PDE5i 既治療
  本配合剤群：タダラフィル単剤投与群＝2：1

二重盲検投与期の治験薬の用量及び投与期間を表 2.7.3-2 に示す。ベースライン時の PAH 治療が未治療で，二重盲検投与期に本配合剤群又はタダラフィル単剤投与群にランダム化された被験者，並びにベースライン時の PAH 治療が ERA 既治療で本配合剤群にランダム化された被験者は，治験薬投与開始後 2 週間でタダラフィルを 20 mg から 40 mg に漸増し，その後本配合剤又はタダラフィル 40 mg を維持投与した。

16 週間の二重盲検投与期を完了した被験者は，24 カ月間のオープンラベル投与期に移行し，全ての被験者に非盲検下で本配合剤を投与した。オープンラベル投与期の治験薬の用量及び投与期間を表 2.7.3-3 に示す。二重盲検投与期にマシテンタン単剤投与群にランダム化され，マシテンタン 10 mg 投与を完了した被験者は，オープンラベル投与期の治験薬初回投与日から 2 週間でタダラフィルを 20 mg から 40 mg に漸増し，その後本配合剤を維持投与した。



BL=ベースライン; EDBT=二重盲検投与期間終了; EOLT=オープンラベル投与期間終了; EOS=試験終了; ERA=エンドセリン受容体拮抗薬; FDC=固定用量配合剤; Macitentan/Tadalafil FDC=マシテンタン／タダラフィル FDC （本配合剤）; PDE5i=ホスホジエステラーゼ 5 阻害薬; V=来院

図 2.7.3-1 A DUE 試験のデザイン

表 2.7.3-2 二重盲検投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目*[1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠
維持投与	マシテンタンプラセボ 1 錠 タダラフィルプラセボ 2 錠 本配合剤 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠 本配合剤プラセボ 1 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠 本配合剤プラセボ 1 錠

*1. 本配合剤群又はタダラフィル単剤投与群で，ベースライン時に事前に規定した範囲内の PDE5i（タダラフィル 40 mg/日，シルデナフィル 60～120 mg/日，又はバルデナフィル 10 mg/日）を服用していた被験者には，漸増投与せず治験薬初回投与日からタダラフィル 40 mg を投与した。

表 2.7.3-3 オープンラベル投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目[1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
維持投与	本配合剤 1 錠	本配合剤 1 錠	本配合剤 1 錠

*1. 二重盲検投与期からの盲検性を維持するために，全被験者で単剤の併用投与から開始した。二重盲検投与期に本配合剤群又はタダラフィル単剤投与群にランダム化され，タダラフィル 40 mg 投与を完了した被験者は，オープンラベル期の治験薬初回投与日からマシテンタン 10 mg 及びタダラフィル 40 mg を投与した。

<u>中間解析</u>

有効性又は無益性が非常に大きい場合の試験の早期中止，若しくはアダプティブな症例数再推定を可能とすることを目的とした中間解析を 2022 年 2 月に実施した。中間解析は治験実施計画書第 6 版に基づき，100 例の被験者が二重盲検投与期間の 16 週の評価を完了した，又は 16 週の評価前に試験を中止した時点で実施した（クリニカルカットオフ日：2021 年 12 月 10 日）。中間解析の結果，安全性の懸念は認められず，事前に規定した有効性の閾値を超えた（本配合剤群とマシテンタン単剤投与群の比較：p=0.0001，本配合剤群とタダラフィル単剤投与群の比較：p＜0.0001）。中間解析結果を踏まえた独立データモニタリング委員会からの勧告に基づき，2022 年 4 月に治験依頼者は試験への更なる被験者募集を中止した。この時点までに組み入れられた被験者は試験を継続した。

2.7.3.1.2 有効性の評価項目

2.7.3.1.2.1 主要評価項目

有効性主要評価項目は「EDBT 時の PVR のベースラインからの変化比（PVR 変化比：EDBT 時の PVR／ベースライン時の PVR）」とした。

有効性主要評価項目の設定根拠は以下のとおりである。

PVR は，右心負荷を反映する客観的パラメータであり，診断や治療効果の判定に利用されている（D'Alonzo 1991; Hoeper 2013; JCS 2021）。過去の ERA 及び PDE5i の臨床試験より，16 週の二重盲検投与期間は，右心カテーテルにより測定した肺血行動態の改善を評価するのに十分な期間であることが示されている（Ghofrani 2017; Galiè 2009）。

2.7.3.1.2.2 副次評価項目

有効性の副次評価項目は以下のとおりとした。

1. EDBT 時の 6MWD のベースラインからの変化
2. 治験薬投与開始 16 週後の PAH-SYMPACT®の心肺症状及び心血管症状のドメインスコアのベースラインからの変化
3. ベースライン時と比較し EDBT 時の WHO FC の悪化が認められない被験者の割合

2.7.3.1.2.3 その他の主な有効性評価項目（二重盲検投与期）

二重盲検投与期のその他の主な有効性評価項目は以下のとおりとした。

1. 以下に定義するベースラインから EDBT の期間で最初の M/M イベントが発現するまでの期間
   - 死因を問わない死亡
   - PAH による予定外の入院
   - PAH の悪化によるプロスタノイド（エポプロステノール，トレプロスチニル）の静脈内又は皮下投与の開始
   - PAH の臨床症状の悪化
2. ベースラインから EDBT の期間で最初の PAH 関連の死亡又は入院までの期間
3. ランダム化から二重盲検投与期のデータベースロックの期間で死因を問わない死亡までの期間
4. EDBT 時の NT-proBNP のベースラインからの変化
5. EDBT 時の肺血行動態パラメータ（PVR 以外）のベースラインからの変化

2.7.3.1.2.4 その他の主な有効性評価項目（オープンラベル投与期）

オープンラベル投与期の主な有効性評価項目は以下のとおりとした。

1. EOLT 時の 6MWD のベースラインからの変化
2. ベースラインから EOLT 時までの WHO FC の変化
3. 以下に定義するベースラインから EOLT の期間で最初の M/M イベントが発現するまでの期間
   - 死因を問わない死亡
   - PAH による予定外の入院

- PAH の悪化によるプロスタノイド（エポプロステノール，トレプロスチニル）の静脈内又は皮下投与の開始
- PAH の臨床症状の悪化

4. ベースラインから EOLT の期間で最初の PAH 関連の死亡又は入院までの期間
5. ランダム化からオープンラベル投与期のデータベースロックの期間で死因を問わない死亡までの期間
6. EOLT 時の NT-proBNP のベースラインからの変化量

2.7.3.1.3 統計解析

2.7.3.1.3.1 解析対象集団

有効性の主解析は，FAS を対象とした。本配合剤群とマシテンタン単剤投与群の有効性の主解析は，前治療が未治療又は ERA 既治療の患者層（未治療及び ERA 既治療層）で評価した。本配合剤群とタダラフィル単剤投与群の有効性の主解析は，前治療が未治療又は PDE5i 既治療の患者層（未治療及び PDE5i 既治療層）で評価した。

2.7.3.1.3.2 有効性の解析

有効性主要評価項目

PVR 変化比は，主要 Estimand（5.3.5.1.1-1 SAP Part 1 Sec 5.2.2）として定めた中間事象のデータ取扱い（表 2.7.3-付録-2）に従い解析した。EDBT 時の PVR 変化比は，本配合剤群とマシテンタン単剤投与群及びタダラフィル単剤投与群をそれぞれ比較するため，PVR 変化比を対数変換した値に関して 2 種類の ANCOVA モデルを適用し解析した。モデルの共変量には，ランダム割付けした投与群，対数変換したベースライン時の PVR 値及び層別因子（未治療，ERA 既治療，PDE5i 既治療）を含めた。ステージ 1（中間解析データ）及びステージ 2（中間解析のクリニカルカットオフ以降に収集したデータ）それぞれで ANCOVA モデルを適用し，本配合剤群と各単剤投与群を比較した中央値不偏推定値，調整済み繰り返し CL 及びステージを併合した調整 p 値を計算した。治療効果は，前述のとおり算出した中央値不偏推定値（各単剤投与群に対する本配合剤群の EDBT 時の PVR 変化比の調整幾何平均値の比）とした。各単剤投与群と本配合剤群との比較に関する帰無仮説がいずれも棄却された場合に，本配合剤の優越性が検証されたものとした。

有効性副次評価項目

階層的検定手順を用いて，有効性副次評価項目を有効性主要評価項目と同じ有意水準で解析した。階層的順序は以下のとおりとし，有意差が認められなかった場合，以降の検定は行わなかった。

1. EDBT 時の 6MWD のベースラインからの変化

2. 治験薬投与開始 16 週後の PAH-SYMPACT®の心肺症状のドメインスコアのベースラインからの変化
3. 治験薬投与開始 16 週後の PAH-SYMPACT®の心血管症状のドメインスコアのベースラインからの変化
4. ベースライン時と比較し EDBT 時の WHO FC の悪化が認められない被験者の割合

部分集団解析

有効性主要評価項目及び有効性副次評価項目について，以下の部分集団解析を行った。

- 米国内外
- 地域（北アメリカ，ラテンアメリカ，アジア，東ヨーロッパ，南及び西ヨーロッパ，オセアニア，アフリカ）
- ベースライン時の WHO FC（class II，class III）
- 年齢（65 歳未満，65 歳以上）
- 性別（男性，女性）
- 人種（白人，黒人，アジア人，その他）

感度分析

有効性主要評価項目の結果の頑健性を確認するため，以下の感度分析を実施した。

1. 感度分析 1（Treatment-policy approach）
   中間事象のデータ取扱い（表 2.7.3-付録-2）に記載された中間事象 3，4，5，6 を治療方針ストラテジーとした解析
2. 感度分析 2（Multiple imputation）
   中間事象のデータ取扱い（表 2.7.3-付録-2）を反映後，多重代入法を用いて欠測値を補完し，主解析に従い実施した解析
3. 感度分析 3（Jump to reference）
   Jump to reference の仮定に基づく多重補完［各ステージ（ステージ 1 及び 2）及び各群間比較について，本配合剤群の欠測値は参照群（マシテンタン単剤投与群又はタダラフィル単剤投与群）の分布と同様になることを想定して補完］を実施した解析
4. 感度分析 4（Rank-based analysis of covariance）
   PVR 変化比に対して正規性を仮定しない Wilcoxon の順位に基づいた共分散分析
5. 感度分析 5（Using data extract from interim analysis for stage 1）
   中間解析時点で利用可能であったデータ（ステージ 1）を用いて，主解析に従い実施した解析

日本人集団

有効性主要評価項目の統計学的有意性が確認された後，事前規定に基づき，全体集団と日本人集団の一貫性を評価した。

オープンラベル投与期

オープンラベル投与期の有効性評価項目は，統計学的検定を行わず，記述的に解析した。

2.7.3.2 個々の試験結果の要約

本項では，A DUE 試験の二重盲検投与期（クリニカルカットオフ日：2022 年 8 月 23 日）の全体集団（日本人含む）及び日本人集団の結果を記載した。

また，オープンラベル投与期を含む全体集団（日本人含む）の結果（クリニカルカットオフ日：2022 年 12 月 31 日）を記載した。なお，2022 年 12 月 31 日のクリニカルカットオフでの報告書は作成していないため，当該結果は参考的位置付けとする。

2.7.3.2.1 試験対象集団

治験薬が 1 回以上投与された 186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例）を FAS とした（5.3.5.1.1-1 CSR TSIDEM03）。

2.7.3.2.1.1 被験者の内訳

FAS の被験者の内訳を表 2.7.3-4 に示す。二重盲検投与期間中に治験薬の投与を中止した被験者の割合は，本配合剤群 15.0%（16/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）であった。主な投与中止理由は，有害事象［本配合剤群 8.4%（9/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）］であった。

表 2.7.3-4 被験者の内訳（FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
Analysis set: Full	35	70	105	44	86	130	107
Subjects receiving different than randomized treatment throughout the whole DB period	0	0	0	0	0	0	0
Completed study treatment[a]	35 (100.0%)	57 (81.4%)	92 (87.6%)	43 (97.7%)	73 (84.9%)	116 (89.2%)	90 (84.1%)
Prematurely discontinued study treatment[b]	0	12 (17.1%)	12 (11.4%)	1 (2.3%)	13 (15.1%)	14 (10.8%)	16 (15.0%)
Reason for discontinuation							
Adverse event	0	7 (10.0%)	7 (6.7%)	1 (2.3%)	8 (9.3%)	9 (6.9%)	9 (8.4%)
Withdrawal by subject	0	3 (4.3%)	3 (2.9%)	0	1 (1.2%)	1 (0.8%)	3 (2.8%)
Death	0	0	0	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Lack of efficacy	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Non-compliance with study drug	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Other	0	0	0	0	1 (1.2%)	1 (0.8%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label.
[a] Completed study treatment in the DB period: the subject took DB study drug up to Visit 8/Week 16.
[b] Prematurely discontinued study treatment in the DB period: the subject discontinued DB treatment prior to Visit 8/Week 16.
All subjects who complete the DB period are assigned to receive M/T FDC in the OL period
Notes:
Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display
One patient did not have the disposition form completed and is missing from this output but has completed the double-blind treatment period

[TSIDS04.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSIDS04.SAS] 21DEC2022, 13:15

二重盲検投与期の治験薬の曝露及び投与期間を表 2.7.3-付録-1 に示す。

二重盲検投与期の治験薬投与期間の平均値（SD）は，本配合剤群 14.85（4.547）週，マシテンタン単剤投与群 16.87（1.307）週，及びタダラフィル単剤投与群 15.98（0.952）週であった。本配合剤群の治験薬投与期間は 4 週間未満が 9.3%（10/107 例），4 週間以上 8 週間未満が 1.9%（2/107 例）であり，マシテンタン単剤投与群及びタダラフィル単剤投与群では，8 週間未満の被験者はいなかった。

2.7.3.2.1.2 人口統計学的特性

FAS の人口統計学的特性を表 2.7.3-5 に示す。年齢の中央値（範囲）は，本配合剤群 48.0（18～79）歳，マシテンタン単剤投与群 51.0（20～80）歳，タダラフィル単剤投与群 54.0（19～78）歳であった。いずれの群も 26～50 歳の割合が最も高かった。女性の割合は，本配合剤群 76.6%（82/107 例），マシテンタン単剤投与群 82.9%（29/35 例），タダラフィル単剤投与群 77.3%（34/44 例）であった。人種は白人の割合が最も高く［本配合剤群 61.7%（66/107 例），マシテンタン単剤投与群 57.1%（20/35 例），タダラフィル単剤投与群 65.9%（29/44 例），以下同順］，次にアジア人の割合が高かった［33.6%（36/107 例），34.3%（12/35 例），25.0%（11/44 例）］。PAH の臨床分類は，いずれの群も特発性 PAH の割合が最も高く［54.2%（58/107

例），45.7%（16/35 例），45.5%（20/44 例）］，次に結合組織疾患に伴う PAH の割合が高かった［33.6%（36/107 例），37.1%（13/35 例），36.4%（16/44 例）］。

PAH の重症度分類である WHO FC は，マシテンタン単剤投与群及びタダラフィル単剤投与群（各単剤投与群）では class III の割合が class II より高かったが，本配合剤群では class II の割合が class III より高かった。一方，ベースライン時の PVR 及び 6MWD の平均値は本配合剤群と各単剤投与群で大きな違いは認められなかった。

前治療は，本配合剤群で未治療が 45.8%（49/107 例），ERA 既治療が 19.6%（21/107 例），PDE5i 既治療が 34.6%（37/107 例）（以下同順）であり，マシテンタン単剤投与群で 68.6%（24/35 例），31.4%（11/35 例），0%（0/35 例），タダラフィル単剤投与群で 56.8%（25/44 例），0%（0/44 例），43.2%（19/44 例）であった（5.3.5.1.1-1 CSR TSIDEM02A）。

表 2.7.3-5 人口統計学的特性（FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
Analysis set: Full	35	70	105	44	86	130	107
Age, years							
N	35	70	105	44	86	130	107
Mean (SD)	51.3 (15.85)	51.8 (16.11)	51.7 (15.95)	53.1 (13.66)	48.7 (16.78)	50.2 (15.88)	48.7 (15.78)
Median	51.0	54.5	54.0	54.0	48.0	50.0	48.0
Range	(20; 80)	(18; 79)	(18; 80)	(19; 78)	(18; 79)	(18; 79)	(18; 79)
18-25	3 (8.6%)	6 (8.6%)	9 (8.6%)	1 (2.3%)	10 (11.6%)	11 (8.5%)	10 (9.3%)
26-50	14 (40.0%)	24 (34.3%)	38 (36.2%)	17 (38.6%)	40 (46.5%)	57 (43.8%)	52 (48.6%)
51-64	10 (28.6%)	23 (32.9%)	33 (31.4%)	16 (36.4%)	17 (19.8%)	33 (25.4%)	25 (23.4%)
Sex							
N	35	70	105	44	86	130	107
Female	29 (82.9%)	53 (75.7%)	82 (78.1%)	34 (77.3%)	62 (72.1%)	96 (73.8%)	82 (76.6%)
Male	6 (17.1%)	17 (24.3%)	23 (21.9%)	10 (22.7%)	24 (27.9%)	34 (26.2%)	25 (23.4%)
Race							
N	35	70	105	44	86	130	107
American Indian or Alaska Native	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Asian	12 (34.3%)	17 (24.3%)	29 (27.6%)	11 (25.0%)	30 (34.9%)	41 (31.5%)	36 (33.6%)
Japanese	1 (2.9%)	6 (8.6%)	7 (6.7%)	1 (2.3%)	5 (5.8%)	6 (4.6%)	6 (5.6%)
Other Asian	11 (31.4%)	11 (15.7%)	22 (21.0%)	10 (22.7%)	25 (29.1%)	35 (26.9%)	30 (28.0%)
Black or African American	1 (2.9%)	2 (2.9%)	3 (2.9%)	2 (4.5%)	2 (2.3%)	4 (3.1%)	2 (1.9%)
White	20 (57.1%)	48 (68.6%)	68 (64.8%)	29 (65.9%)	52 (60.5%)	81 (62.3%)	66 (61.7%)
Not reported	2 (5.7%)	2 (2.9%)	4 (3.8%)	2 (4.5%)	1 (1.2%)	3 (2.3%)	2 (1.9%)
WHO FC							
N	35	70	105	44	86	130	107
Class II	11 (31.4%)	42 (60.0%)	53 (50.5%)	19 (43.2%)	51 (59.3%)	70 (53.8%)	65 (60.7%)
Class III	24 (68.6%)	28 (40.0%)	52 (49.5%)	25 (56.8%)	35 (40.7%)	60 (46.2%)	42 (39.3%)
PAH etiology							
N	35	70	105	44	86	130	107
Idiopathic	16 (45.7%)	36 (51.4%)	52 (49.5%)	20 (45.5%)	47 (54.7%)	67 (51.5%)	58 (54.2%)
Heritable	3 (8.6%)	3 (4.3%)	6 (5.7%)	2 (4.5%)	2 (2.3%)	4 (3.1%)	4 (3.7%)
Drug- and- toxin induced	0	1 (1.4%)	1 (1.0%)	2 (4.5%)	1 (1.2%)	3 (2.3%)	1 (0.9%)
PAH associated with connective tissue disease	13 (37.1%)	27 (38.6%)	40 (38.1%)	16 (36.4%)	29 (33.7%)	45 (34.6%)	36 (33.6%)
PAH associated with HIV infection	0	2 (2.9%)	2 (1.9%)	2 (4.5%)	3 (3.5%)	5 (3.8%)	4 (3.7%)

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
PAH associated with portal hypertension	1 (2.9%)	0	1 (1.0%)	1 (2.3%)	1 (1.2%)	2 (1.5%)	1 (0.9%)
PAH associated with congenital heart disease	2 (5.7%)	1 (1.4%)	3 (2.9%)	1 (2.3%)	3 (3.5%)	4 (3.1%)	3 (2.8%)
PVR calculated by central reader, dyn.sec/cm^5							
N	35	70	105	44	86	130	107
Mean (SD)	827.2 (403.87)	845.3 (636.57)	839.3 (567.67)	812.4 (559.03)	888.7 (639.12)	862.9 (612.08)	881.6 (627.19)
Median	794.0	632.1	723.7	690.7	729.6	708.4	723.5
Range	(265; 1555)	(194; 3888)	(194; 3888)	(244; 3277)	(194; 3888)	(194; 3888)	(194; 3888)
6MWD, m							
N	35	70	105	44	86	130	107
Mean (SD)	347.2 (88.82)	354.3 (103.49)	351.9 (98.47)	361.8 (70.44)	351.0 (98.85)	354.7 (90.11)	352.3 (96.07)
Median	368.0	379.0	374.0	378.5	370.5	373.0	373.0
Range	(102; 500)	(2; 550)	(2; 550)	(135; 450)	(2; 550)	(2; 550)	(2; 550)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; WHO FC = World Health Organization Functional Classification; PAH = Pulmonary arterial hypertension; PVR = Pulmonary vascular resistance; 6MWD = 6-minute walk distance.
Note: N's for each parameter reflect non-missing values. Baseline is defined as the last observation prior to the first study treatment administration.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

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2.7.3.2.2 有効性の結果

2.7.3.2.2.1 有効性主要評価項目（PVR）

(1) 主解析

有効性主要評価項目は EDBT 時の PVR のベースラインからの変化比（EDBT 時の PVR／ベースライン時の PVR）とした。この値が 1 より小さいほど，EDBT 時の PVR はベースライン時に比べ「低下した（つまり，PVR が改善した）」ことを意味する。治療効果は，各単剤投与群に対する本配合剤群の EDBT 時の PVR 変化比の調整幾何平均値の比とした。この値は，各単剤投与群と比較した本配合剤群のベースラインからの PVR の相対的減少率を示しており，1 未満の場合は本配合剤群の方が有効性が高いことを意味する。

EDBT 時の PVR のベースラインからの変化を表 2.7.3-6 に示す。

マシテンタン単剤投与群に対する本配合剤群の治療効果は 0.71［調整 95%CI：0.61～0.82，調整 p<0.0001（ANCOVA モデル）］であり，マシテンタン単剤投与群に比べて本配合剤群では PVR が有意に改善（PVR 変化比が相対的に 29%減少）した。また，本配合剤群とマシテンタン単剤投与群の EDBT 時の PVR のベースラインからの変化量の平均値は，それぞれ 370.5 dyn.sec/cm^5 の低下及び 162.0 dyn.sec/cm^5 の低下であり，マシテンタン単剤投与群と比較して本配合剤群では PVR が 178（95% CI：-269～-86.8） dyn.sec/cm^5 低下した（5.3.5.1.1-1 CSR TEFPVR11）。

タダラフィル単剤投与群に対する本配合剤群の治療効果は 0.72［調整 95%CI：0.64～0.80，調整 p<0.0001（ANCOVA モデル）］であり，タダラフィル単剤投与群に比べて本配合剤群では PVR が有意に改善（PVR 変化比が相対的に 28%減少）した。また，本配合剤群とタダラフィル単剤投与群の EDBT 時の PVR のベースラインからの変化量の平均値は，それぞれ 384.5 dyn.sec/cm^5 の低下及び 180.8 dyn.sec/cm^5 の低下であり，タダラフィル単剤投与群と比較して本配合剤群では PVR が 174（95% CI：-251～-97.4） dyn.sec/cm^5 低下した（5.3.5.1.1-1 CSR TEFPVR11）。

以上のとおり，有効性主要評価項目である EDBT 時の PVR のベースラインからの変化比について，マシテンタン単剤投与又はタダラフィル単剤投与に対する本配合剤の優越性が示された。

表 2.7.3-6 EDBT 時の PVR のベースラインからの変化（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	35	70	44	86
Number of subjects included in the analysis	35	70	44	86
Baseline				
N	35	70	44	86
Mean (SD)	815.9 (401.22)	834.3 (630.93)	802.1 (551.98)	884.7 (640.34)
Median	785.3	638.5	664.6	697.6
Range	(261; 1525)	(192; 3802)	(244; 3322)	(192; 3802)
EDBT				
N	34	58	41	75
Mean (SD)	665.8 (381.88)	457.3 (329.29)	640.3 (378.48)	513.2 (359.25)
Median	584.5	360.0	647.5	405.4
Range	(142; 1613)	(50; 1838)	(189; 2171)	(50; 1838)
Ratio of EDBT to baseline				
N	35	70	44	86
Geometric mean	0.77	0.55	0.78	0.56
Geometric CV	0.344	0.405	0.255	0.366
95% CL of geometric mean	(0.69, 0.87)	(0.50, 0.60)	(0.72, 0.84)	(0.52, 0.60)
Number of subjects with intercurrent events[a]	4	15	3	14
Number of subjects with imputation of missing values[a]	1	3	2	2
Treatment effect: Adjusted geometric mean ratio vs. monotherapy (Median unbiased estimate)[b]		0.71		0.72
Adjusted repeated CL		(0.61, 0.82)		(0.64, 0.80)
Adjusted two-sided combined p-value		<.0001		<.0001

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; SD = Standard deviation.
PVR is expressed in dyn·s/cm^5
[a] See details on Intercurrent events and missing data handling in Section 5.2 of the SAP
[b] Ratio of EDBT to baseline PVR is log-transformed (base e) and analyzed using one analysis of covariance (ANCOVA) for each pairwise comparison and each stage, with factors for randomized treatment group, stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) and a continuous covariate for log-transformed baseline PVR
Results of these stage-wise ANCOVAs are used to compute Median unbiased estimate, adjusted repeated CL and adjusted combined p-value for each comparison of interest.
Notes:
PVR values are derived by the sponsor using the assessments provided by the central reader (WCC).
The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.
Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display (see Mod5.3.5.1/ADUE/CSR/App9).
Modified from [TEFPVR01A.RTF] [JNJ-68150420/AC-077A301/ DBR_CSR/ RE_FINAL/ PROD/ TEFPVR01A.SAS] 22DEC2022, 11:38

(2) 部分集団解析

PVR のベースラインからの変化について，前治療別に評価した。その結果を表 2.7.3-7 に示す。前治療別の治療効果は以下のとおりであり，前治療の有無や種類によらず，各単剤投与群に比べて本配合剤群では PVR が改善した（5.3.5.1.1-1 CSR TEFPVR15）。

- マシテンタン単剤投与群に対する本配合剤群の治療効果
  - 未治療の被験者：0.70（95%CI：0.58～0.84）
  - ERA 既治療の被験者：0.68（95%CI：0.53～0.86）

- タダラフィル単剤投与群に対する本配合剤群の治療効果
  - 未治療の被験者：0.66（95%CI：0.56～0.78）
  - PDE5i 既治療の被験者：0.81（95%CI：0.70～0.94）

その他の部分集団別の PVR 変化比を図 2.7.3-2 に示す。少数例の部分集団の一部で 95%CI が 1 を超えたものの，治療効果は部分集団間で一貫していた。

表 2.7.3-7 EDBT 時の PVR のベースラインからの変化（二重盲検投与期，前治療別）

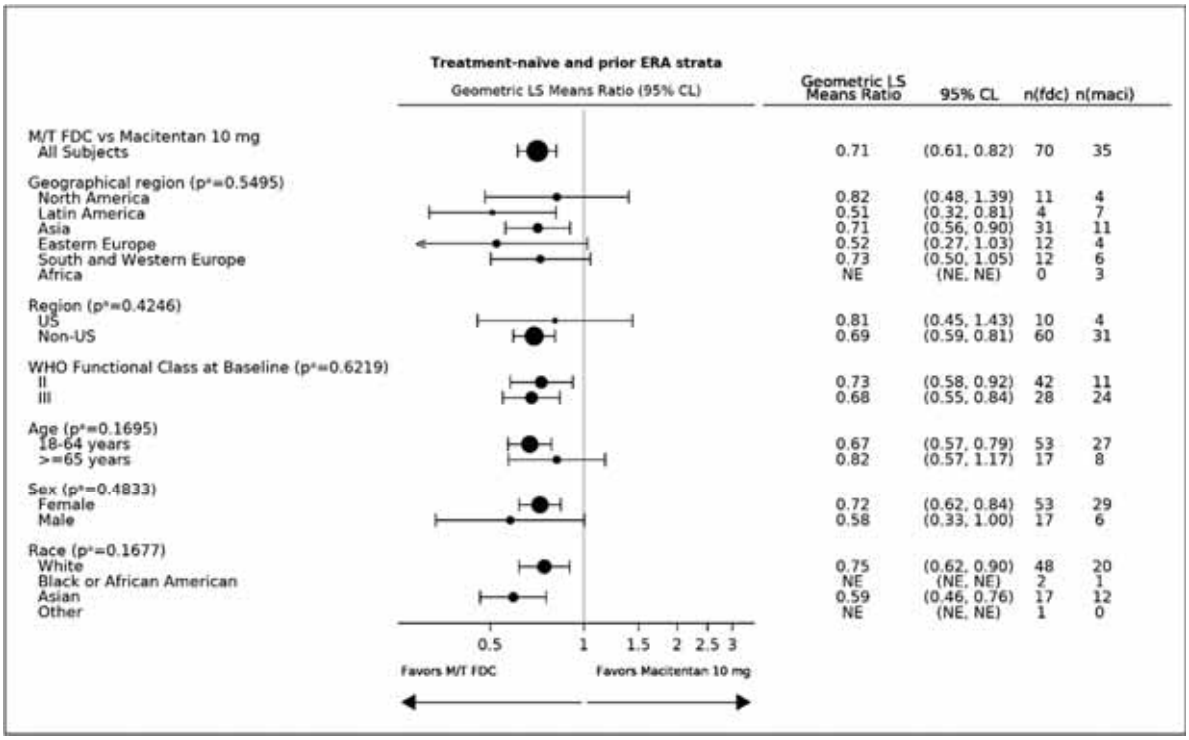
	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Baseline							
N	24	25	49	11	21	19	37
Mean (SD)	897.3 (350.86)	923.2 (659.85)	830.6 (655.36)	638.1 (462.06)	842.7 (585.19)	642.7 (316.43)	956.3 (621.47)
Median	856.9	746.9	604.1	461.4	673.1	559.1	812.2
Range	(263; 1464)	(244; 3322)	(192; 3802)	(261; 1525)	(263; 2381)	(249; 1236)	(322; 2779)
EDBT							
N	23	23	42	11	16	18	33
Mean (SD)	667.2 (328.37)	705.3 (450.21)	421.6 (321.19)	662.8 (493.99)	551.1 (342.23)	557.3 (248.47)	629.9 (375.78)
Median	657.7	662.9	342.7	523.7	442.4	469.0	552.6
Range	(142; 1329)	(189; 2171)	(50; 1838)	(241; 1613)	(104; 1441)	(253; 1048)	(197; 1591)
Ratio of EDBT to baseline							
N	24	25	49	11	21	19	37
Geometric mean	0.70	0.75	0.51	0.96	0.66	0.82	0.64
Geometric CV	0.354	0.268	0.394	0.174	0.362	0.233	0.270
95% CL of GM	(0.60, 0.81)	(0.67, 0.83)	(0.45, 0.56)	(0.86, 1.08)	(0.56, 0.78)	(0.73, 0.91)	(0.59, 0.70)

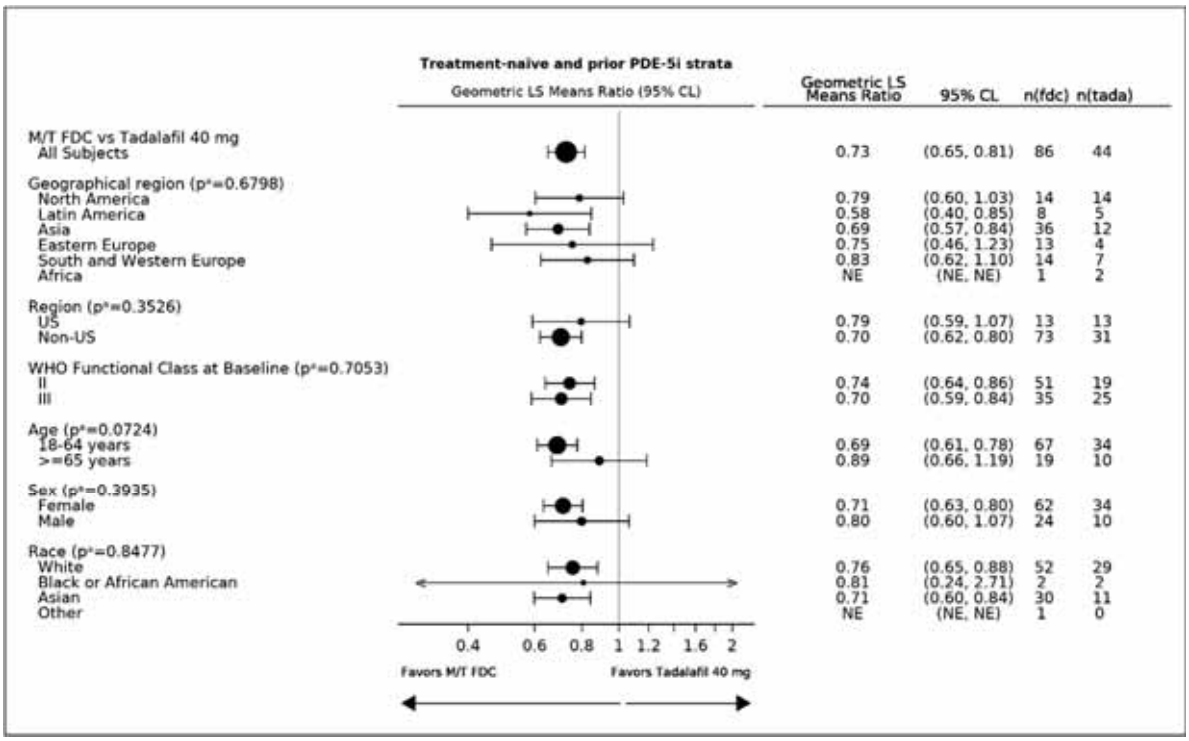
Source: TEFPVR15

Key: ERA = Endothelin receptor antagonist; GM = Geometric mean, PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; SD = Standard deviation

Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.

Note: Ratio of EDBT to baseline PVR is log-transformed (base e) and analyzed using 2 analyses of covariance (ANCOVAs), one for each pairwise comparison, with factor for randomized treatment group and a continuous covariate for baseline log PVR.





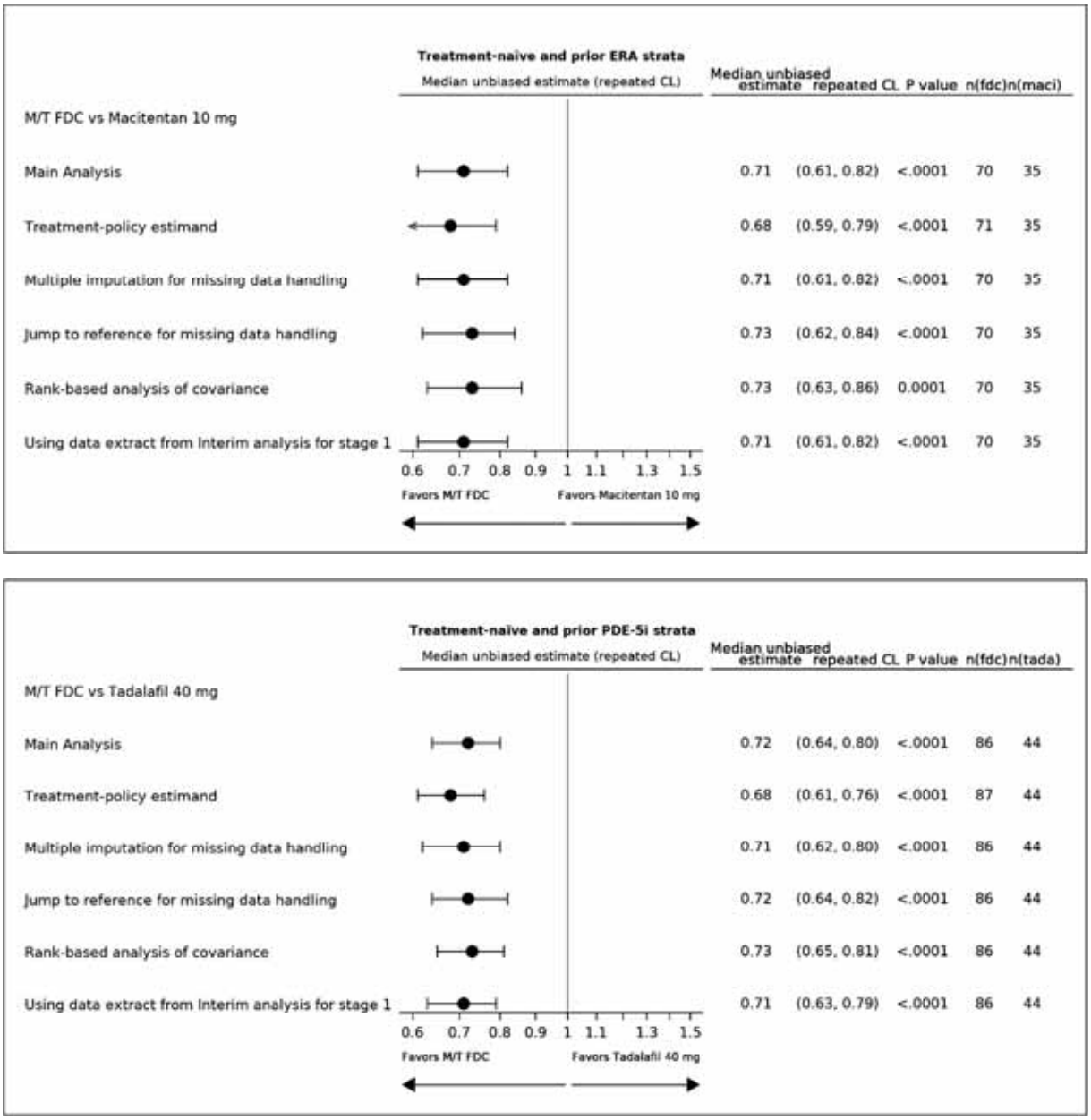
Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CL = Confidence limit; WHO FC = World Health Organization Functional Classification; n(fdc) = No. subjects in M/T FDC; n(mon) = No. subjects in monotherapy group.
[a] interaction p-value obtained from model analyzing ratio of EDBT to baseline PVR using 2 analyses of covariance (ANCOVAs), one for each pairwise comparison, with factors for randomized treatment group, stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i), subgroup, subgroup*treatment interaction and a continuous covariate for baseline log PVR.
Note: PVR values are derived by the sponsor using the assessments provided by the central reader (WCC).
Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.Note: Marker size for subgroups is based on number of subjects per group (if feasible).
[GEFPVR01.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/GEFPVR01.SAS] 18DEC2022, 09:36

図 2.7.3-2 EDBT 時の PVR 変化比のフォレストプロット
（二重盲検投与期，部分集団別，FAS）

(3) 感度分析

A DUE 試験の有効性主要評価項目である EDBT 時の PVR 変化比は，主要 Estimand のデータ取扱いに従い解析した（5.3.5.1.1-1 SAP Part 1 Sec 5.2.2）。この結果の頑健性を確認するために，感度分析を実施した。

最も高頻度に認められた中間事象（表 2.7.3-付録-2）は「EDBT 来院直前の 2 日を超える治験薬の投与中断又は中止：死亡，疾患進行又は悪化を伴わない」であり，この中間事象及び欠測値の数は，本配合剤群の方がマシテンタン単剤投与群及びタダラフィル単剤投与群より多かった。これらの中間事象の多くは中間解析前に認められたものの，ステージ 1（中間解析データ）及びステージ 2（中間解析後に収集されたデータ）の結果は一貫していた（5.3.5.1.1-1 CSR TEFPVR01b）。また，その他事前に計画した感度分析の結果は，主解析の結果と同様であった（図 2.7.3-3）



Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; n(fdc) = No. subjects in M/T FDC; n(mon) = No. subjects in monotherapy group.
Note: PVR values are derived by the sponsor using the assessments provided by the central reader (WCC).
Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.
[GEFPVR02.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/GEFPVR02.SAS] 18DEC2022, 09:37

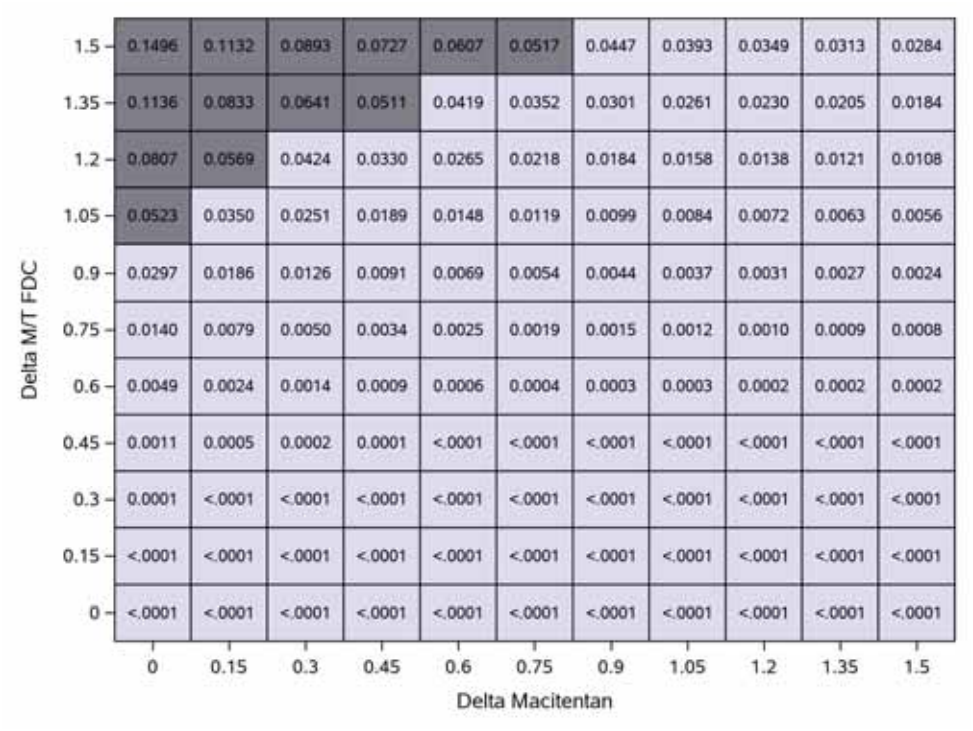
図 2.7.3-3 EDBT 時の PVR 変化比のフォレストプロット
（二重盲検投与期，感度分析，FAS）

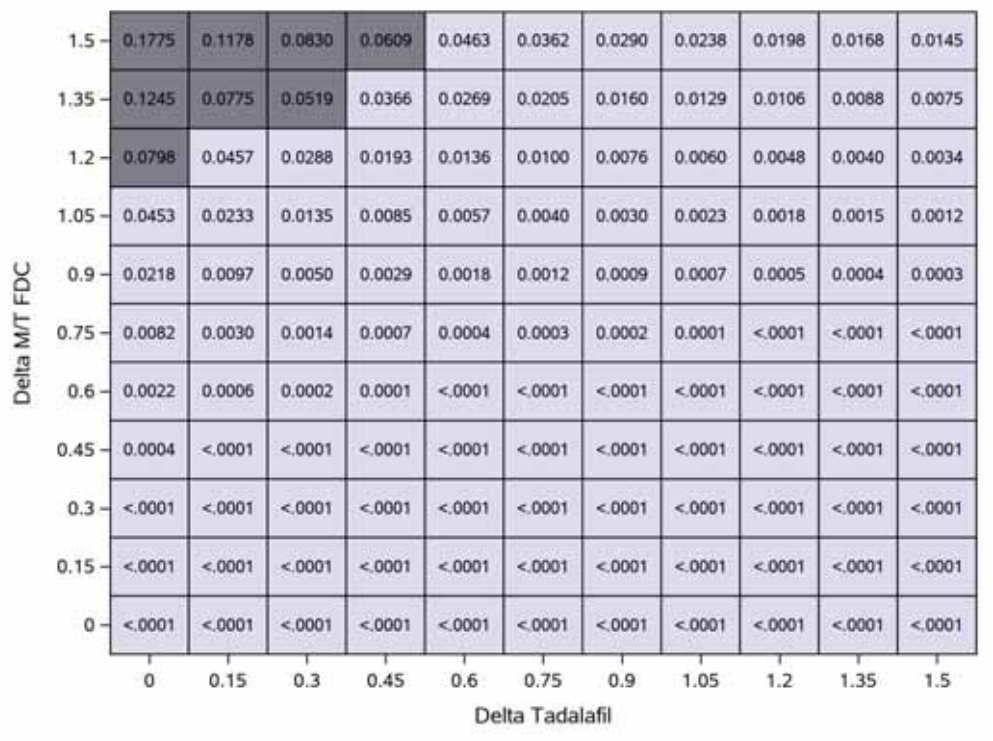
続いて，事前計画に基づき，中間事象を考慮した後に欠測値がある被験者（未治療及び ERA 既治療層の本配合剤群 3 例，未治療及び PDE5i 既治療層の本配合剤群 2 例）に焦点を当てた Tipping point analysis を実施した。本解析では，欠測値がある全ての被験者について多重代入法を用いて欠測値を補完した後，これらの被験者の PVR 変化比を 0.15 ごとに移動し，本配合剤群及び各単剤投与群の全範囲の値を探索した。その結果，各単剤投与群の PVR 変化比が悪化しなかった被験者（すなわち，$\Delta=0$）に注目すると，本配合剤群の被験者の PVR 変化比を 3 にまで悪

化させた結果でも，各単剤投与群と比べて本配合剤群では，PVR が統計学的に有意に改善した（5.3.5.1.1-1 CSR GEFPVR05）。

中間事象がなく欠測値のみがある被験者は非常に少なかったため，中間事象又は欠測値のいずれかにより補完された被験者（本配合剤群 14 例）を考慮した Tipping point analysis も事後解析として実施した（図 2.7.3-4）。その結果，統計学的有意差が「あり」から「なし」に換わる転換点は，これら 14 例の PVR 変化比を 1 より大きい量だけ悪化させたときであった（すなわち，多重代入法後のこれら 14 例の PVR 変化比が 0.78，0.85，…，1.22 である場合，治療効果の統計的有意差が「あり」から「なし」に換わる転換点は，これら 14 例の PVR 変化比が少なくとも 1.78，1.85，…，2.22 に悪化した場合であった）。

以上の結果から，主解析結果の高い頑健性が確認された。





ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment;
Notes:All patients having imputed data for the main analysis (due to intercurrent event or missing data) are taken into account for this analysis and considered as missing as a starting point. For each comparison of interest and each stage, multiple imputation with delta worsening is applied. For each arm, the mean effect (EDBT/Baseline PVR ratio) following dropout will be worsened by an amount of 0.15 starting with delta = 0. Final p-values are calculated using the inversne normal combination method (INC)
[GEFPVR06.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/GEFPVR06.SAS] 30MAR2023, 17:14

図 2.7.3-4 EDBT 時の PVR のベースラインからの変化比の Tipping point analysis

（事後解析）

2.7.3.2.2.2 有効性副次評価項目

(1) 6MWD

1) 主解析

EDBT 時の 6MWD のベースラインからの変化を表 2.7.3-8 に示す。

マシテンタン単剤投与群又はタダラフィル単剤投与群に対する本配合剤の治療効果（EDBT 時の 6MWD のベースラインからの変化量の群間差）はそれぞれ 16.04m［調整 95%CI：-17.0～49.08 m，調整 p=0.3802（ANCOVA モデル）］及び 25.37 m［調整 95%CI：-0.93～51.59 m，調整 p=0.0591（ANCOVA モデル）］であった。

副次評価項目である EDBT 時の 6MWD のベースラインからの変化では，マシテンタン単剤投与群又はタダラフィル単剤投与群と比較した際の本配合剤群の統計学的な優越性は示されなかったものの，数値上の増加（改善）傾向が認められた。

表 2.7.3-8 EDBT 時の 6MWD のベースラインからの変化（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	35	70	44	86
Number of subjects included in the analysis	35	70	44	86
Baseline				
N	35	70	44	86
Mean (SD)	347.2 (88.82)	354.3 (103.49)	361.8 (70.44)	351.0 (98.85)
Median	368.0	379.0	378.5	370.5
Range	(102; 500)	(2; 550)	(135; 450)	(2; 550)
EDBT				
N	33	61	41	79
Mean (SD)	383.2 (88.56)	413.6 (103.21)	381.1 (78.00)	398.3 (103.91)
Median	370.0	419.0	408.0	410.0
Range	(140; 540)	(120; 600)	(133; 490)	(120; 600)
Change from baseline to EDBT				
N	35	70	44	86
Mean (SD)	38.5 (70.42)	52.9 (88.23)	15.9 (45.04)	43.4 (78.03)
Median	30.0	34.0	16.5	37.9
Range	(-100; 233)	(-135; 454)	(-78; 102)	(-141; 454)
Number of subjects with intercurrent events[a]	4	13	3	12
Number of subjects with imputation of missing values[a]	2	3	3	2
Disease progression (confirmed) prior to Week 16	0	0	0	0
No disease progression (confirmed) prior to Week 16	2 (5.7%)	3 (4.3%)	3 (6.8%)	2 (2.3%)
Treatment effect: Adjusted change from baseline difference vs. monotherapy (Median unbiased estimate)[b]		16.04		25.37
Adjusted repeated CL		(-17.0,49.08)		(-0.93,51.59)
Adjusted two-sided combined p-value		0.3802		0.0591

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; EDBT = End of Double-blind Treatment; CL = Confidence limit; SD = Standard deviation.

a See details on Intercurrent events and missing data handling in Section 5.3 of the SAP

b Change from baseline to EDBT in 6MWD is analyzed using one analysis of covariance (ANCOVA) for each pairwise comparison and each stage, with factors for randomized treatment group, stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) and a continuous covariate for baseline 6MWD

Results of these stage-wise ANCOVAs are used to compute Median unbiased estimate, adjusted repeated CL and adjusted combined p-value for each comparison of interest.

Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.

Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

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2) 部分集団解析

EDBT 時の 6MWD のベースラインからの変化について，前治療別に評価した。その結果を表 2.7.3-9 に示す。PAH 治療歴が未治療の被験者では，タダラフィル単剤投与群と比較して本配合剤群で 6MWD が大きく増加した（表 2.7.3-10）。

表 2.7.3-9 EDBT 時の 6MWD のベースラインからの変化（二重盲検投与期，前治療別）

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Baseline							
N	24	25	49	11	21	19	37
Mean (SD)	324.1 (95.99)	349.6 (81.60)	352.9 (111.02)	397.6 (39.37)	357.6 (85.73)	377.9 (49.95)	348.6 (81.41)
Median	347.0	378.0	373.0	394.0	387.0	383.0	363.0
Range	(102; 500)	(135; 448)	(2; 550)	(338; 455)	(140; 463)	(282; 450)	(120; 460)
EDBT							
N	22	24	45	11	16	17	34
Mean (SD)	362.9 (93.98)	375.0 (84.02)	407.2 (113.99)	423.9 (61.77)	431.5 (63.46)	389.7 (70.20)	386.4 (89.11)
Median	365.0	406.5	420.0	441.0	416.5	419.0	404.0
Range	(140; 540)	(133; 480)	(120; 600)	(304; 501)	(326; 531)	(281; 490)	(198; 537)
Change from baseline to EDBT							
N	24	25	49	11	21	19	37
Mean (SD)	41.7 (81.17)	22.0 (35.53)	53.0 (92.38)	26.3 (54.06)	48.0 (74.97)	9.0 (50.58)	30.7 (42.60)
Median	31.5	19.0	40.0	27.0	17.0	0.0	32.0
Range	(-116; 233)	(-46; 96)	(-135; 454)	(-71; 103)	(-25; 273)	(-78; 102)	(-78; 119)

Source: Q0209C0301TEF6MWD02A
Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; EDBT = End of Double-blind Treatment; SD = Standard deviation.

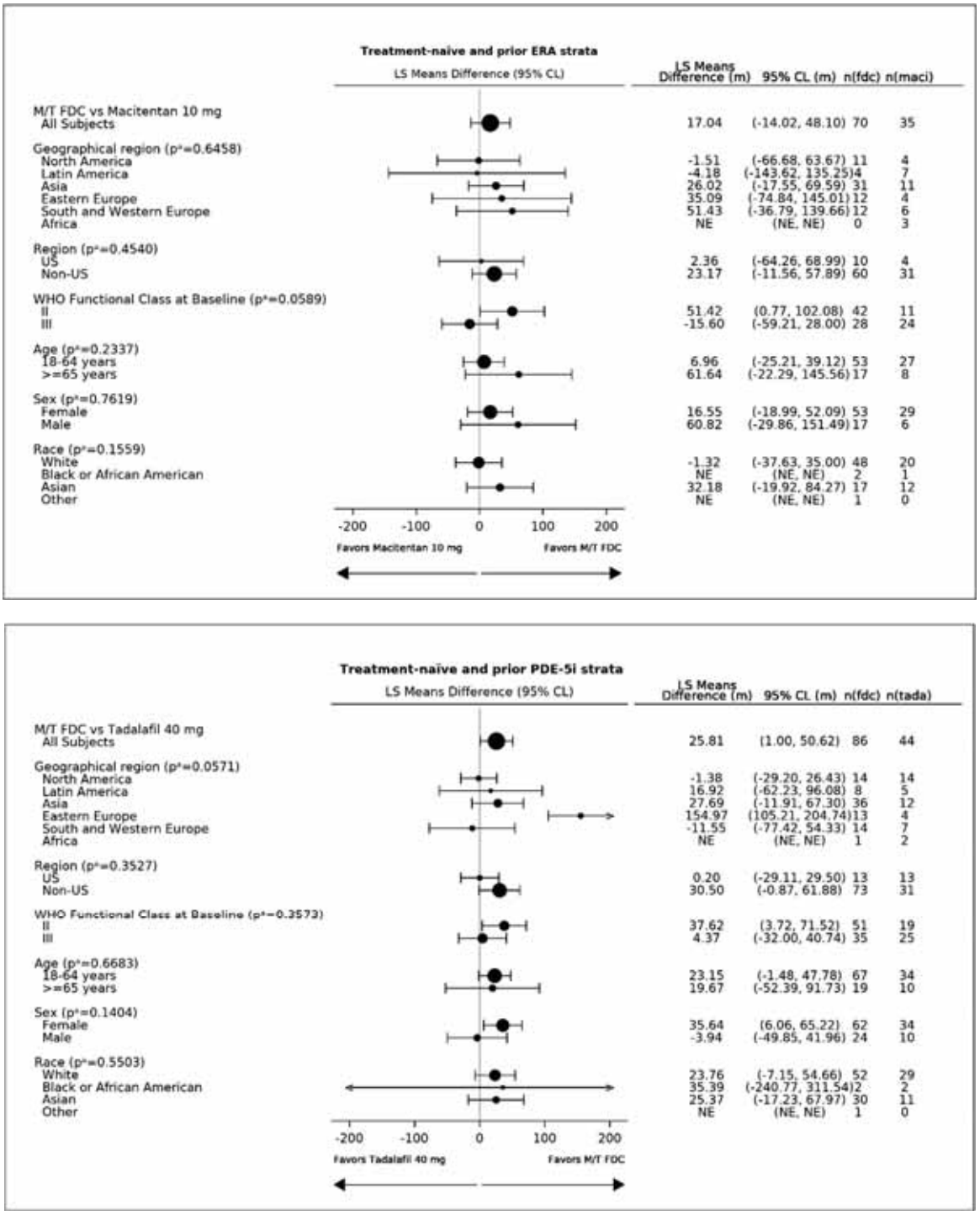
表 2.7.3-10 EDBT 時の 6MWD のベースラインからの変化で評価した治療効果
（二重盲検投与期，前治療別）

Comparison	Treatment-naïve at baseline Macitentan 10 mg	Tadalafil 40 mg	M/T 10/40 mg FDC	Treatment effect	95% CI	Raw p-value
M/T 10/40 mg FDC vs macitentan 10 mg	24	--	49	20.38	-20.3, 61.08	0.3214
M/T 10/40 mg FDC vs tadalafil 40 mg	--	25	49	33.04	-5.31, 71.39	0.0902
Comparison	**Prior ERA/PDE-5i Status at Baseline Macitentan 10 mg**	**Tadalafil 40 mg**	**M/T 10/40 mg FDC**	**Treatment Effect**	**95% CI**	**Raw p-value**
M/T 10/40 mg FDC vs macitentan 10 mg	11	--	21	8.49	-41.0, 57.95	0.7279
M/T 10/40 mg FDC vs tadalafil 40 mg	--	19	37	25.89	0.88, 50.90	0.0427

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; EDBT = End of Double-blind Treatment
For 6MWD by stratum, treatment effect is reported as the adjusted change from baseline difference for M/T 10/40 mg FDC vs monotherapy (Least Square mean).
Change from baseline to EDBT in 6MWD in each stratum is analyzed using 2 analyses of covariance (ANCOVAs), one for each pairwise comparison, with factor for randomized treatment group and a continuous covariate for baseline 6MWD.
Raw p-values do not take into account the adaptive design of the study

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その他の部分集団別の EDBT 時の 6MWD のベースラインからの変化を図 2.7.3-5 に示す。WHO FC の class 別の部分集団を除き，治療効果は部分集団間でおおむね一貫していた。



Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; EDBT = End of Double-blind Treatment; CL = Confidence limit; WHO FC = World Health Organization Functional Classification; n(fdc) = No. subjects in M/T FDC; n(mon) = No. subjects in monotherapy group.

[a] interaction p-value obtained from model analyzing change from baseline to EDBT in 6MWD using 2 analyses of covariance (ANCOVAs), one for each pairwise comparison, with factors for randomized treatment group, stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i), subgroup, subgroup*treatment interaction and a continuous covariate for baseline 6MWD.

Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.

Note: Marker size for subgroups is based on number of subjects per group (if feasible).

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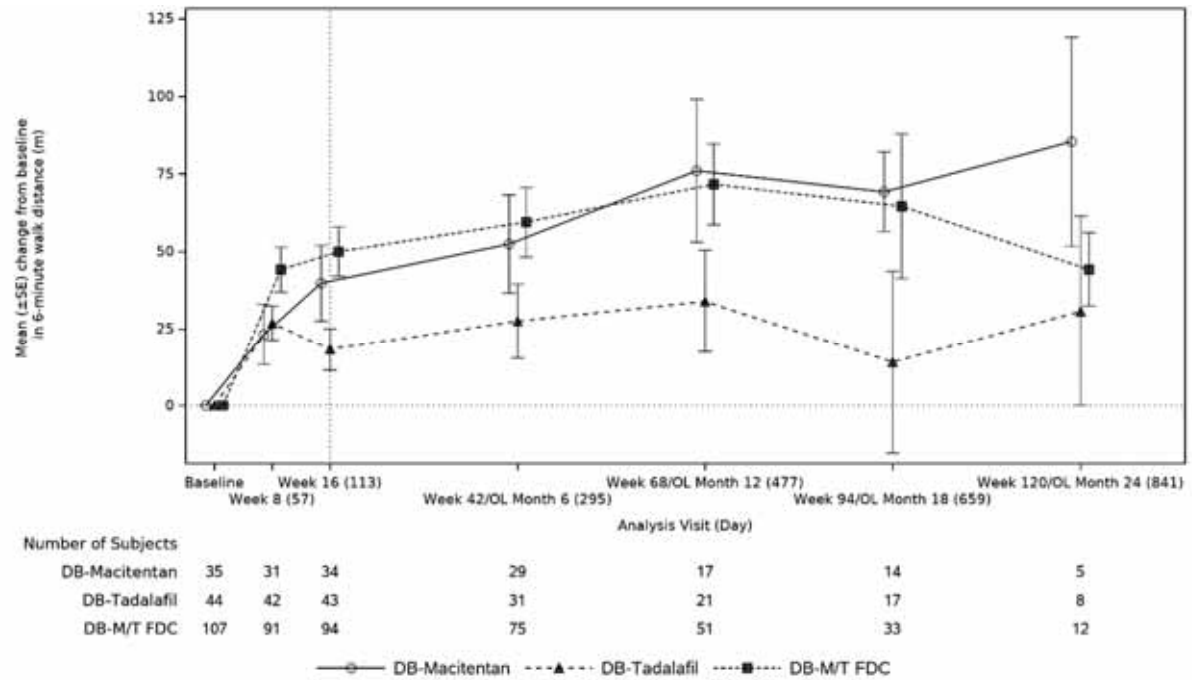
図 2.7.3-5 EDBT 時の 6MWD のベースラインからの変化のフォレストプロット
（二重盲検投与期，部分集団）

3）二重盲検投与期及びオープンラベル投与期

治験薬を 1 回以上投与された被験者 186 例（FAS）を対象に，二重盲検投与期及びオープンラベル投与期 24 カ月目までに得られた 6MWD について二重盲検投与期の群別［二重盲検投与期に本配合剤を投与された被験者（DB-本配合剤群）107 例，二重盲検投与期にマシテンタン単剤を投与された被験者（DB-マシテンタン群）35 例，二重盲検投与期にタダラフィル単剤を投与された被験者（DB タダラフィル群）44 例］に解析した。

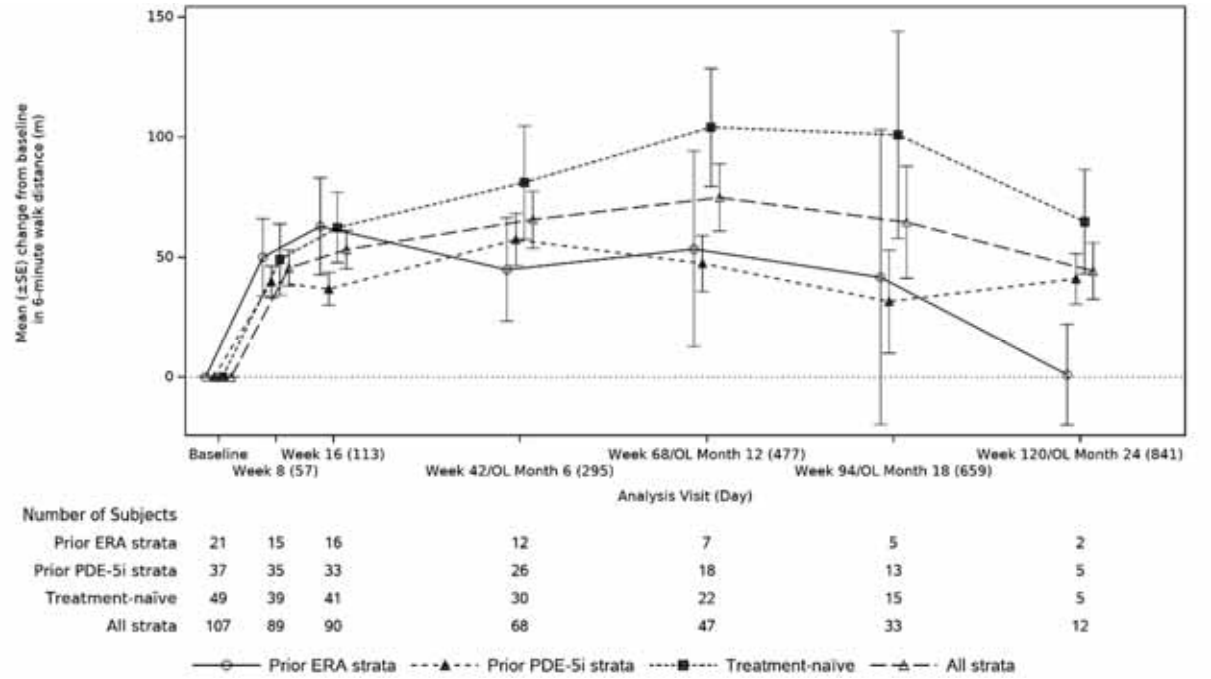
二重盲検投与期のベースラインからオープンラベル投与期 12 カ月目までの変化量の平均値（SD）は，DB-本配合剤群（51 例）で 71.8（93.12） m の増加，DB-マシテンタン群（17 例）で 76.1（95.18） m の増加，DB-タダラフィル群（21 例）で 33.9（75.59） m の増加であった（図 2.7.3-6，表 2.7.3-付録-3）。二重盲検投与期からオープンラベル投与期 12 カ月目まで 6MWD は増加（改善）傾向を示した。

DB-本配合剤群のうち，前治療が未治療であった被験者で 6MWD の最大かつ持続的な改善が認められた（図 2.7.3-7，表 2.7.3-付録-4）。前治療が PDE5i 既治療であった被験者及び／又は DB-タダラフィル群の 6MWD の改善は小さかった。



Key: M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; SE = Standard error; EOT = End of treatment; OL = Open-label.
Note: Number of subjects for measured value is the number of subjects with non-missing values at both baseline and the postbaseline time point.
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図 2.7.3-6 6MWD のベースラインからの変化量の推移
（二重盲検投与期＋オープンラベル投与期，FAS）



Number of Subjects							
Prior ERA strata	21	15	16	12	7	5	2
Prior PDE-5i strata	37	35	33	26	18	13	5
Treatment-naïve	49	39	41	30	22	15	5
All strata	107	89	90	68	47	33	12

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; SE = Standard error; EOT = End of treatment.
Note: On-treatment measurements (from the first study treatment administration up to EOT + 7 days) are included.
Note: Number of subjects for measured value is the number of subjects with non-missing values at both baseline and the postbaseline time point.
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図 2.7.3-7 6MWD のベースラインから変化量の推移
（二重盲検投与期＋オープンラベル投与期，DB-本配合剤群）

(2) PAH-SYMPACT®の心肺症状及び心血管症状ドメインスコア

PAH-SYMPACT®心肺症状及び心血管症状ドメインスコアの範囲は 0～4 であり，スコアが高いほど症状の重症度が高いことを示す。

6MWD で有意差が認められなかったため，階層的検定手順（2.7.3.1.3.2 参照）に従い PAH-SYMPACT®の心肺症状及び心血管症状ドメインスコアについて検定は行わず，二重盲検投与期のベースラインから EDBT 時までの変化量を探索的に解析した。

全ての群で，心肺症状及び心血管症状ドメインスコアはベースライン時と比較して EDBT 時で低下した（表 2.7.3-11）。また，未治療の被験者では，ERA 既治療又は PDE5i 既治療の被験者と比較して心肺症状及び心血管症状ドメインスコアがより低下した（5.3.5.1.1-1 CSR TEFPAHSS12 及び TEFPAHSS14）。

表 2.7.3-11 PAH-SYMPACT®の心肺症状及び心血管症状ドメインスコアの要約
（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata		
	Macitentan (N=35)	**M/T FDC (N=70)**	**M/T FDC vs Macitentan**	**Tadalafil (N=44)**	**M/T FDC (N=86)**	**M/T FDC vs Tadalafil**
	Mean (SD)		Adj. change from BL difference (Adj. repeated CL) [Adj. 2-sided combined p-value]	Mean (SD)		Adj. change from BL difference (Adj. repeated CL) [Adj. 2-sided combined p-value]
Change from BL to EDBT in PAH-SYMPACT cardiopulmonary symptoms domain score	-0.14 (0.478)	-0.20 (0.394)[$3]	-0.03 (-0.21, 0.15) [0.8763]	-0.13 (0.554)	-0.15 (0.404)[$4]	-0.04 (-0.21, 0.13) [0.7883]
Change from BL to EDBT in PAH-SYMPACT cardiovascular symptoms domain score	-0.14 (0.473)	-0.15 (0.349)[$3]	0.01 (-0.17, 0.19) [1.0000]	-0.18 (0.612)	-0.10 (0.318)[$4]	0.02 (-0.15, 0.19) [0.9619]

Key: BL = Baseline; ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PAH-SYMPACT = Pulmonary Arterial Hypertension-Symptoms and Impact; EDBT = End of Double-blind Treatment; SE = Standard error; CL = Confidence limit; SD = Standard deviation
N included in analysis for Macitentan and M/T FDC: [$3] 33 and 66.
N included in analysis for Tadalafil and M/T FDC: [$4] 42 and 81.
Source: 5.3.5.1.1-1 CSR TEFPAHSS01A, TEFPAHSS02A.

(3) WHO FC

1) 主解析

WHO FC は class I～IV に分類され，class が大きいほど PAH の重症度が高いことを示す。ベースライン時と比較して，WHO FC が 1 class 以上増加した場合を「WHO FC の悪化」と定義した。

6MWD で有意差が認められなかったため，階層的検定手順（2.7.3.1.3.2 項参照）に従い WHO FC の悪化については統計学的な検定を行わず，探索的に解析した。WHO FC の主解析はステージ別（ステージ 1 及び 2）に実施した（5.3.5.1.1-1 CSR Sec 5.1.3.3）。

補完したデータでは，EDBT 時に WHO FC の悪化が認められた被験者の割合は，各単剤投与群と比較して本配合剤群で高かった（表 2.7.3-12，5.3.5.1.1-1 CSR Table 16）。これは，中間事象及び欠測値の影響と考えられた。

実際に観測された（補完されていない）データでは，EDBT 時に WHO FC の悪化が認められた被験者の割合は，本配合剤群及びマシテンタン単剤投与群の比較ではそれぞれ 3.2%及び 2.9%であり，本配合剤群及びタダラフィル単剤投与群の比較ではそれぞれ 2.5%及び 4.5%であった（5.3.5.1.1-1 CSR TEFWHOFC06）。

表 2.7.3-12 EDBT 時に WHO FC の悪化が認められなかった被験者の割合
（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata		
	Macitentan (N=35)	**M/T FDC (N=70)**	**M/T FDC vs Macitentan**	**Tadalafil (N=44)**	**M/T FDC (N=86)**	**M/T FDC vs Tadalafil**
Proportion of participants with absence of worsening in WHO FC from BL to EDBT	n (%)		Adjusted odds ratio (95% CL) [two-sided p-value]	n (%)		Adjusted odds ratio (95% CL) [two-sided p-value]
	Stage 1[$5]: 17 (94.4)	29 (76.3)	0.199 (0.004, 1.731) [0.216]	Stage 1[$6]: 20 (90.9)	41 (87.2)	0.987 (0.082, 7.743) [1.000]
	Stage 2[$7]: 17 (100.0)	30 (93.8)	0.765 (NE, 6.561) [0.422]	Stage 2[$8]: 21 (95.5)	35 (89.7)	0.436 (0.008, 4.935) [0.837]

Key: BL = Baseline; ERA = Endothelin receptor antagonist; IA = Interim analysis; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; WHO FC = World Health Organization Functional Classification; EDBT = End of Double-blind Treatment; CL = Confidence limit.
N included in analysis for Macitentan and M/T FDC: [$5] 18 and 38; [$7] 17 and 32.
N included in analysis for Tadalafil and M/T FDC: [$6] 22 and 47; [$8] 22 and 39.
Stage 1 (data evaluated for the IA) and stage 2 (data collected after the cut-off for the IA).
Results are presented by stage only because the number of worsening events was too low in some stages and some treatment groups to allow CI to be estimated and then combined for the overall result
Source: 5.3.5.1.1-1 CSR TEFWHOFC01B

2) 二重盲検投与期及びオープンラベル投与期

治験薬を 1 回以上投与された被験者 186 例（FAS）を対象に，二重盲検投与期及びオープンラベル投与期 24 カ月目までに得られた WHO FC のデータについて二重盲検投与期の群別に解析した。

オープンラベル投与期 12 カ月目までに WHO FC が評価可能であった被験者（DB-本配合剤群 50 例，DB-マシテンタン群 20 例，DB-タダラフィル群 23 例）の 90%超で，WHO FC の悪化は認められなかった（表 2.7.3-付録-5）。WHO FC の悪化は，DB-タダラフィル群及び DB-本配合剤群の被験者でのみ認められた（表 2.7.3-付録-6）。

2.7.3.2.2.3 その他の有効性評価項目

(1) M/M イベント

1) 主解析

報告された M/M イベントは，CEC によって評価された。二重盲検投与期間中に認められた M/M イベントは，2 例 2 件の「死因を問わない死亡」と 3 例 3 件の「PAH による予定外の入院」であり，いずれも本配合剤群で認められた（5.3.5.1.1-1 CSR TEFMM02 及び TEFDTH02）。二重盲検投与期間が 16 週間と短くイベント数が少なかったため，「最初の M/M イベントが発現するまでの期間」，「最初の PAH 関連の死亡又は入院までの期間」，及び「死因を問わない死亡までの期間」に関して，結果から十分な評価ができなかった。

2) 二重盲検投与期及びオープンラベル投与期

2022 年 12 月 31 日のクリニカルカットオフまでに報告され，2023 年 2 月 9 日までに CEC が評価した M/M イベントを解析した。

二重盲検投与期及びオープンラベル投与期を通じて，治験薬最終投与日から 7 日後までに，DB-本配合剤群で 6 例 7 件の M/M イベントが認められた。その内訳は，2 件の「死因を問わない死亡」及び 5 件の「PAH による予定外の入院」であった（二重盲検投与期に認められた M/M イベントは 2.7.3.2.2.3(1)1）項参照）。DB-マシテンタン群及び DB-タダラフィル群では，それぞれ 1 例 2 件の M/M イベントが認められた。その内訳は，いずれも 1 件の「PAH による予定外の入院」及び 1 件の「PAH の悪化によるプロスタノイドの静脈内又は皮下投与の開始」であった（表 2.7.3-付録-7）。治験薬投与開始から 120 週目までの評価では，DB-本配合剤群で 2 例 3 件の M/M イベントが追加で認められた。その内訳は 2 件の「死因を問わない死亡」及び 1 件の「PAH による予定外の入院」であった（表 2.7.3-付録-8）。イベント数が少なかったため，「最初の M/M イベントが発現するまでの期間」，「最初の PAH 関連の死亡又は入院までの期間」，及び「死因を問わない死亡までの期間」に関して，結果から十分な評価ができなかった。

(2) NT-proBNP

1) 主解析

有効性主要評価項目と同様の ANCOVA モデルを用いて，NT-proBNP のベースラインから EDBT までの変化を解析した。マシテンタン単剤投与群に対する本配合剤群の治療効果（EDBT 時の NT-proBNP の変化比の調整幾何平均値の比）は 0.57（95%CI：0.41～0.80）であり，タダラフィル単剤投与群に対する本配合剤群の治療効果は 0.57（95%CI：0.42～0.77）であった（5.3.5.1.1-1 CSR Table 18）。各単剤投与群に比べて本配合剤群では NT-proBNP がより改善（相対的に 40%以上減少）した。

2) 事後解析

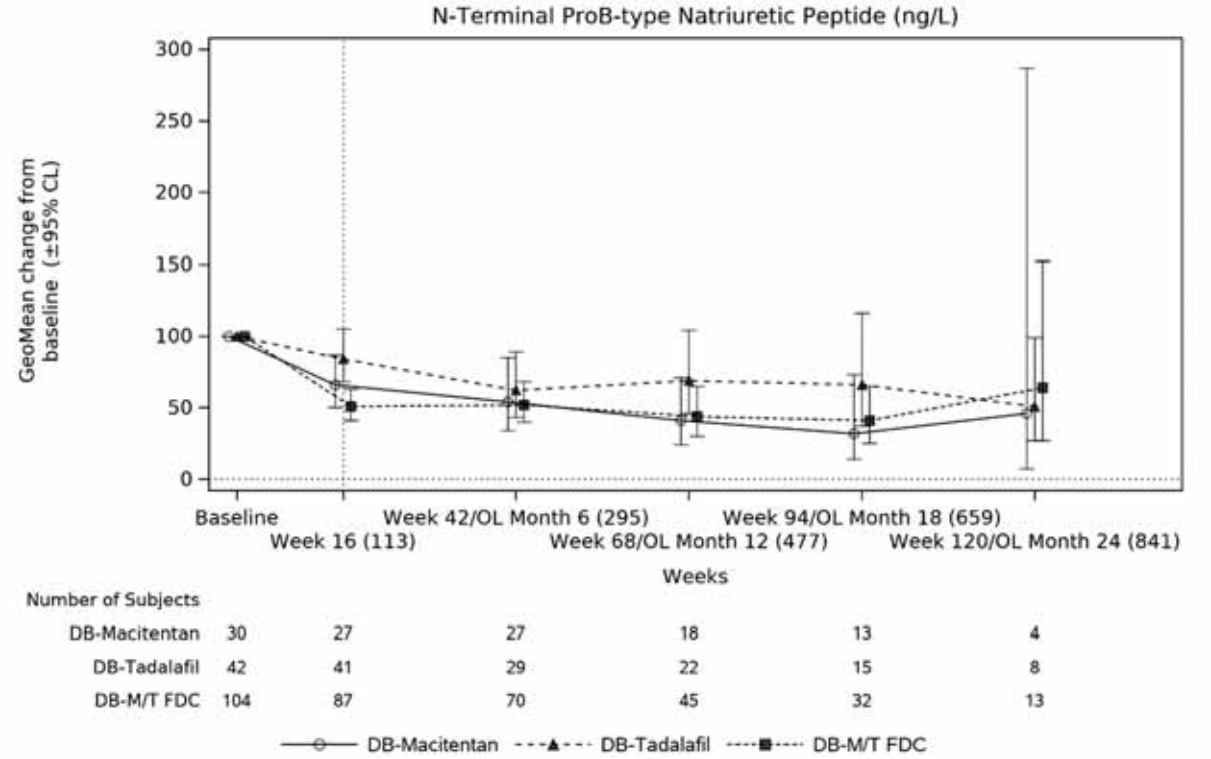
有効性主要評価項目の Estimand（5.3.5.1.1-1 SAP Part 1 Sec 5.2.2）を用いて，NT-proBNP のベースラインから EDBT までの変化量について事後解析を実施し，欠測値の影響を評価した。

マシテンタン単剤投与群に対する本配合剤群の治療効果は 0.70（95%CI：0.50～0.98）であり，タダラフィル単剤投与群に対する本配合剤群の治療効果は 0.64（95%CI：0.47～0.86）であった（表 2.7.3-付録-9）。

3) 二重盲検投与期及びオープンラベル投与期

治験薬を 1 回以上投与された被験者 186 例（FAS）を対象に，二重盲検投与期及びオープンラベル投与期 24 カ月目までに得られた NT-proBNP のデータについて二重盲検投与期の群別に解析した。その結果，二重盲検投与期及びオープンラベル投与期を通じて，全ての群で NT-proBNP はベースラインから低下（改善）し，本配合剤群でより低下した（図 2.7.3-8）。ベースライン時と比較したオープンラベル投与期 12 カ月目の変化率の幾何平均値は，DB-本配合剤群（45 例）

で 44.3%，DB-マシテンタン群（18 例）で 41.3%，DB-タダラフィル群（22 例）で 69.2%であった （表 2.7.3-付録-10）。NT-proBNP が最も低下したのは，DB-本配合剤群の未治療の被験者であり，この低下はオープンラベル投与期の 12 カ月目まで持続した（図 2.7.3-付録-1）。



Key: M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label; NT-proBNP = N-terminal pro B-type natriuretic peptide; CL = Confidence Limits.
Note: N for measured value is the number of subjects with a non-missing value for the lab test at the specified time point and at baseline.
[GEFBNPOL02B.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/GEFBNPOL02B.SAS] 07MAR2023, 11:08

図 2.7.3-8 NT-proBNP のベースラインからの変化率
（二重盲検投与期＋オープンラベル投与期，FAS）

(3) 肺血行動態パラメータ（PVR 以外）

EDBT 時の PVR 以外の肺血行動態パラメータ（mRAP，mPAP，Cardiac Index，SVI，SvO_2，及び CO）のベースラインからの変化を表 2.7.3-13 に示す。各単剤投与群と比較して，本配合剤群では各肺血行動態パラメータがより改善する傾向が認められた。

本配合剤群とマシテンタン単剤投与群の EDBT 時の mPAP のベースラインからの変化量の平均値（SD）は，それぞれ 9.99 (8.64) mmHg の低下及び 3.56 (8.22) mmHg の低下であり，本配合剤群とタダラフィル単剤投与群の EDBT 時の mPAP のベースラインからの変化量の平均値（SD）は，それぞれ 9.20 (8.16) mmHg の低下及び 2.96 (6.14) mmHg の増加であった。

EDBT 時に右房圧が 8 mmHg 以下となった被験者の割合は，本配合剤群と各単剤投与群で明らかな差は認められなかった。

表 2.7.3-13 EDBT 時の肺血行動態パラメータのベースラインからの変化（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata		
	Macitentan (N=35)	**M/T FDC (N=70)**		**Tadalafil (N=44)**	**M/T FDC (N=86)**	
Change from Baseline to EDBT in hemodynamic variables	Mean (SD)			Mean (SD)		
mRAP (mmHg)	-0.3 (5.70)	-1.4 (5.03)[$11]		0.4 (3.26)	-0.5 (5.22)[$12]	
mPAP (mmHg)	-3.56 (8.22)	-9.99 (8.64)[$13]		-2.96 (6.14)	-9.20 (8.16)[$14]	
Cardiac Index (L/min/m^2)	0.16 (0.62)	0.52 (0.58)[$15]		0.15 (0.56)	0.60 (0.54)[$16]	
CO (Indirect Fick – L/min)	0.36 (1.04)	0.78 (1.13)[$17]		0.26 (1.14)	0.94 (1.11)[$18]	
CO (Mean Thermodilution – L/min)	0.20 (1.16)	1.03 (0.87)[$19]		0.33 (0.85)	1.09 (0.76)[$20]	
SvO_2 (%)	1.82 (7.13)	4.82 (7.29)[$21]		2.39 (5.62)	4.00 (6.99)[$22]	
SVI (mL/m^2/beat)	2.399 (9.78)	10.39 (9.49)[$23]		3.90 (7.96)	10.13 (7.98)[$24]	
Proportion of participants achieving a right atrial pressure of ≤8 mmHg at EDBT	n (%)		M/T FDC vs Macitentan Risk ratio (95% CL)	n (%)		M/T FDC vs Tadalafil Risk ratio (95% CL)
	22 (62.9)	34 (48.6)	0.8 (0.5, 1.2)	24 (54.5)	40 (46.5)	0.9 (0.6, 1.3)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; Classification; EDBT = End of Double-blind Treatment; CL = Confidence limit.
N included in analysis for Macitentan and M/T FDC: [$11] 33 and 54; [$13] 34 and 58; [$15] 34 and 57; [$17] 16 and 34; [$19] 18 and 23; [$21] 32 and 54; [$23] 34 and 57.
N included in analysis for Tadalafil and M/T FDC[$12] 40 and 71; [$14] 41 and 75; [$16] 40 and 74; [$18] 24 and 38; [$20] 17 and 36; [$22] 39 and 71; [$24] 40 and 74.
Source: 5.3.5.1.1-1 CSR Table19, TEFHEMD01A, TEFHEMD01C.

2.7.3.2.3　部分集団における結果の比較

2.7.3.2.3.1　日本人集団

本項では，二重盲検投与期の日本人集団の結果を示す。

(1) 被験者の内訳

日本人被験者の内訳を表 2.7.3-14 に示す。計 8 例の日本人患者を組み入れ，本配合剤群に 6 例，マシテンタン単剤投与群に 1 例，タダラフィル単剤投与群に 1 例が割り付けられた。前治療は，本配合剤群では未治療が 5 例，ERA 既治療が 1 例であった。マシテンタン単剤投与群の 1 例は ERA 既治療，タダラフィル単剤投与群の 1 例は PDE5i 既治療であった。ERA 既治療の 2 例が使用していた前治療薬はいずれもマシテンタンであり，PDE5i 既治療の 1 例が使用していた前治療薬はタダラフィルであった（5.3.5.1.1-1 Japan analysis LSIDEM01J）。

二重盲検投与期間中に本配合剤群の 2 例が重篤な有害事象により治験薬の投与を中止し，残りの 6 例（本配合剤群 4 例，マシテンタン単剤投与群 1 例，タダラフィル単剤投与群 1 例）は 16 週後の二重盲検投与期間の最終評価を完了した。

表 2.7.3-14 日本人被験者の内訳

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
Analysis set: Full	1	6	7	1	5	6	6
Completed study treatment[a]	1 (100.0%)	4 (66.7%)	5 (71.4%)	1 (100.0%)	3 (60.0%)	4 (66.7%)	4 (66.7%)
Prematurely discontinued study treatment[b]	0	2 (33.3%)	2 (28.6%)	0	2 (40.0%)	2 (33.3%)	2 (33.3%)
Reason for discontinuation							
Adverse event	0	2 (33.3%)	2 (28.6%)	0	2 (40.0%)	2 (33.3%)	2 (33.3%)
Subjects entering OL treatment period and treated in OL	-	-	-	-	-	-	-
Subjects entering OL treatment period and not treated in OL	0	1 (16.7%)	1 (14.3%)	0	1 (20.0%)	1 (16.7%)	1 (16.7%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label.
[a] Completed study treatment in the DB period: the subject took DB study drug up to Visit 8/Week 16.
[b] Prematurely discontinued study treatment in the DB period: the subject discontinued DB treatment prior to Visit 8/Week 16.
All subjects who complete the DB period are assigned to receive M/T FDC in the OL period
[TSIDS04J.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TSIDS04J.SAS] 10JAN2023, 09:03

(2) 人口統計学的特性

本配合剤群の年齢の中央値（範囲）は，75.5（5[redacted]～7[redacted]）歳，マシテンタン単剤投与群は[redacted]歳，タダラフィル単剤投与群は[redacted]歳であった。WHO FC は，本配合剤群では class II が 4 例（66.7%），class III が 2 例（33.3%）であり，マシテンタン単剤投与群及びタダラフィル単剤投与群の各 1 例ではいずれも class III であった。ベースライン時の PVR 値は，本配合剤群の 6 例の平均値は 458.6 dyn.sec/cm^5 であり，マシテンタン単剤投与群の 1 例の値は 469.1 dyn.sec/cm^5，タ

ダラフィル単剤投与群 1 例の値は 987.6 dyn.sec/cm^5 であった（5.3.5.1.1-1 Japan analysis TSIDEM01J）。

(3) PVR

日本人集団の EDBT 時の PVR のベースラインからの変化を表 2.7.3-15 に示す。また，前治療別の EDBT 時の PVR のベースラインからの変化を表 2.7.3-付録-11 に示す。

本配合剤群（未治療及び ERA 既治療層）のベースライン時に対する EDBT 時の PVR 変化比の幾何平均値（95%CI）は 0.51（0.35～0.73）であり，マシテンタン単剤投与群 1 例のベースライン時に対する EDBT 時の PVR 変化比は 1.06 であった。

本配合剤群（未治療及び PDE5i 既治療層）のベースライン時に対する EDBT 時の PVR 変化比の幾何平均値（95%CI）は 0.50（0.31～0.81）であり，タダラフィル単剤投与群 1 例のベースライン時に対する EDBT 時の PVR 変化比は 0.85 であった。

以上のとおり，日本人集団の EDBT 時の PVR 変化比は，各単剤投与群と比較して本配合剤群でより改善する傾向が認められた。

表 2.7.3-15 EDBT 時の PVR のベースラインからの変化（二重盲検投与期，日本人）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	1	6	1	5
Baseline, dyn.sec/cm^5				
N	1	6	1	5
Mean (SD)	461.4 (-)	458.6 (219.26)	949.7 (-)	497.8 (220.37)
Median	461.4	373.7	949.7	376.5
Range	(461; 461)	(263; 880)	(950; 950)	(366; 880)
EDBT, dyn.sec/cm^5				
N	1	5	1	4
Mean (SD)	489.5 (-)	224.5 (118.78)	810.0 (-)	244.4 (127.22)
Median	489.5	190.8	810.0	209.7
Range	(489; 489)	(132; 426)	(810; 810)	(132; 426)
Ratio of EDBT to baseline				
N	1	6	1	5
Geometric mean	1.06	0.51	0.85	0.50
Geometric CV	NE	0.362	NE	0.405
95% CL of geometric mean	(NE, NE)	(0.35, 0.73)	(NE, NE)	(0.31, 0.81)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; SD = Standard deviation.
Note: PVR values are derived by the sponsor using the assessments provided by the central reader (WCC).
Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.
早期中止例 2 例のうち 1 例は治験薬投与中止日（Day 47）に右心カテーテル検査を実施しており，得られた検査値が解析に用いられた。他の 1 例は，ベースライン時の測定以降，右心カテーテル検査を実施しなかったため，解析計画書で事前規定した方法に従い代表値を代入し解析した。

Modified from [TEFPVR14AJ.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TEFPVR14AJ.SAS] 10JAN2023, 09:03

1) 一貫性評価

全体集団及び日本人集団の PVR 変化比について，事前規定した下記の基準に照らして一貫性を評価した。その結果，両基準を満たし，全体集団と日本人集団の結果の一貫性が示された。

- FDC vs Macitentan: $\log(GM_{FDC}) - \log(GM_{macitentan\ 10\ mg}) < 0.0$
- FDC vs Tadalafil: $\log(GM_{FDC}) - \log(GM_{tadalafil\ 40\ mg}) < 0.0$

FDC = 本配合剤; GM = 幾何平均値

2) ベースライン時の PVR 値の差が有効性評価へ与えた影響（事後解析）

A DUE 試験の全体集団（FAS）及び日本人集団のベースライン時の PVR の記述統計量を表 2.7.3-16 に示す。ベースライン時の PVR（平均値±SD）は，全体集団で 855.0 ± 573.58 dyn.sec/cm^5 であったのに対し，日本人集団では 526.1 ± 262.33 dyn.sec/cm^5 と低かった。そこで，ベースライン時の PVR が全体集団と比較して日本人集団で低値であったことが有効性評価に与えた影響を検証する事後解析を実施した。

表 2.7.3-16 ベースライン時の PVR の記述統計量

（全体集団及び日本人集団）

	全体集団 N=186	日本人集団 N=8
PVR (dyn.sec/cm^5)		
Mean±SD	855.0 ± 573.58	526.1 ± 262.33
Min, Max	194, 3888	266, 988
Median	727.7	438.5
Q1, Q3	441.0, 1109.1	350.4, 688.6

Key: PVR = Pulmonary vascular resistance.
Source: TEFPVR02AA, TEFPVR02AAJ
CRF で記録されたベースライン値を示す。

EDBT 時の PVR のベースラインからの変化比について，ベースライン時の PVR 値で層別化した。層別のカットオフ値は，A DUE 試験全体集団の中央値（中央判定）である 710.1 dyn.sec/cm^5 を採用した。

ベースライン時の PVR 値で層別化した PVR 変化比を表 2.7.3-17 に示す。各単剤投与群及び本配合剤群の PVR の変化比は，ベースライン時の PVR 値が 710.1 dyn.sec/cm^5 未満の被験者に比べ 710.1 dyn.sec/cm^5 以上の被験者で同等又はより低下（改善）していたものの，大きな違いは認められなかった。また，層別化したいずれの集団でも各単剤投与群に比べ本配合剤群の EDBT 時の PVR 変化比は改善していた。

以上より，ベースライン時の PVR 値が本配合剤又は各単剤を投与した際の PVR 変化に与える影響は小さいと考えられた。

表 2.7.3-17 EDBT 時の PVR のベースラインからの変化比

（全体集団，ベースライン時の PVR 値による層別解析）

	Baseline PVR <710.1 (dyn.sec/cm^5)				Baseline PVR ≥710.1 (dyn.sec/cm^5)			
	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Ratio of EDBT to baseline								
N	15	38	24	43	20	32	20	43
GM	0.84	0.61	0.78	0.61	0.72	0.49	0.78	0.52
Geometric CV	0.361	0.407	0.289	0.385	0.322	0.369	0.216	0.328
95% CL of GM	0.70, 1.02	0.53, 0.69	0.69, 0.88	0.54, 0.68	0.62, 0.84	0.43, 0.55	0.70, 0.86	0.47, 0.57

Key: PVR = Pulmonary vascular resistance; ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; GM = Geometric mean.
Notes: PVR values and baseline PVR values are derived by the sponsor using the assessments provided by the central reader (WCC).
The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.
Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display
Source: TEFPVR01ABJ

(4) 6MWD

日本人集団の EDBT 時の 6MWD のベースラインからの変化を表 2.7.3-18 に示す。

本配合剤群（未治療及び ERA 既治療層）の EDBT 時の 6MWD のベースラインからの変化量の平均値（SD）は 48.7（99.59） m の増加であり，マシテンタン単剤投与群 1 例の EDBT 時の 6MWD のベースラインからの変化量は 103.0 m の増加であった。

本配合剤群（未治療及び PDE5i 既治療層）の EDBT 時の 6MWD のベースラインからの変化量の平均値（SD）は 27.6（94.10） m の増加であり，タダラフィル単剤投与群 1 例の EDBT 時の 6MWD のベースラインからの変化量は 78.0 m の減少であった。

表 2.7.3-18 EDBT 時の 6MWD のベースラインからの変化（二重盲検投与期，日本人）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	1	6	1	5
Baseline, m				
N	1	6	1	5
Mean (SD)	338.0 (-)	318.8 (89.76)	367.0 (-)	349.0 (56.97)
Median	338.0	344.5	367.0	360.0
Range	(338; 338)	(168; 400)	(367; 367)	(261; 400)
EDBT, m				
N	1	6	1	5
Mean (SD)	441.0 (-)	352.7 (120.16)	289.0 (-)	358.0 (133.55)
Median	441.0	349.0	289.0	372.0
Range	(441; 441)	(218; 500)	(289; 289)	(218; 500)
Change from baseline to EDBT, m				
N	1	6	1	5
Mean (SD)	103.0 (-)	48.7 (99.59)	-78.0 (-)	27.6 (94.10)
Median	103.0	60.5	-78.0	50.1
Range	(103; 103)	(-135; 158)	(-78; -78)	(-135; 105)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; EDBT = End of Double-blind Treatment; SD = Standard deviation.
Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.
One subject in M/T FDC was included in the analysis with following imputation: 6MWD assessments obtained more than 7 days after study treatment discontinuation/interruption will be disregarded, and the 75th percentile of the 6MWD change from baseline from all participants in the same stratum (without any ICE for which a composite strategy is also applied) will be used instead.
Modified from [TEF6MWD11AJ.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TEF6MWD11AJ.SAS] 10JAN2023, 09:03

(5) PAH-SYMPACT®の心肺症状及び心血管症状ドメインスコア

日本人集団のベースライン時に対する EDBT 時の心肺症状ドメインスコア変化量の平均値は，マシテンタン単剤投与群及び本配合剤群（未治療及び ERA 既治療層）の比較では，それぞれ 0.14 及び 0.20 の低下であった。タダラフィル単剤投与群及び本配合剤群（未治療及び ERA 既治療層）の比較では，それぞれ 0.43 の増加及び 0.18 の低下であった（5.3.5.1.1-1 Japan analysis TEFPAHSS11AJ）。

日本人集団のベースライン時に対する EDBT 時の心血管症状ドメインスコア変化量の平均値は，マシテンタン単剤投与群及び本配合剤群（未治療及び ERA 既治療層）の比較では，それぞれ 0.09 及び 0.15 の低下であった。タダラフィル単剤投与群及び本配合剤群（未治療及び ERA 既治療層）の比較では，それぞれ 0.09 の増加及び 0.18 の低下であった（5.3.5.1.1-1 Japan analysis TEFPAHSS13AJ）。

以上のとおり，PAH-SYMPACT®の心肺症状及び心血管症状ドメインスコアは，各単剤投与群に比べて本配合剤群でより低下する傾向が認められた。

(6) WHO FC

本配合剤群で 1 例が EDBT 時までに WHO FC の悪化を認めた。当該被験者のベースライン時の WHO FC は class III であったが，投与開始 18 日目（規定外 visit）に class II と判定され，投与開始後 22 日目に重篤な有害事象（貧血）の発現により治験薬の投与を中止した。マシテンタン単剤投与群及びタダラフィル単剤投与群の各 1 例は，EDBT 時までに WHO FC の悪化を認めなかった（5.3.5.1.1-1 Japan analysis TEFWHOFC07AJ）。

2.7.3.2.3.2 その他の部分集団

主要有効性解析（PVR 変化比）及び副次有効性解析（6WMD）について，以下の部分集団別に解析した結果，日本人集団を含むかどうかに関わらず，いずれの部分集団でも結果はおおむね一貫していた（2.7.3.2.2.1(2) 項及び 2.7.3.2.2.2 (1) 2)項参照）。

- 米国内外
- 地域（北アメリカ，ラテンアメリカ，アジア，東ヨーロッパ，南及び西ヨーロッパ，オセアニア，アフリカ）
- ベースライン時の WHO FC（class II，class III）
- 年齢（65 歳未満，65 歳以上）
- 性別（男性，女性）
- 人種（白人，黒人，アジア人，その他）

2.7.3.3 全試験を通しての結果の比較と解析

PAH に対する本配合剤の有効性を検討した試験は A DUE 試験のみであるため，試験間の結果を比較する本項の内容は該当しない。

2.7.3.4 その他の臨床試験情報

A DUE 試験の前治療（未治療，ERA 既治療，PDE5i 既治療）別の各群の日本人登録状況を表 2.7.3-19 に示す。A DUE 試験の被験者を前治療及び投与群別に分類すると 7 つのカテゴリーに分けられるが，A DUE 試験内での日本人患者の組入れは 8 例であり，以下の 3 つのカテゴリーの日本人データが得られなかった。

① 前治療：未治療，投与群：マシテンタン単剤投与群
② 前治療：未治療，投与群：タダラフィル単剤投与群
⑦ 前治療：PDE5i 既治療，投与群：本配合剤群

表 2.7.3-19 前治療別の各群の日本人組入れ数（A DUE 試験）

前治療	未治療			ERA 既治療		PDE5i 既治療	
投与群	マシテンタン単剤投与群	タダラフィル単剤投与群	本配合剤群	マシテンタン単剤投与群	本配合剤群	タダラフィル単剤投与群	本配合剤群
カテゴリー番号	①	②	③	⑥	⑤	⑥	⑦
日本人組入れ数	-	-	N=5	N=1	N=1	N=1	-

N = 被験者数

そこで，以下に示す 2 つの外部臨床試験［AC-055-307 試験（以下，307 試験）及び PHIRST-1 試験／H6D-MC-LVGY（以下，PHIRST-1 試験）（Galiè 2009; PMDA 2009）］から A DUE 試験で不足している日本人データを補足した。

2.7.3.4.1.1 使用する外部臨床試験の適切性

使用する外部臨床試験の概要を表 2.7.3-20 に示す。また，外部臨床試験データ使用の適切性を，(1) 肺血行動態に関する評価項目，(2) 試験前から試験中に使用した PAH 治療薬，(3) 試験実施時期の 3 つの観点から検討した。その結果を以下に示す。

(1) 肺血行動態に関する評価項目

1) 307 試験

307 試験の肺血行動態の測定タイミングは投与開始 24 週後（以下，24 週後）であり，A DUE 試験の 16 週後と異なっていた。一方，海外ガイドラインでは右心カテーテル実施を考慮すべきタイミングとして治療薬変更後 3～6 カ月が提案されている（Humbert 2022）。したがって，いずれの測定タイミングも薬効評価時点として妥当と考えた。

2) PHIRST-1 試験

PHIRST-1 試験の肺血行動態の測定タイミングはベースライン時及び 16 週後であり，A DUE 試験と同様であった。PHIRST-1 の評価では PVR ではなく「PVR×体表面積」で算出する PVRi を用いていた。一方，PVRi 変化比は，同一被験者での「EDBT 時の PVRi÷ベースライン時の PVRi」で算出されるため，体表面積の影響を受けない。したがって，PVR 変化比と PVRi 変化比は同等のものとして比較可能と考えた。

(2) 試験前及び試験中に使用した PAH 治療薬

1) 307 試験

307 試験では，ERA 及び非経口プロスタノイド製剤は併用不可とし，それ以外の PAH 治療薬はベースライン時の右心カテーテル検査 90 日以上前から投与している場合は併用可能としていた。そこで，307 試験のベースライン時に未治療又はタダラフィル 40 mg のみを服用していた被験者を対象とすることで，それぞれ A DUE 試験の被験者として比較可能と考えた。

2) PHIRST-1 試験

PHIRST-1 試験では，スクリーニング 12 週以上前から一定用量のボセンタン（ERA）及び／又は日本のみベラプロストを投与している場合，両薬剤の併用が可能であった。タダラフィル 40 mg を服用した日本人 PAH 患者（2 例）の PAH 治療薬併用状況は不明であった。一方で，上記規定より，ベースライン時のボセンタン及び／又はベラプロストによる効果は安定していたと考えられた。以上より，仮にボセンタン及び／又はベラプロストを併用していた場合でも，PHIRST-1 試験の結果から日本人 PAH 患者にタダラフィルを投与した際の肺血行動態の変化を評価可能と考えた。

(3) 試験実施時期

各試験（A DUE 試験，307 試験，PHIRST-1 試験）実施時の右心カテーテルを用いた PAH の診断基準は同様であった。また，各試験で許容された前治療薬及び併用薬に大きな違いはなかったことから，各試験実施時に承認されていた PAH 治療薬の違いは，薬効評価に殆ど影響を及ぼさなかったと考えられる（表 2.7.3-20）。以上より，試験実施時期の違いによる薬効評価への影響は最小限と考えた。

表 2.7.3-20 試験デザイン及び日本人患者背景の比較（A DUE 試験，307 試験，PHIRST-1 試験）

	A DUE 試験	AC-055-307 試験	PHIRST-1 試験
試験実施期間	2019 年～実施中	2012 年 10 月～2015 年 12 月	2005 年 8 月～2007 年 8 月
国内試験依頼者	ヤンセンファーマ株式会社	アクテリオン ファーマシューティカルズ ジャパン株式会社（現ヤンセンファーマ株式会社）/日本新薬株式会社	日本イーライリリー株式会社
デザイン	国際共同，二重盲検，ランダム化，実薬対照，第 III 相試験	国内，非盲検，単群，第 II/III 相試験	国際共同，二重盲検，ランダム化，プラセボ対照，第 III 相試験
対象患者	PAH 患者	PAH 患者	PAH 患者
主要評価項目	EDBT 時の PVR のベースラインからの変化比	ベースラインから治験薬投与開始 24 週後の PVR の変化率	ベースラインから治験薬投与開始 16 週後の 6MWD の変化量
日本人被験者数	8 例（FAS：186 例）	30 例	2 例 [1)]（全体：405 例）
組入れ基準： PVR 下限値（dyn.sec/cm^5）	240	320	240
WHO FC	II，III	I～IV	I～IV
許容する PAH 前治療薬	ベースライン 3 カ月前から投与している ・ERA，又は ・PDE5i	ベースライン時の右心カテーテル検査の 90 日以上前から一定用量で投与している（以下，併用可） ・タダラフィル，シルデナフィル ・ベラプロスト	スクリーニング 12 週前から一定用量で投与している（以下，併用可） ・ボセンタン ・ベラプロスト（日本のみ）
併用可能 PAH 治療薬（主要評価期間中）	・治験薬	・治験薬 ・ベースライン時右心カテーテル検査の 90 日以上前から投与している許容された PAH 治療薬	・治験薬 ・スクリーニング 12 週前から投与している許容された PAH 治療薬
治験薬の用法用量	割り付けられた治験薬を 1 日 1 回経口投与（二重盲検投与期） ・マシテンタン 10 mg ・タダラフィル 40 mg ・本配合剤	マシテンタン 10 mg を 1 日 1 回経口投与	プラセボ又はタダラフィル（2.5 mg，10 mg，20 mg，又は 40 mg）を 1 日 1 回経口投与
PVR 測定タイミング	ベースライン時，16 週後	ベースライン時，24 週後	ベースライン時，16 週後
ベースライン時 PVR（平均値 ± SD）（dyn.sec/cm^5）：日本人	526.1 ± 262.33	667.4 ± 293.21 [2)]	-
ベースライン時 PVRi（平均値±SD）（dyn.sec.m^2/cm^5）：日本人	746.0 ± 303.53	1024.1 ± 461.41 [2)]	414.2, 1105.9 [3)]

1) タダラフィル 40 mg で PVRi が測定されている患者
2) 主解析として定義していた Per-Protocol Set（n=28）の平均値
3) 対象が 2 例であるため，個々の被験者の値を記載
Source: 5.3.5.1.1-1 Japan analysis TEFPVR02AAJ, TEFPVR03AAJ, AC-055-307 試験総括報告書（24 週時）（2014 年 5 月 26 日申請 オプスミット錠 10mg CTD 5.3.5.2.1），アドシルカ錠 20 mg 審査報告書（PMDA 2009）

2.7.3.4.1.2 ADUE 試験と外部臨床試験の比較

日本人併合集団（A DUE 試験，307 試験，PHIRST-1 試験）の被験者数を，前治療及び試験期間中の投与薬別に表 2.7.3-21 に示す。307 試験はマシテンタン 10 mg の有効性及び安全性を評価した試験であるが，タダラフィル 40 mg を前治療としてベースラインから服用していた患者は試験中でタダラフィル 40 mg とマシテンタン 10 mg を併用したため，A DUE 試験の本配合剤群と同等の集団として評価した。PHIRST-1 試験はタダラフィル 40 mg 投与群での PVRi 値が測定されている患者の PAH 前治療が不明であるため，未治療患者として取り扱った。

表 2.7.3-21 日本人の有効性検討に用いた患者数

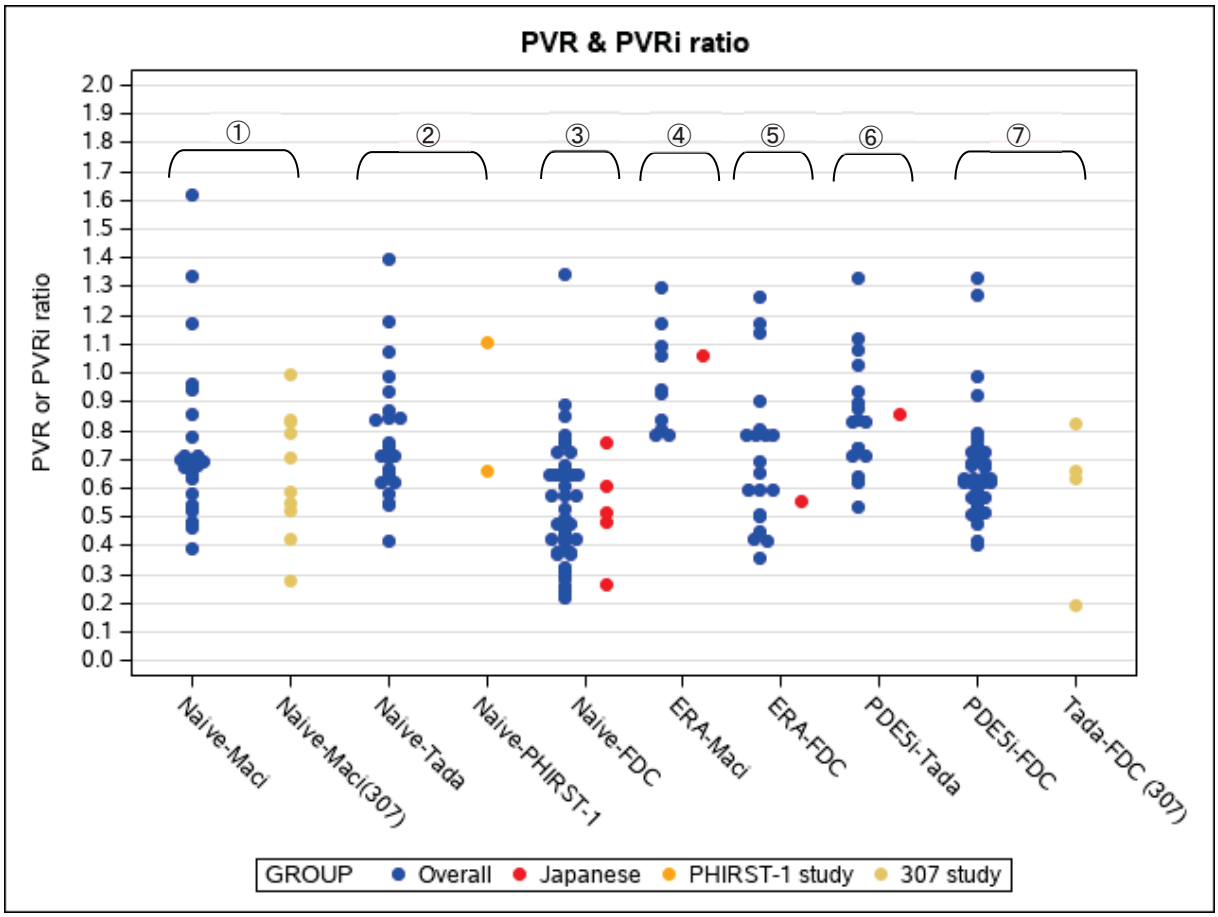
（A DUE 試験，307 試験，PHIRST-1 試験）

前治療	未治療			ERA 既治療		PDE5i 既治療	
投与群	マシテンタン単剤投与群	タダラフィル単剤投与群	本配合剤群*	マシテンタン単剤投与群	本配合剤群*	タダラフィル単剤投与群	本配合剤群*
カテゴリー番号	①	②	③	⑥	⑤	⑥	⑦
A DUE 試験	-	-	N=5	N=1	N=1	N=1	-
307 試験	N=10	-	-	-	-	-	N=4
PHIRST-1 試験	-	N=2**	-	-	-	-	-

N = 被験者数
*本配合剤群：A DUE 試験では本配合剤，307 試験ではマシテンタン 10 mg とタダラフィル 40 mg の各単剤の併用
** PAH に対する前治療の有無が不明であるため，未治療患者として割り当てた

次に，A DUE 試験全体集団と日本人併合集団での，ベースライン時に対する 16 週後又は 24 週後の個別 PVR 及び PVRi 変化比（前治療及び治験中の治療別）を図 2.7.3-9 に示す。前治療，試験中の治療別のいずれの層でも，日本人併合集団の PVR 及び PVRi 変化比の個別値は，おおむね A DUE 試験全体集団の PVR 変化比の範囲内にあった。

以上より，A DUE 試験全体集団と，A DUE 試験で不足している日本人データを補強した日本人併合集団で得られた PVR 又は PVRi 変化比の成績は，同様の傾向を示していることが確認された。



●Overall：A DUE 試験（全体），●Japanese：A DUE 試験（日本人），●PHIRST-1 試験（日本人，タダラフィル 40 mg）
●307 試験（日本人）
縦軸：PHIRST-1 試験は PVRi 変化比，A DUE 試験及び 307 試験は PVR 変化比で表示
横軸：前治療-治験中投与薬剤を表示
① Naïve-Maci = 未治療→マシテンタン 10 mg; Naïve-Maci (307) = 未治療→マシテンタン 10 mg
② Naïve-Tada = 未治療→タダラフィル 40 mg; Naïve→PHIRST-1 = 未治療→タダラフィル 40 mg
③ Naïve→FDC = 未治療→本配合剤
④ ERA-Maci = ERA→マシテンタン 10 mg
⑤ ERA-FDC = ERA→本配合剤
⑥ PDE5i-Tada = PDE5i→タダラフィル 40 mg
⑦ PDE5i-FDC = PDE5i→本配合剤;
Tada-FDC (307) = タダラフィル 40 mg→マシテンタン 10 mg 及びタダラフィル 40 mg の各単剤併用
（矢印は，前が前治療，後ろが治験中の投与薬剤を示す）
Source: 5.3.5.1.1-1 Japan analysis GEFPVR03J

図 2.7.3-9 A DUE 試験全体集団と日本人併合集団の個別 PVR／PVRi 変化比
（A DUE 試験，307 試験，PHIRST-1 試験）

2.7.3.5 推奨用法・用量に関する臨床情報の解析

本配合剤の含有用量の選択根拠

マシテンタン及びタダラフィルの成人 PAH 患者に対する用法用量は，それぞれ，通常 1 日 1 回 10 mg 及び 40 mg であり，日本，米国，及び欧州を含め世界的に同一である。また，マシテンタン及びタダラフィル間の薬物動態学的な薬物相互作用はなく，民族は本配合剤の用法用量の設定に影響を与えうる要因ではないと想定された【2.7.2.3】。以上より，本配合剤の含有用量はマシテンタン 10 mg 及びタダラフィル 40 mg とし，日本人と外国人で同一の用法用量で開発を進めた。

本配合剤と配合成分の単剤との生物学的同等性

外国人健康成人被験者を対象とした生物学的同等性試験（67896062PAH1006 試験）から，本配合剤はマシテンタン 10 mg 及びタダラフィル 40 mg の各単剤の併用投与と生物学的に同等であることが示された【2.7.1.3.1】。

食事の影響

67896062PAH1006 試験から，マシテンタン及びタダラフィルを本配合剤として投与した際の PK に対して，食事は臨床的に問題となる影響を与えないことが確認された【2.7.1.3.2】。

臨床成績

国際共同第 III 相試験（A DUE 試験）では，PAH 患者に対する本配合剤 1 日 1 回経口投与の優れた有効性，良好な安全性が確認された。また，全体集団と日本人集団の有効性・安全性に明確な差は認められなかった（2.7.3.2.3.1，【2.7.4.6.1】）。よって，日本人 PAH 患者に対する本配合剤の用量を 1 日 1 回 1 錠とすることは妥当と考えられた。

以上より，日本人 PAH 患者に対する本配合剤の用法・用量は以下のとおり設定した。

用法用量

通常，成人には 1 日 1 回 1 錠（マシテンタンとして 10 mg 及びタダラフィルとして 40 mg）を経口投与する。

2.7.3.6 効果の持続，耐薬性

マシテンタンとタダラフィルは，いずれも PAH 患者の長期治療に有効であることが示されている（Tahara 2020; Yamazaki 2017）。耐薬性又は反跳現象を示唆するデータはない。

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2.7.3.7 付録

表 2.7.3-付録-1 Summary of Double-blind Treatment; Safety Set (Study AC-077A301)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Total duration of treatment (weeks)[a]					
N	35	70	44	86	107
Mean (SD)	16.87 (1.307)	14.38 (5.201)	15.98 (0.952)	14.92 (4.412)	14.85 (4.547)
Median	16.43	16.21	16.00	16.14	16.14
Range	(15.1; 20.1)	(0.6; 21.1)	(11.0; 18.0)	(0.7; 21.1)	(0.6; 21.1)
Total duration of treatment (weeks)[a]					
< 4	0	9 (12.9%)	0	8 (9.3%)	10 (9.3%)
4 - < 8	0	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
8 - < 12	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
12 - < 16	7 (20.0%)	16 (22.9%)	17 (38.6%)	18 (20.9%)	25 (23.4%)
>= 16	28 (80.0%)	43 (61.4%)	26 (59.1%)	58 (67.4%)	69 (64.5%)
Total duration of treatment excluding interruptions (weeks)[b]					
N	35	70	44	86	107
Mean (SD)	16.79 (1.289)	14.26 (5.200)	15.86 (1.317)	14.85 (4.408)	14.76 (4.554)
Median	16.43	16.14	16.00	16.14	16.14
Range	(14.9; 20.1)	(0.6; 20.9)	(8.1; 18.0)	(0.7; 20.9)	(0.6; 20.9)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; EOT-DB = End of treatment in double-blind treatment period.

[a] Total duration of treatment is defined as (date of EOT-DB – date of first dose of study treatment +1)/7.

[b] Total duration of treatment excluding interruptions is defined as (date of EOT-DB – date of first dose of study treatment – days without study treatment administration + 1)/7. Duration of treatment interruptions is defined as the number of days without study treatment administration in the DB treatment period. Summary includes only subjects with at least one interruption.

[c] Duration of treatment interruptions is defined as the number of days without study treatment administration in the DB treatment period. Summary includes only subjects with at least one interruption.

Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Total duration of treatment excluding interruptions (weeks)[b]					
< 4	0	9 (12.9%)	0	8 (9.3%)	10 (9.3%)
4 - < 8	0	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
8 - < 12	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
12 - < 16	7 (20.0%)	18 (25.7%)	19 (43.2%)	20 (23.3%)	27 (25.2%)
>= 16	28 (80.0%)	41 (58.6%)	24 (54.5%)	56 (65.1%)	67 (62.6%)
Duration of treatment interruptions (days)[c]					
N	3	11	4	11	13
Mean (SD)	6.33 (3.215)	5.64 (4.433)	9.25 (8.261)	4.00 (3.435)	5.15 (4.259)
Median	5.00	5.00	8.00	4.00	4.00
Range	(4.0; 10.0)	(1.0; 13.0)	(1.0; 20.0)	(1.0; 12.0)	(1.0; 13.0)
Cumulative duration of treatment (weeks)[a]					
>=4	35 (100.0%)	61 (87.1%)	44 (100.0%)	78 (90.7%)	97 (90.7%)
>=8	35 (100.0%)	59 (84.3%)	44 (100.0%)	77 (89.5%)	95 (88.8%)
>=12	35 (100.0%)	59 (84.3%)	43 (97.7%)	76 (88.4%)	94 (87.9%)
>=16	28 (80.0%)	43 (61.4%)	26 (59.1%)	58 (67.4%)	69 (64.5%)

表 2.7.3-付録-2　主解析の中間事象とストラテジー（A DUE 試験）

中間事象		ストラテジー[a]
1	EDBT 来院前の死亡	複合ストラテジー：未観察の EDBT 時の PVR 値の変化比は，次の i) と ii) 間の最大値で使用する。i) 同一層[b]（複合ストラテジーが適用される他の ICE も除く）の全ての被験者における変化比の最大値，ii) 1
2	EDBT 来院前の疾患進行及び悪化	治療方針ストラテジー：EDBT 来院前に CEC によって確認された疾患進行及び悪化に関わらず，EDBT 時の PVR 値の変化比があれば使用する。
3	EDBT 来院前の PAH 関連の併用禁止薬の使用：死亡を伴わず，疾患進行又は悪化を伴う	複合ストラテジー：EDBT 時の PVR 値の変化比は使用せず，同一層（複合ストラテジーを適用する他の ICE も除く）の全ての被験者について，ベースライン時に対する最終時の PVR 値の変化比の 75%点を使用する。
4	EDBT 来院前の PAH 関連の併用禁止薬の使用：死亡，疾患進行又は悪化を伴わない	複合ストラテジー：EDBT 時の PVR 値の変化比は使用せず，同一層（複合ストラテジーを適用する他の ICE も除く）の全ての被験者について，ベースライン時に対する最終時の PVR 値の変化比の 50%点を使用する。
5	EDBT 来院直前の 2 日を超える治験薬の投与中断又は中止：死亡を伴わず，疾患進行又は悪化を伴う	複合ストラテジー：EDBT 時の PVR 値の変化比は使用せず，同一層（複合ストラテジーが適用される他の ICE も除く）の全ての被験者について，ベースライン時に対する最終時の PVR 値の変化比の 75%点を使用する。
6	EDBT 来院直前の 2 日を超える治験薬の投与中断又は中止：死亡，疾患進行又は悪化を伴わない	複合ストラテジー：EDBT 時の PVR 値の変化比は使用せず，同一の層（複合ストラテジーが適用される他の ICE も除く）の全ての被験者について，ベースライン時に対する最終時の PVR 値の変化比の 50%点を使用する。
7	EDBT 来院前の任意の時点での治験薬の用量調節（1 週目及び 2 週目に計画されていた増量と，ICE1, 3, 4, 5, 6 は除く）	治療方針ストラテジー：EDBT 来院前の治験薬の用量調節の時点及び量に関わらず EDBT 時の PVR 値の変化比があれば使用する。

[a] ストラテジー：全ての複合ストラテジーについて，同一ステージで観察された治療中の値から決定する。
[b] 層：未治療，ERA 既治療，PDE5i 既治療
なお，本表に記載したルールを適用した後も EDBT 時の PVR 値が欠測している場合，以下のようにデータを補完する。
EDBT 来院前に CEC による疾患進行及び悪化が認められた場合，同一層及び同じステージの全ての被験者におけるベースライン時に対する最終時の PVR 値の変化比の 75%点を使用する。
被験者が死亡せず，EDBT 来院前の CEC による疾患進行及び悪化が認められなかった場合，同一層及び投与群の同じステージの全ての被験者におけるベースライン時に対する最終時の PVR 値の変化比の 50%点を使用する。

表 2.7.3-付録-3 Summary of 6MWD Values and Change From Baseline Over Time in the Combined Double-blind and Open-label Period; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Measured Value						Change From Baseline						
	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SD	Med	Min	Max
Analysis set: Full Analysis Set													
DB-Macitentan	35							35					
DB-Tadalafil	44							44					
DB-M/T FDC	107							107					
DB-Macitentan													
Baseline	35	347.2	88.82	368.0	102	500							
Week 8	31	370.3	90.94	384.0	103	485	347.1	31	23.2	54.65	13.0	-116	176
Week 16	34	382.5	87.30	369.5	140	540	342.7	34	39.8	71.43	31.5	-100	233
Week 42/OL Month 6	29	400.8	98.35	405.0	164	600	348.4	29	52.4	85.15	36.0	-150	238
Week 68/OL Month 12	17	434.3	91.92	450.0	242	608	358.2	17	76.1	95.18	60.0	-133	251
Week 94/OL Month 18	14	431.1	68.84	447.5	270	555	361.9	14	69.3	47.95	56.0	18	180
Week 120/OL Month 24	5	438.4	106.37	450.0	280	553	353.0	5	85.4	75.34	64.0	25	214
DB-Tadalafil													
Baseline	44	361.8	70.44	378.5	135	450							
Week 8	42	386.7	78.93	401.5	126	483	359.9	42	26.9	36.43	30.5	-45	93
Week 16	43	379.7	77.90	408.0	133	490	361.4	43	18.3	44.57	18.0	-70	102
Week 42/OL Month 6	31	390.8	86.51	413.0	212	525	363.3	31	27.5	67.31	27.0	-171	181
Week 68/OL Month 12	21	390.2	92.23	419.0	210	570	356.3	21	33.9	75.59	18.0	-105	235
Week 94/OL Month 18	17	359.7	115.09	395.0	150	561	345.6	17	14.1	121.51	37.0	-259	226
Week 120/OL Month 24	8	385.6	90.74	391.5	257	505	354.9	8	30.8	86.75	17.0	-78	170

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; SD = Standard deviation; EOT = End of treatment, DB= Double-blind; OL = Open-label.

Note: Baseline and post-baseline measurements (including measurements after EOT) are included.

Note: N for measured value is the number of subjects with a non-missing value for the 6MWD at the specified time point. N for change from baseline is the number of subjects with non-missing values at both baseline and the postbaseline time point.

	Measured Value						Change From Baseline						
	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SD	Med	Min	Max
DB-M/T FDC													
Baseline	107	352.3	96.07	373.0	2	550							
Week 8	91	397.7	96.36	401.0	133	642	353.5	91	44.2	69.19	39.0	-135	382
Week 16	94	402.1	95.89	410.0	120	565	352.1	94	50.0	77.19	38.5	-134	454
Week 42/OL Month 6	75	411.6	106.70	418.0	180	820	352.1	75	59.5	97.40	45.0	-140	497
Week 68/OL Month 12	51	417.9	98.71	440.0	225	565	346.1	51	71.8	93.12	60.0	-50	478
Week 94/OL Month 18	33	396.1	115.06	405.0	111	572	331.5	33	64.6	134.08	30.0	-136	538
Week 120/OL Month 24	12	387.3	91.95	410.0	216	510	343.0	12	44.3	40.89	45.0	-20	144

[TEF6MWDOL01B.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEF6MWDOL01B.SAS] 02MAR2023, 09:59

表 2.7.3-付録-4 Summary of 6MWD Values and Change From Baseline Over Time in the Combined Double-blind and Open-label Period; Long-term M/T FDC Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Measured Value						Change From Baseline						
	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SD	Med	Min	Max
Analysis set: Long-term M/T FDC Set													
Prior ERA strata	21							21					
Prior PDE-5i strata	37							37					
Treatment-naïve	49							49					
All Strata	107							107					
Prior ERA strata													
Baseline	21	357.6	85.73	387.0	140	463							
Week 8	15	416.0	57.92	426.0	305	517	366.1	15	49.9	62.74	40.0	-25	219
Week 16	16	431.5	63.46	416.5	326	531	368.6	16	62.9	80.55	30.5	-25	273
Week 42/OL Month 6	12	421.9	65.38	395.5	345	588	377.1	12	44.8	74.55	20.5	-20	189
Week 68/OL Month 12	7	426.0	70.27	420.0	310	527	372.6	7	53.4	107.72	31.0	-50	282
Week 94/OL Month 18	5	409.2	73.56	375.0	335	496	367.6	5	41.6	137.37	20.0	-83	273
Week 120/OL Month 24	2	415.0	35.36	415.0	390	440	414.0	2	1.0	29.70	1.0	-20	22
Prior PDE-5i strata													
Baseline	37	348.6	81.41	363.0	120	460							
Week 8	35	384.1	88.07	399.0	221	560	344.4	35	39.7	39.08	39.0	-43	134
Week 16	33	385.1	90.12	398.0	198	537	348.3	33	36.8	39.32	36.0	-75	119
Week 42/OL Month 6	26	397.9	91.29	415.5	180	540	340.6	26	57.3	55.94	63.0	-90	170
Week 68/OL Month 12	18	374.3	101.12	384.5	225	530	326.9	18	47.3	49.62	46.5	-27	152
Week 94/OL Month 18	13	352.4	107.35	346.0	163	499	320.9	13	31.5	77.86	22.0	-136	172
Week 120/OL Month 24	5	352.8	112.90	366.0	216	495	311.8	5	41.0	23.52	45.0	6	70

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; 6MWD = 6-minute walk distance; SD = Standard deviation; EOT = End of treatment, DB= Double-blind; OL = Open-label.
Note: Baseline and on-treatment measurements (from the first study treatment administration up to EOT + 7 days) are included.
Note: N for measured value is the number of subjects with a non-missing value for the 6MWD at the specified time point. N for change from baseline is the number of subjects with non-missing values at both baseline and the postbaseline time point.

	Measured Value						Change From Baseline						
	N	Mean	SD	Med	Min	Max	Base Mean	N	Mean	SD	Med	Min	Max
Treatment-naïve													
Baseline	49	352.9	111.02	373.0	2	550							
Week 8	39	406.9	117.43	401.0	133	642	357.9	39	49.0	92.19	39.0	-135	382
Week 16	41	413.1	107.23	435.0	120	565	350.8	41	62.4	94.07	44.0	-75	454
Week 42/OL Month 6	30	425.6	132.29	442.0	210	820	344.5	30	81.1	129.55	63.5	-70	497
Week 68/OL Month 12	22	446.0	99.58	460.0	229	565	342.0	22	104.0	115.06	78.5	-12	478
Week 94/OL Month 18	15	429.6	125.69	450.0	111	572	328.6	15	101.0	166.96	50.0	-130	538
Week 120/OL Month 24	5	410.6	87.42	420.0	273	510	345.8	5	64.8	48.45	50.0	15	144
All Strata													
Baseline	107	352.3	96.07	373.0	2	550							
Week 8	89	399.5	98.24	401.0	133	642	354.0	89	45.5	70.06	39.0	-135	382
Week 16	90	406.1	95.23	412.0	120	565	353.0	90	53.1	76.04	40.0	-75	454
Week 42/OL Month 6	68	414.4	107.51	416.0	180	820	348.8	68	65.6	97.75	56.5	-90	497
Week 68/OL Month 12	47	415.6	100.39	438.0	225	565	340.8	47	74.8	96.13	62.0	-50	478
Week 94/OL Month 18	33	396.1	115.06	405.0	111	572	331.5	33	64.6	134.08	30.0	-136	538
Week 120/OL Month 24	12	387.3	91.95	410.0	216	510	343.0	12	44.3	40.89	45.0	-20	144

表 2.7.3-付録-5 Summary of WHO FC Over Time in the Combined Double-blind and Open-label Period; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Analysis set: Full Analysis Set	35	44	107
Baseline			
N	35	44	107
Class I	0	0	0
Class II	11 (31.4%)	19 (43.2%)	65 (60.7%)
Class III	24 (68.6%)	25 (56.8%)	42 (39.3%)
Class IV	0	0	0
Week 8			
N	32	43	96
Class I	2 (6.3%)	2 (4.7%)	5 (5.2%)
Class II	17 (53.1%)	25 (58.1%)	61 (63.5%)
Class III	13 (40.6%)	16 (37.2%)	30 (31.3%)
Class IV	0	0	0
Change from baseline to Week 8			
N	32	43	96
Worsening	1 (3.1%)	0	1 (1.0%)
No worsening	31 (96.9%)	43 (100.0%)	95 (99.0%)
Week 16			
N	35	44	97
Class I	3 (8.6%)	3 (6.8%)	10 (10.3%)
Class II	19 (54.3%)	26 (59.1%)	63 (64.9%)
Class III	13 (37.1%)	15 (34.1%)	24 (24.7%)
Class IV	0	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; WHO FC = World Health Organization Functional Classification; EOT = End of treatment, DB= Double-blind; OL = Open-label, DB= Double-blind; OL = Open-label.
Note: Baseline and post-baseline measurements (including measurements after EOT) are included.

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Change from baseline to Week 16			
N	35	44	97
Worsening	1 (2.9%)	2 (4.5%)	2 (2.1%)
No worsening	34 (97.1%)	42 (95.5%)	95 (97.9%)
Week 42/OL Month 6			
N	30	34	80
Class I	6 (20.0%)	4 (11.8%)	12 (15.0%)
Class II	14 (46.7%)	19 (55.9%)	49 (61.3%)
Class III	10 (33.3%)	10 (29.4%)	19 (23.8%)
Class IV	0	1 (2.9%)	0
Change from baseline to Week 42/OL Month 6			
N	30	34	80
Worsening	1 (3.3%)	3 (8.8%)	2 (2.5%)
No worsening	29 (96.7%)	31 (91.2%)	78 (97.5%)
Week 68/OL Month 12			
N	20	23	50
Class I	6 (30.0%)	2 (8.7%)	10 (20.0%)
Class II	13 (65.0%)	16 (69.6%)	30 (60.0%)
Class III	1 (5.0%)	5 (21.7%)	10 (20.0%)
Class IV	0	0	0
Change from baseline to Week 68/OL Month 12			
N	20	23	50
Worsening	0	2 (8.7%)	1 (2.0%)
No worsening	20 (100.0%)	21 (91.3%)	49 (98.0%)

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Week 94/OL Month 18			
N	14	16	34
Class I	5 (35.7%)	0	9 (26.5%)
Class II	9 (64.3%)	12 (75.0%)	16 (47.1%)
Class III	0	4 (25.0%)	9 (26.5%)
Class IV	0	0	0
Change from baseline to Week 94/OL Month 18			
N	14	16	34
Worsening	0	1 (6.3%)	3 (8.8%)
No worsening	14 (100.0%)	15 (93.8%)	31 (91.2%)
Week 120/OL Month 24			
N	5	8	14
Class I	2 (40.0%)	1 (12.5%)	2 (14.3%)
Class II	3 (60.0%)	5 (62.5%)	10 (71.4%)
Class III	0	2 (25.0%)	2 (14.3%)
Class IV	0	0	0
Change from baseline to Week 120/OL Month 24			
N	5	8	14
Worsening	0	1 (12.5%)	1 (7.1%)
No worsening	5 (100.0%)	7 (87.5%)	13 (92.9%)

[TEFWHOFCOL01B.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEFWHOFCOL01B.SAS] 02MAR2023, 09:59

表 2.7.3-付録-6 Summary of WHO FC Over Time in the Combined Double-blind and Open-label Period, by Prior-strata; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan	DB-M/T FDC	DB-Tadalafil	DB-M/T FDC	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Analysis set: Full Analysis Set	11	21	19	37	24	25	49
Baseline							
N	11	21	19	37	24	25	49
Class I	0	0	0	0	0	0	0
Class II	7 (63.6%)	14 (66.7%)	11 (57.9%)	23 (62.2%)	4 (16.7%)	8 (32.0%)	28 (57.1%)
Class III	4 (36.4%)	7 (33.3%)	8 (42.1%)	14 (37.8%)	20 (83.3%)	17 (68.0%)	21 (42.9%)
Class IV	0	0	0	0	0	0	0
Week 8							
N	9	16	19	36	23	24	44
Class I	0	1 (6.3%)	2 (10.5%)	3 (8.3%)	2 (8.7%)	0	1 (2.3%)
Class II	8 (88.9%)	11 (68.8%)	10 (52.6%)	22 (61.1%)	9 (39.1%)	15 (62.5%)	28 (63.6%)
Class III	1 (11.1%)	4 (25.0%)	7 (36.8%)	11 (30.6%)	12 (52.2%)	9 (37.5%)	15 (34.1%)
Class IV	0	0	0	0	0	0	0
Change from baseline to Week 8							
N	9	16	19	36	23	24	44
Worsening	0	0	0	0	1 (4.3%)	0	1 (2.3%)
No worsening	9 (100.0%)	16 (100.0%)	19 (100.0%)	36 (100.0%)	22 (95.7%)	24 (100.0%)	43 (97.7%)
Week 16							
N	11	18	19	35	24	25	44
Class I	1 (9.1%)	1 (5.6%)	1 (5.3%)	5 (14.3%)	2 (8.3%)	2 (8.0%)	4 (9.1%)
Class II	7 (63.6%)	14 (77.8%)	12 (63.2%)	20 (57.1%)	12 (50.0%)	14 (56.0%)	29 (65.9%)
Class III	3 (27.3%)	3 (16.7%)	6 (31.6%)	10 (28.6%)	10 (41.7%)	9 (36.0%)	11 (25.0%)
Class IV	0	0	0	0	0	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; WHO FC = World Health Organization Functional Classification; EOT = End of treatment, DB= Double-blind; OL = Open-label.
Note: Baseline and post-baseline measurements (including measurements after EOT) are included.

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan	DB-M/T FDC	DB-Tadalafil	DB-M/T FDC	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Change from baseline to Week 16							
N	11	18	19	35	24	25	44
Worsening	1 (9.1%)	0	1 (5.3%)	0	0	1 (4.0%)	2 (4.5%)
No worsening	10 (90.9%)	18 (100.0%)	18 (94.7%)	35 (100.0%)	24 (100.0%)	24 (96.0%)	42 (95.5%)
Week 42/OL Month 6							
N	8	15	15	30	22	19	35
Class I	1 (12.5%)	1 (6.7%)	1 (6.7%)	5 (16.7%)	5 (22.7%)	3 (15.8%)	6 (17.1%)
Class II	7 (87.5%)	12 (80.0%)	9 (60.0%)	16 (53.3%)	7 (31.8%)	10 (52.6%)	21 (60.0%)
Class III	0	2 (13.3%)	4 (26.7%)	9 (30.0%)	10 (45.5%)	6 (31.6%)	8 (22.9%)
Class IV	0	0	1 (6.7%)	0	0	0	0
Change from baseline to Week 42/OL Month 6							
N	8	15	15	30	22	19	35
Worsening	0	0	2 (13.3%)	1 (3.3%)	1 (4.5%)	1 (5.3%)	1 (2.9%)
No worsening	8 (100.0%)	15 (100.0%)	13 (86.7%)	29 (96.7%)	21 (95.5%)	18 (94.7%)	34 (97.1%)
Week 68/OL Month 12							
N	6	7	9	20	14	14	23
Class I	2 (33.3%)	1 (14.3%)	1 (11.1%)	5 (25.0%)	4 (28.6%)	1 (7.1%)	4 (17.4%)
Class II	4 (66.7%)	5 (71.4%)	7 (77.8%)	10 (50.0%)	9 (64.3%)	9 (64.3%)	15 (65.2%)
Class III	0	1 (14.3%)	1 (11.1%)	5 (25.0%)	1 (7.1%)	4 (28.6%)	4 (17.4%)
Class IV	0	0	0	0	0	0	0
Change from baseline to Week 68/OL Month 12							
N	6	7	9	20	14	14	23
Worsening	0	0	1 (11.1%)	0	0	1 (7.1%)	1 (4.3%)
No worsening	6 (100.0%)	7 (100.0%)	8 (88.9%)	20 (100.0%)	14 (100.0%)	13 (92.9%)	22 (95.7%)

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan	DB-M/T FDC	DB-Tadalafil	DB-M/T FDC	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Week 94/OL Month 18							
N	5	5	7	14	9	9	15
Class I	2 (40.0%)	1 (20.0%)	0	4 (28.6%)	3 (33.3%)	0	4 (26.7%)
Class II	3 (60.0%)	2 (40.0%)	6 (85.7%)	8 (57.1%)	6 (66.7%)	6 (66.7%)	6 (40.0%)
Class III	0	2 (40.0%)	1 (14.3%)	2 (14.3%)	0	3 (33.3%)	5 (33.3%)
Class IV	0	0	0	0	0	0	0
Change from baseline to Week 94/OL Month 18							
N	5	5	7	14	9	9	15
Worsening	0	0	1 (14.3%)	1 (7.1%)	0	0	2 (13.3%)
No worsening	5 (100.0%)	5 (100.0%)	6 (85.7%)	13 (92.9%)	9 (100.0%)	9 (100.0%)	13 (86.7%)
Week 120/OL Month 24							
N	2	2	4	5	3	4	7
Class I	1 (50.0%)	0	1 (25.0%)	1 (20.0%)	1 (33.3%)	0	1 (14.3%)
Class II	1 (50.0%)	2 (100.0%)	2 (50.0%)	4 (80.0%)	2 (66.7%)	3 (75.0%)	4 (57.1%)
Class III	0	0	1 (25.0%)	0	0	1 (25.0%)	2 (28.6%)
Class IV	0	0	0	0	0	0	0
Change from baseline to Week 120/OL Month 24							
N	2	2	4	5	3	4	7
Worsening	0	0	1 (25.0%)	0	0	0	1 (14.3%)
No worsening	2 (100.0%)	2 (100.0%)	3 (75.0%)	5 (100.0%)	3 (100.0%)	4 (100.0%)	6 (85.7%)

[TEFWHOFCOL01BSTR.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEFWHOFCOL01BSTR.SAS] 02MAR2023, 09:59

表 2.7.3-付録-7 Summary of Morbidity/Mortality Events Confirmed by CEC Occurring Between Baseline and EOT + 7 days; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Analysis set: Full Analysis Set	35	44	107
Number of subjects with morbidity/mortality event	1(2.9%)	1(2.3%)	6(5.6%)
Number of morbidity/mortality events[a]			
Death (all causes)	0	0	2
Non-planned PAH-related hospitalization	1	1	5
Initiation of IV or Subcutaneous prostacyclin or prostacyclin analog for worsening PAH	1	1	0
Clinical worsening[b]	0	0	0

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; EOT = End of Treatment; PAH = Pulmonary arterial hypertension; IV = Intravenous; 6MWD = 6-minute walk distance; WHO FC = World Health Organization Functional Classification; RHF = Right heart failure; CEC = Clinical Event Committee; DB = Double-blind; OL = Open-label.

[a] If a subject experiences several events, all events are counted separately unless the subject experiences several events at the same time, this is counted only as one event, the most serious one.

[b] Clinical worsening defined as decrease in 6MWD of ≥15% from baseline (Day 1 in DB) confirmed on 2 different days within 2 weeks AND worsening of PAH symptoms (increase in WHO FC OR appearance or worsening of RHF signs/symptoms not responding to optimized oral diuretics).

Note: All on-treatment cases (from the first study treatment administration up to EOT + 7 days) confirmed by the CEC are included.

[TEFMMOL02B1.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEFMMOL02B1.SAS] 02MAR2023, 09:59

表 2.7.3-付録-8 Summary of Morbidity/Mortality Event Confirmed by CEC Occurring Between Baseline and Week 120; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Analysis set: Full Analysis Set	35	44	107
Number of subjects with morbidity/mortality event	1(2.9%)	1(2.3%)	8(7.5%)
Number of morbidity/mortality events[a]			
Death (all causes)	0	0	4
Non-planned PAH-related hospitalization	1	1	6
Initiation of IV or Subcutaneous prostacyclin or prostacyclin analog for worsening PAH	1	1	0
Clinical worsening[b]	0	0	0

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; PAH = Pulmonary arterial hypertension; IV = Intravenous; 6MWD = 6-minute walk distance; WHO FC = World Health Organization Functional Classification; RHF = Right heart failure; CEC = Clinical Event Committee; DB = Double-blind; OL = Open-label.

[a] If a subject experiences several events, all events are counted separately unless the subject experiences several events at the same time, this is counted only as one event, the most serious one.

[b] Clinical worsening defined as decrease in 6MWD of ≥15% from baseline (Day 1 in DB) confirmed on 2 different days within 2 weeks AND worsening of PAH symptoms (increase in WHO FC OR appearance or worsening of RHF signs/symptoms not responding to optimized oral diuretics).

Note: All cases from first study treatment administration up to Week 120 confirmed by the CEC are included.

[TEFMMOL02B2.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEFMMOL02B2.SAS] 02MAR2023, 09:59

表 2.7.3-付録-9 Change from Baseline to EDBT in NT-proBNP (ng/L) (ANCOVA) – Primary endpoint estimand strategy; Full Analysis Set (Study AC-077A301)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	35	70	44	86
Number of subjects included in the analysis	30	67	42	84
Baseline				
N	30	67	42	84
Mean (SD)	1306.6 (1622.40)	1594.4 (3404.78)	842.0 (1148.48)	1188.8 (1717.37)
Median	632.8	461.0	428.9	466.1
Range	(51; 5704)	(51; 23662)	(51; 6433)	(51; 8420)
EDBT				
N	27	48	40	66
Mean (SD)	746.6 (965.19)	323.3 (330.19)	756.3 (984.29)	499.1 (977.75)
Median	434.7	228.4	392.5	216.1
Range	(51; 3704)	(51; 1415)	(53; 5112)	(51; 7202)
Ratio of EDBT to baseline				
N	30	67	42	84
Geometric mean	0.65	0.46	0.85	0.53
Geometric CV	0.771	1.274	0.795	1.275
95% CL of geometric mean	(0.50, 0.84)	(0.36, 0.58)	(0.69, 1.06)	(0.43, 0.66)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; SD = Standard deviation.

[a] See details on Intercurrent events and missing data handling in Section 5.2 of the SAP

[b] Ratio of EDBT to baseline NT-proBNP is log-transformed (base e) and analyzed using one analysis of covariance (ANCOVA) for each pairwise comparison and each stage, with factors for randomized treatment group, stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) and a continuous covariate for log-transformed baseline NT-proBNP

Results of these stage-wise ANCOVAs are used to compute Median unbiased estimate, adjusted repeated CL and adjusted combined p-value for each comparison of interest.

Notes:

Patients with missing baseline are excluded from the analysis

Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Number of subjects with intercurrent events[a] (n, %)				
N	3	14	3	14
Death occurring prior to EDBT date	0	1 (1.5%)	0	1 (1.2%)
Disease progression/worsening confirmed by CEC prior to EDBT visit	0	2 (3.0%)	0	2 (2.4%)
Prohibited PAH-specific medication prior to EDBT without death and with disease progression	0	0	0	0
Prohibited PAH-specific medication prior to EDBT without death and without disease progression	2 (6.7%)	1 (1.5%)	2 (4.8%)	2 (2.4%)
Treatment discontinuation/interruption for more than 2 days prior to EDBT without death and with disease progression	0	1 (1.5%)	0	1 (1.2%)
Treatment discontinuation/interruption for more than 2 days prior to EDBT without death and without disease progression	0	8 (11.9%)	2 (4.8%)	8 (9.5%)
Treatment dose adjustments prior to EDBT	1 (3.3%)	3 (4.5%)	0	2 (2.4%)
Number of subjects with imputation of missing values[a] (n, %)				
N	3	10	1	8
Disease progression (confirmed) prior to Week 16	0	1 (1.5%)	0	1 (1.2%)
No disease progression (confirmed) prior to Week 16	3 (10.0%)	9 (13.4%)	1 (2.4%)	7 (8.3%)
Treatment effect: Adjusted geometric mean ratio vs. monotherapy (Median unbiased estimate)[b]		0.70		0.64
Adjusted repeated CL		(0.50, 0.98)		(0.47, 0.86)
Adjusted two-sided combined p-value		0.0353		0.0029

[TEFBNP02.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TEFBNP02.SAS] 09MAR2023, 08:04

表 2.7.3-付録-10 Percent of baseline of NT-proBNP Over Time in the Combined Double-blind and Open-label Period; Full Analysis Set (DB-OL combined) (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Analysis set: Full Analysis Set	35	44	107
Percent of baseline at Week 16			
N	27	41	87
Geometric mean	66.4	84.4	50.6
Geometric CV	0.8	0.8	1.4
95% CL of geometric mean	(50.5; 87.4)	(67.6; 105.3)	(40.6; 63.0)
Percent of baseline at Week 42/OL Month 6			
N	27	29	70
Geometric mean	53.6	61.8	51.7
Geometric CV	1.7	1.2	1.6
95% CL of geometric mean	(33.8; 84.8)	(43.0; 88.8)	(39.6; 67.6)
Percent of baseline at Week 68/OL Month 12			
N	18	22	45
Geometric mean	41.3	69.2	44.3
Geometric CV	1.5	1.1	2.0
95% CL of geometric mean	(24.2; 70.6)	(46.1; 103.9)	(30.3; 64.9)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; NT-proBNP = N-terminal pro B-type natriuretic peptide; CL = Confidence Limits; CV = Coefficient of Variation; EOT = End of treatment.
Note: N for percent of baseline is the number of subjects with non-missing values at both baseline and the postbaseline time point.

	All strata		
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC
Percent of baseline at Week 94/OL Month 18			
N	13	15	32
Geometric mean	32.3	65.7	40.6
Geometric CV	2.3	1.4	2.2
95% CL of geometric mean	(14.2; 73.2)	(37.4; 115.5)	(25.1; 65.5)
Percent of baseline at Week 120/OL Month 24			
N	4	8	13
Geometric mean	46.1	51.2	64.4
Geometric CV	1.7	0.9	2.6
95% CL of geometric mean	(7.4; 286.9)	(26.5; 99.0)	(27.3; 151.9)

[TEFBNPOL02B.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TEFBNPOL02B.SAS] 02MAR2023, 09:59

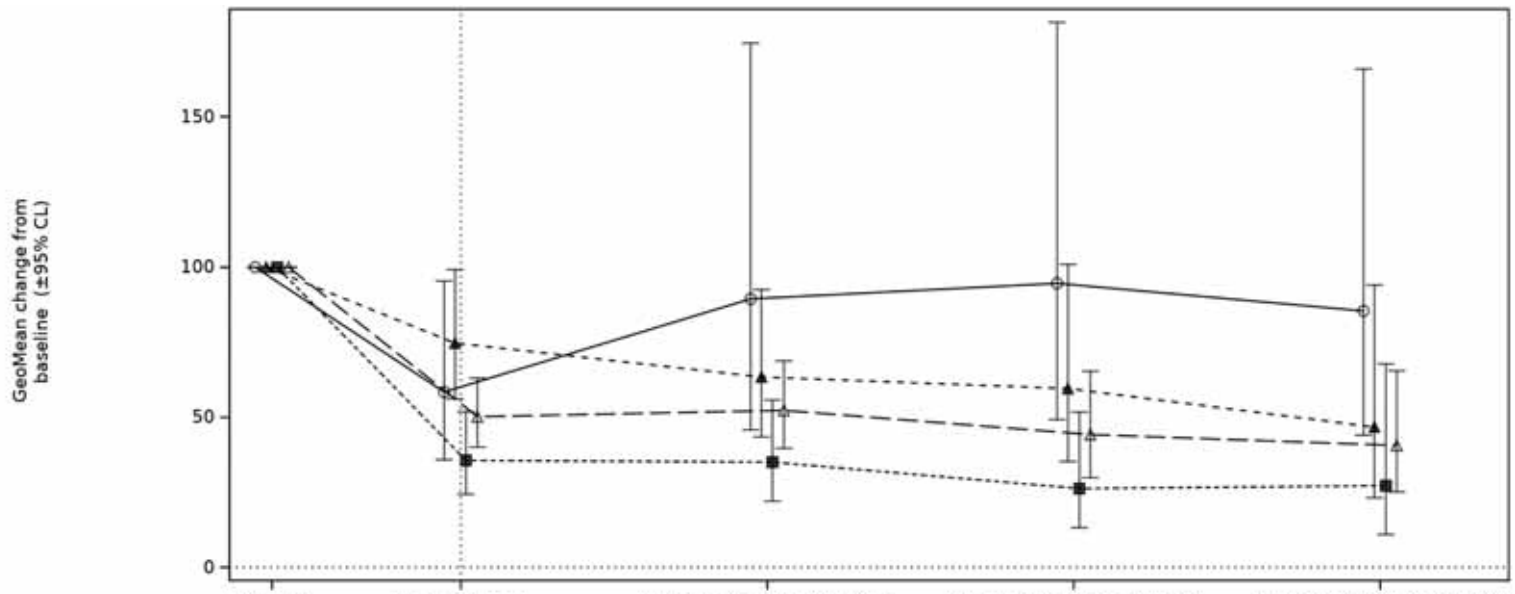
表 2.7.3-付録-11 Ratio of EDBT to Baseline PVR by Stratum by Japanese subgroup

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full and Japanese subgroup	0	0	5	1	1	1	0
Number of subjects included in the analysis	0	0	5	1	1	1	0
Baseline dyn.sec/cm^5							
N	0	0	5	1	1	1	0
Mean (SD)	0	0	497.8 (220.37)	461.4 (-)	262.6 (-)	949.7 (-)	0
Median	0	0	376.5	461.4	262.6	949.7	0
Range	0	0	(366; 880)	(461; 461)	(263; 263)	(950; 950)	0
EDBT dyn.sec/cm^5							
N	0	0	4	1	1	1	0
Mean (SD)	0	0	244.4 (127.22)	489.5 (-)	145.1 (-)	810.0 (-)	0
Median	0	0	209.7	489.5	145.1	810.0	0
Range	0	0	(132; 426)	(489; 489)	(145; 145)	(810; 810)	0
Ratio of EDBT to baseline							
N	0	0	5	1	1	1	0
Geometric mean	0	0	0.50	1.06	0.55	0.85	0
Geometric CV	0	0	0.405	NE	NE	NE	0
95% CL of geometric mean	0	0	(0.31, 0.81)	(NE, NE)	(NE, NE)	(NE, NE)	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; PVR = Pulmonary vascular resistance; EDBT = End of Double-blind Treatment; CV = Coefficient of variation; CL = Confidence limit; SD = Standard deviation.
Note: The EDBT value corresponds to the assessment done at Visit 8/Week 16 or at the premature EDBT visit if the subject prematurely discontinues DB study treatment.

[TEFPVR15AJ.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TEFPVR15AJ.SAS] 09FEB2023, 02:53

図 2.7.3-付録-1 Percent of Baseline (Geometric Mean and 95% CL) in NT-proBNP by Analysis Visit up to Week 94; Long-term M/T FDC Set (Study AC-077A301) [Cutoff Date: 31DEC2022]



Number of Subjects					
Prior ERA strata	20	13	12	7	5
Prior PDE-5i strata	37	31	26	17	13
Treatment-naïve	47	41	29	20	14
All strata	104	85	67	44	32

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label; NT-proBNP = N-terminal pro B-type natriuretic peptide; CL = Confidence Limits.
Note: Baseline and on-treatment measurements (from the first study treatment administration up to EOT + 7 days) are included.
Note: N for measured value is the number of subjects with a non-missing value for the lab test at the specified time point and at baseline.

[GEFBNPOL02A.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/GEFBNPOL02A.SAS] 15MAR2023, 08:51

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略号一覧表

略号又は略称	名称及び内容
ALP	alkaline phosphatase（アルカリホスファターゼ）
ALT	alanine aminotransferase（アラニンアミノトランスフェラーゼ）
AST	aspartate aminotransferase（アスパラギン酸アミノトランスフェラーゼ）
CCO	clinical cut off（クリニカルカットオフ）
COVID-19	coronavirus disease 2019（新型コロナウイルス感染症）
CSS	combination safety set
DB	double blind（二重盲検）
eGFR	estimated glomerular filtration rate（推定糸球体濾過率）
ERA	endothelin receptor antagonist（エンドセリン受容体拮抗薬）
FAS	full analysis set
MedDRA	Medical Dictionary for Regulatory Activities（国際医薬用語集）
PAH	pulmonary arterial hypertension（肺動脈性肺高血圧症）
PDE5i	phosphodiesterase type 5 inhibitor（ホスホジエステラーゼ 5 阻害薬）
PT	preferred term（基本語）
SMQ	standardised MedDRA queries （MedDRA 標準検索式）
SOC	system organ class（器官別大分類）
WHO FC	world health organization functional class（世界保健機関機能分類）
ULN	upper limit normal（基準値上限）

2.7.4 臨床的安全性

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

2.7.4.1.1.1 安全性の評価に用いた臨床試験

PAH 患者に対するマシテンタン／タダラフィル配合剤（ACT-064992D，以下，本配合剤）の安全性の評価には，AC-077A301 試験（以下，A DUE 試験）の結果を用いた。A DUE 試験は継続中であり，以下の CCO 時点での成績を示した。

1. 二重盲検投与期：2022 年 8 月 23 日
2. 二重盲検投与期＋オープンラベル投与期①：2022 年 12 月 31 日（全例が半年間の治験薬投与を完了した時点の長期安全性評価）
3. 二重盲検投与期＋オープンラベル投与期②：2023 年 4 月 28 日（全例が 1 年間の治験薬投与を完了した時点の長期安全性評価）

主な安全性は，上記 1 及び 3 の CCO 時点での成績で評価し，2 の結果をまとめた報告書は作成していないため，当該結果は参考的位置づけとした。

全体集団の二重盲検投与期及び二重盲検投与期＋オープンラベル投与期の成績は各項に記載し，日本人集団の成績は 2.7.4.6.1 に記載した。

A DUE 試験の概要を表 2.7.4-1 に示す。

表 2.7.4-1 安全性の評価に用いた臨床試験

試験番号／実施時期	実施国・地域 実施医療機関数*	試験デザイン 対象患者 主要評価項目	用法・用量 治験薬投与期間	登録被験者数
AC-077A301 2019 年 10 月 15 日～ CCO 日：2022 年 8 月 23 日（二重盲検投与期），2022 年 12 月 31 日（二重盲検投与期＋オープンラベル投与期①），2023 年 4 月 28 日（二重盲検投与期＋オープンラベル投与期②） 試験継続中	日本，欧州，米国，カナダ等， 全 16 カ国／地域 76 施設	オープンラベル投与期を有する，ランダム化，二重盲検，実薬対照，トリプルダミー，国際共同，多施設共同第 III 相試験 PAH 患者 EDBT 時の PVR 変化比	二重盲検投与期： 本配合剤，マシテンタン 10 mg，又はタダラフィル 40 mg を 1 日 1 回投与 16 週 オープンラベル投与期： 本配合剤を 1 日 1 回投与 24 カ月	186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例）， うち日本人 8 例（本配合剤群 6 例，マシテンタン単剤投与群 1 例，タダラフィル単剤投与群 1 例）

*被験者が組み入れられた国，治験実施医療機関

2.7.4.1.1.2 安全性の評価項目及び解析方法

(1) 解析対象集団

FAS はいずれかの投与群にランダム化され，治験薬を 1 回以上投与された全被験者とした。

安全性解析対象集団は二重盲検投与期に治験薬を 1 回以上投与された全被験者とした。二重盲検投与期の安全性は，安全性解析対象集団を用いて評価した。

CSS は二重盲検投与期間に本配合剤群にランダム化され，治験薬を 1 回以上投与された全被験者，及びオープンラベル投与期間に治験薬を 1 回以上投与された全被験者とした。二重盲検投与期＋オープンラベル投与期の安全性は，CSS を用いて評価した。二重盲検投与期に本配合剤群にランダム化された被験者は，二重盲検投与期及びオープンラベル投与期のデータを評価した。二重盲検投与期に各単剤投与群にランダム化された被験者は，オープンラベル投与期のデータを評価し，二重盲検投与期のデータは評価しなかった。ただし，二重盲検投与期のベースラインのデータは評価に含めた。CSS のベースラインは，以下のように定義した。

- 二重盲検投与期に本配合剤群にランダム化された被験者：二重盲検投与期の治験薬初回投与前の評価
- 二重盲検投与期に各単剤投与群にランダム化された被験者：オープンラベル投与期の治験薬初回投与前の評価

二重盲検投与期＋オープンラベル投与期①では，CSS 全体及び二重盲検投与期の投与群別の結果を示した。二重盲検投与期＋オープンラベル投与期②では，CSS 全体の結果を示した。

(2) 有害事象

1) 定義

有害事象とは，治験担当医師により判断された治験薬との因果関係の有無を問わず，治験中に被験者に生じた臨床検査値異常，症状，疾患等のあらゆる好ましくない又は意図しない徴候と定義した。

治験治療下で発現した有害事象とは，治験薬との因果関係の有無を問わず，治験薬使用下（治験薬投与開始から投与中止 30 日後まで）に発現した有害事象とした。

二重盲検投与期の有害事象の収集期間は，治験薬の初回投与後からオープンラベル期の治験薬投与開始日又は二重盲検投与期の治験薬終了後 30 日のいずれか早い時点までとした。二重盲検投与期＋オープンラベル投与期の有害事象の収集期間は，二重盲検投与期又はオープンラベル投与期のいずれかの治験薬の初回投与から治験薬投与終了後 30 日又は CCO のいずれか早い時点までとした。

2) 有害事象名のコーディング

有害事象名は，二重盲検投与期は MedDRA Version 25.0，二重盲検投与期＋オープンラベル投与期は MedDRA Version 25.1 を用いてコーディングし，同バージョンの MedDRA/J で日本語に置き換えた。

3) 治験薬との関連性

有害事象と治験薬との因果関係は，治験担当医師が関連あり（Related）又は関連なし（Not related）を判定した。

4) 重症度

有害事象の重症度は，治験担当医師が軽度，中等度，重度の 3 段階で判定した。

(3) 注目すべき有害事象

本配合剤の注目すべき有害事象として，「肝障害」，「貧血」，「低血圧」，及び「浮腫及び体液貯留」を評価した。各注目すべき有害事象は，SMQ 等により抽出した PT で評価した。各カテゴリーに含めた PT を統計解析計画書に示した（5.3.5.1.1-1 SAP Part 1）。

(4) 臨床検査

治験薬投与後に発現した臨床検査値異常の発現割合を要約した。顕著な臨床検査値異常の定義は統計解析計画書に示した（5.3.5.1.1-1 SAP Part 1 Sec 6.2 及び 5.3.5.1.1-2 SAP Part 2 Sec 5.6.3.1）。

血液生化学検査，血液学的検査及び血液凝固検査について，各規定来院時点の記述統計量及びベースラインから各規定来院時までの変化量を投与群別に評価した。

(5) その他の安全性評価項目

バイタルサイン（脈拍数，収縮期及び拡張期血圧），体重は各規定来院時のパラメータ及びベースラインから各規定来院時までの変化量，並びに治験薬投与後に発現した顕著なバイタルサイン異常の発現割合を要約した。顕著なバイタルサイン異常の定義は統計解析計画書に示した（5.3.5.1.1-1 SAP Part 1 Sec 6.3 及び 5.3.5.1.1-2 SAP Part 2 Sec 5.6.3.2）。

(6) 部分集団解析

治験治療下で発現した有害事象は，年齢，性別，人種，PAH に対する前治療，及び地理的地域について部分集団解析した。部分集団の定義は統計解析計画書に示した（5.3.5.1.1-1 SAP Part 1 Sec 2.4）。

2.7.4.1.2 全般的な曝露状況

2.7.4.1.2.1 被験者の内訳

<u>二重盲検投与期</u>

FAS 及び安全性解析対象集団は 186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例）であった。

二重盲検投与期に治験薬の投与を中止した被験者の割合は，本配合剤群 15.0%（16/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）であった。主な投与中止理由は，有害事象［本配合剤群 8.4%（9/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）］であった（表 2.7.4-2）。

表 2.7.4-2 被験者の内訳（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
Analysis set: Full	35	70	105	44	86	130	107
Subjects receiving different than randomized treatment throughout the whole DB period	0	0	0	0	0	0	0
Completed study treatment[a]	35 (100.0%)	57 (81.4%)	92 (87.6%)	43 (97.7%)	73 (84.9%)	116 (89.2%)	90 (84.1%)
Prematurely discontinued study treatment[b]	0	12 (17.1%)	12 (11.4%)	1 (2.3%)	13 (15.1%)	14 (10.8%)	16 (15.0%)
Reason for discontinuation							
Adverse event	0	7 (10.0%)	7 (6.7%)	1 (2.3%)	8 (9.3%)	9 (6.9%)	9 (8.4%)
Withdrawal by subject	0	3 (4.3%)	3 (2.9%)	0	1 (1.2%)	1 (0.8%)	3 (2.8%)
Death	0	0	0	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Lack of efficacy	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Non-compliance with study drug	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Other	0	0	0	0	1 (1.2%)	1 (0.8%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label.

[a] Completed study treatment in the DB period: the subject took DB study drug up to Visit 8/Week 16.

[b] Prematurely discontinued study treatment in the DB period: the subject discontinued DB treatment prior to Visit 8/Week 16.

All subjects who complete the DB period are assigned to receive M/T FDC in the OL period

Notes:

Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

One patient did not have the disposition form completed and is missing from this output but has completed the double-blind treatment period

[TSIDS04.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSIDS04.SAS] 21DEC2022, 13:15

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS は 185 例であり，二重盲検投与期の投与群の内訳は，本配合剤（DB-本配合剤）群 107 例，マシテンタン単剤投与（DB-マシテンタン）群 35 例，タダラフィル単剤投与（DB-タダラフィル）群 43 例であった。DB-本配合剤群で，オープンラベル投与期に治験薬を 1 回以上投与された被験者割合は，85.0%（91/107 例）であった（表 2.7.4-3）。

オープンラベル投与期に治験薬の投与を中止した被験者の割合は，CSS 全体では 11.9%（22/185 例），二重盲検投与期の投与群別では DB-本配合剤群 10.3%（11/107 例），DB-マシテンタン群 17.1%（6/35 例），DB-タダラフィル群 11.6%（5/43 例）であった。主な投与中止理由は，有害事象であった［DB-本配合剤群 2.8%（3/107 例），DB-マシテンタン群 11.4%（4/35 例），DB-タダラフィル群 4.7%（2/43 例）］（表 2.7.4-3）。

表 2.7.4-3 被験者の内訳（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects receiving OL study treatment	35 (100.0%)	43 (100.0%)	91 (85.0%)	169 (91.4%)
Subjects receiving M/T FDC DB study treatment	0	0	107 (100.0%)	107 (57.8%)
Subjects receiving M/T FDC DB and OL study treatment	0	0	91 (85.0%)	91 (49.2%)
Completed study treatment in DB period[a]	35 (100.0%)	43 (100.0%)	90 (84.1%)	168 (90.8%)
Prematurely discontinued study treatment in DB period [b]	0	0	16 (15.0%)	16 (8.6%)
Reason for discontinuation				
Adverse event	0	0	9 (8.4%)	9 (4.9%)
Withdrawal by subject	0	0	3 (2.8%)	3 (1.6%)
Death	0	0	1 (0.9%)	1 (0.5%)
Lack of efficacy	0	0	1 (0.9%)	1 (0.5%)
Non-compliance with study drug	0	0	1 (0.9%)	1 (0.5%)
Other	0	0	1 (0.9%)	1 (0.5%)
Completed study treatment in OL period [c]	4 (11.4%)	7 (16.3%)	14 (13.1%)	25 (13.5%)
Prematurely discontinued study treatment in OL period [d]	6 (17.1%)	5 (11.6%)	11 (10.3%)	22 (11.9%)
Reason for discontinuation				
Adverse event	4 (11.4%)	2 (4.7%)	3 (2.8%)	9 (4.9%)
Physician decision	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
Withdrawal by subject	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
Death	0	0	1 (0.9%)	1 (0.5%)
Pregnancy	0	0	1 (0.9%)	1 (0.5%)
Technical problems	0	0	1 (0.9%)	1 (0.5%)
Other	1 (2.9%)	2 (4.7%)	2 (1.9%)	5 (2.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label.
[a] Completed study treatment in the DB: the subject took study drug up to Visit 8/Week 16, for DB-Macitentan and DB-Tadalafil arms this comprises monotherapy.
[b] Prematurely discontinued study treatment in the DB period: the subject discontinued treatment prior to Visit 8/Week 16.
[c] Completed study treatment in the OL: the subject took study drug up to Visit 14/Week 120.
[d] Prematurely discontinued study treatment in the OL period: the subject discontinued treatment prior to Visit 14/Week 120.
One subject is not counted in category Completed study treatment in the DB, because corresponding disposition form was not completed but has completed both DB and OL treatment period.

[TSIDSOL02C.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSIDSOL02C.SAS] 02MAR2023, 07:50

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

オープンラベル投与期に治験薬の投与を中止した被験者の割合は，14.6%（27/185 例）であった。主な投与中止理由は，有害事象 4.9%（9/185 例），医師判断及び同意撤回各 1.6%（各 3/185 例），並びに死亡 1.1%（2/185 例）であった（表 2.7.4-4）。

表 2.7.4-4 被験者の内訳（二重盲検投与期＋オープンラベル投与期②，CSS）

	M/T FDC (Total)
	D120 cut-off
Analysis set: Combination Safety Set	185
Subjects receiving OL study treatment	169 (91.4%)
Subjects receiving M/T FDC DB study treatment	107 (57.8%)
Subjects receiving M/T FDC DB and OL study treatment	91 (49.2%)
Completed study treatment in DB period[a]	168 (90.8%)
Prematurely discontinued study treatment in DB period [b]	16 (8.6%)
Reason for discontinuation	
Adverse event	9 (4.9%)
Withdrawal by subject	3 (1.6%)
Death	1 (0.5%)
Lack of efficacy	1 (0.5%)
Non-compliance with study drug	1 (0.5%)
Other	1 (0.5%)
Completed study treatment in OL period [c]	39 (21.1%)
Prematurely discontinued study treatment in OL period [d]	27 (14.6%)
Reason for discontinuation	
Adverse event	9 (4.9%)
Physician decision	3 (1.6%)
Withdrawal by subject	3 (1.6%)
Death	2 (1.1%)
Pregnancy	1 (0.5%)
Technical problems	1 (0.5%)
Initiated prohibited medication	1 (0.5%)
Lost to follow-up	2 (1.1%)
Other	5 (2.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind; OL = Open-label.
[a] Completed study treatment in the DB: the subject took study drug up to Visit 8/Week 16, for DB-Macitentan and DB-Tadalafil arms this comprises monotherapy.
[b] Prematurely discontinued study treatment in the DB period: the subject discontinued treatment prior to Visit 8/Week 16.
[c] Completed study treatment in the OL: the subject took study drug up to Visit 14/Week 120.
[d] Prematurely discontinued study treatment in the OL period: the subject discontinued treatment prior to Visit 14/Week 120.
One subject is not counted in category Completed study treatment in the DB, because corresponding disposition form was not completed but has completed both DB and OL treatment period.
Modified from [TSIDSOL02C.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/TSIDSOL02C.SAS] 08JUN2023, 11:54

2.7.4.1.2.2 全体的な曝露及び投与期間

二重盲検投与期

治験薬投与期間の中央値（範囲）は本配合剤群 16.14（0.6～21.1）週，マシテンタン単独投与群 16.43（15.1～20.1）週，及びタダラフィル単剤投与群 16.00（11.0～18.0）週と各投与群で同程度であった（表 2.7.4-5）。

二重盲検投与期にタダラフィル 40 mg からタダラフィル 20 mg に減量した被験者の割合は，本配合剤群で 2.8%（3/107 例）であり，タダラフィル単剤投与群では認められなかった（5.3.5.1.1-1 CSR TSIEX10）。

表 2.7.4-5 曝露及び投与期間（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Total duration of treatment (weeks)[a]					
N	35	70	44	86	107
Mean (SD)	16.87 (1.307)	14.38 (5.201)	15.98 (0.952)	14.92 (4.412)	14.85 (4.547)
Median	16.43	16.21	16.00	16.14	16.14
Range	(15.1; 20.1)	(0.6; 21.1)	(11.0; 18.0)	(0.7; 21.1)	(0.6; 21.1)
Total duration of treatment (weeks)[a]					
< 4	0	9 (12.9%)	0	8 (9.3%)	10 (9.3%)
4 - < 8	0	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
8 - < 12	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
12 - < 16	7 (20.0%)	16 (22.9%)	17 (38.6%)	18 (20.9%)	25 (23.4%)
>= 16	28 (80.0%)	43 (61.4%)	26 (59.1%)	58 (67.4%)	69 (64.5%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; EOT-DB = End of treatment in double-blind treatment period.
[a] Total duration of treatment is defined as (date of EOT-DB – date of first dose of study treatment +1)/7.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSIEX01.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSIEX01.SAS] 13DEC2022, 16:45

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の治験薬投与期間の中央値（範囲）は 59.86（0.6～151.6）週であった。二重盲検投与期の投与群別では，DB-本配合剤群 59.86（0.6～151.6）週，DB-マシテンタン群 58.57（4.7～113.1）週，及び DB-タダラフィル群 61.43（1.0～129.7）週］であった（M274 付録_二重盲検投与期＋オープンラベル投与期①_TSIEXOL01C）。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体の治験薬投与期間の中央値（範囲）は，75.43（0.6～151.6）週であった（表 2.7.4-6）。

表 2.7.4-6 曝露及び投与期間（二重盲検投与期＋オープンラベル投与期②，CSS）

	All strata			
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	OL M/T FDC (Total)
Analysis set: Combination Safety Set	35	43	107	185
Total duration of treatment (weeks) for CSS[a]				
N	35	43	107	185
Mean (SD)	69.44 (32.642)	71.48 (34.908)	75.32 (41.465)	73.32 (38.360)
Median	71.29	78.29	74.43	75.43
Range	(4.7; 120.0)	(1.0; 146.6)	(0.6; 151.6)	(0.6; 151.6)
Total duration of treatment (weeks) for CSS[a]				
< 4	0	2 (4.7%)	10 (9.3%)	12 (6.5%)
4 - < 16	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
16 - < 42	6 (17.1%)	5 (11.6%)	10 (9.3%)	21 (11.4%)
42 - < 68	9 (25.7%)	10 (23.3%)	23 (21.5%)	42 (22.7%)

	All strata			
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	OL M/T FDC (Total)
68 - < 94	5 (14.3%)	8 (18.6%)	17 (15.9%)	30 (16.2%)
94 - < 120	12 (34.3%)	15 (34.9%)	23 (21.5%)	50 (27.0%)
>= 120	1 (2.9%)	1 (2.3%)	20 (18.7%)	22 (11.9%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; EOT = End of treatment; DB = Double-blind; OL = Open-label; LC = Loose combination.
[a] Total duration of treatment is defined as (date of EOT – date of first dose of study treatment +1)/7.
Note: First dose of study treatment refers to first dose of M/T FDC (or LC macitentan and tadalafil) in DB or OL.
Modified from [TSIEXOL01C.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/TSIEXOL01C.SAS] 08JUN2023, 11:54

2.7.4.1.3 人口統計学的特性

FAS の人口統計学的特性を表 2.7.4-7 に示す。年齢の中央値（範囲）は，本配合剤群 48.0（18～79）歳，マシテンタン単剤投与群 51.0（20～80）歳，タダラフィル単剤投与群 54.0（19～78）歳であり，各投与群で同程度であった。PAH の重症度分類である WHO FC は，マシテンタン単剤投与群及びタダラフィル単剤投与群（以下，各単剤投与群）では class III の割合が class II より高かったが，本配合剤群では class II の割合が class III より高かった。

CSS の人口統計学的特性及びベースラインの疾患特性は，M274 付録_二重盲検投与期＋オープンラベル投与期①_TSIDEMOL01C に示す。

表 2.7.4-7 人口統計学的特性（二重盲検投与期，FAS）

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
Analysis set: Full	35	70	105	44	86	130	107
Age, years							
N	35	70	105	44	86	130	107
Mean (SD)	51.3 (15.85)	51.8 (16.11)	51.7 (15.95)	53.1 (13.66)	48.7 (16.78)	50.2 (15.88)	48.7 (15.78)
Median	51.0	54.5	54.0	54.0	48.0	50.0	48.0
Range	(20; 80)	(18; 79)	(18; 80)	(19; 78)	(18; 79)	(18; 79)	(18; 79)
Sex							
N	35	70	105	44	86	130	107
Female	29 (82.9%)	53 (75.7%)	82 (78.1%)	34 (77.3%)	62 (72.1%)	96 (73.8%)	82 (76.6%)
Male	6 (17.1%)	17 (24.3%)	23 (21.9%)	10 (22.7%)	24 (27.9%)	34 (26.2%)	25 (23.4%)
Race							
N	35	70	105	44	86	130	107
American Indian or Alaska Native	0	1 (1.4%)	1 (1.0%)	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Asian	12 (34.3%)	17 (24.3%)	29 (27.6%)	11 (25.0%)	30 (34.9%)	41 (31.5%)	36 (33.6%)
Japanese	1 (2.9%)	6 (8.6%)	7 (6.7%)	1 (2.3%)	5 (5.8%)	6 (4.6%)	6 (5.6%)
Other Asian	11 (31.4%)	11 (15.7%)	22 (21.0%)	10 (22.7%)	25 (29.1%)	35 (26.9%)	30 (28.0%)
Black or African American	1 (2.9%)	2 (2.9%)	3 (2.9%)	2 (4.5%)	2 (2.3%)	4 (3.1%)	2 (1.9%)
White	20 (57.1%)	48 (68.6%)	68 (64.8%)	29 (65.9%)	52 (60.5%)	81 (62.3%)	66 (61.7%)
Not reported	2 (5.7%)	2 (2.9%)	4 (3.8%)	2 (4.5%)	1 (1.2%)	3 (2.3%)	2 (1.9%)
WHO FC							
N	35	70	105	44	86	130	107
Class I	0	0	0	0	0	0	0
Class II	11 (31.4%)	42 (60.0%)	53 (50.5%)	19 (43.2%)	51 (59.3%)	70 (53.8%)	65 (60.7%)
Class III	24 (68.6%)	28 (40.0%)	52 (49.5%)	25 (56.8%)	35 (40.7%)	60 (46.2%)	42 (39.3%)
Class IV	0	0	0	0	0	0	0

	Treatment-naive and prior ERA strata			Treatment-naive and prior PDE-5i strata			All strata
	Macitentan	M/T FDC	Total	Tadalafil	M/T FDC	Total	M/T FDC
PAH etiology							
N	35	70	105	44	86	130	107
Idiopathic	16 (45.7%)	36 (51.4%)	52 (49.5%)	20 (45.5%)	47 (54.7%)	67 (51.5%)	58 (54.2%)
Heritable	3 (8.6%)	3 (4.3%)	6 (5.7%)	2 (4.5%)	2 (2.3%)	4 (3.1%)	4 (3.7%)
Drug- and- toxin induced	0	1 (1.4%)	1 (1.0%)	2 (4.5%)	1 (1.2%)	3 (2.3%)	1 (0.9%)
PAH associated with connective tissue disease	13 (37.1%)	27 (38.6%)	40 (38.1%)	16 (36.4%)	29 (33.7%)	45 (34.6%)	36 (33.6%)
PAH associated with HIV infection	0	2 (2.9%)	2 (1.9%)	2 (4.5%)	3 (3.5%)	5 (3.8%)	4 (3.7%)
PAH associated with portal hypertension	1 (2.9%)	0	1 (1.0%)	1 (2.3%)	1 (1.2%)	2 (1.5%)	1 (0.9%)
PAH associated with congenital heart disease	2 (5.7%)	1 (1.4%)	3 (2.9%)	1 (2.3%)	3 (3.5%)	4 (3.1%)	3 (2.8%)
PAH associated with schistosomiasis	0	0	0	0	0	0	0
Long-term responders to calcium channel blockers	0	0	0	0	0	0	0
With overt features of venous/capillaries (PVOD/PCH) involvement	0	0	0	0	0	0	0
Time since diagnosis, years							
N	35	70	105	44	86	130	107
Mean (SD)	3.174 (6.1489)	1.487 (2.8740)	2.050 (4.2987)	0.930 (2.2573)	1.375 (2.2414)	1.225 (2.2480)	1.828 (2.8016)
Median	0.104	0.137	0.131	0.329	0.164	0.268	0.411
Range	(0.03; 27.65)	(0.02; 14.84)	(0.02; 27.65)	(0.02; 12.83)	(0.02; 10.71)	(0.02; 12.83)	(0.02; 14.84)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; WHO FC = World Health Organization Functional Classification; PAH = Pulmonary arterial hypertension.

Note: N's for each parameter reflect non-missing values. Baseline is defined as the last observation prior to the first study treatment administration.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

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2.7.4.1.4 前治療及び併用療法

PAH に対する前治療で分けた治療層（未治療層，ERA 既治療層，及び PDE5i 既治療層）ごとの被験者数は，本配合剤群の 107 例では，未治療層 49 例，ERA 既治療層 21 例，及び PDE5i 既治療層 37 例，マシテンタン単剤投与群の 35 例では，未治療層 24 例及び ERA 既治療層 11 例，並びにタダラフィル単剤投与群の 44 例では，未治療層 25 例及び PDE5i 既治療層 19 例であった（表 2.7.4-8）。

PAH に対する前治療薬は，主に ERA（マシテンタン，アンブリセンタン，及びボセンタン）及び PDE5i（タダラフィル及びシルデナフィル）であった（表 2.7.4-8）。

未治療層の被験者のうち，本配合剤群の 2 例で PAH 治療薬の投与歴があった。1 例はベースラインの右心カテーテル検査中に実施医療機関の手順に従って血管反応性検査のためイロプロストを単回吸入投与され，1 例はランダム化の 2 日前までタダラフィルを投与されていたが誤ってランダム化された。

表 2.7.4-8 PAH に対する前治療薬（二重盲検投与期，FAS）

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	24	25	49	11	21	19	37
Subjects with one or more PAH-specific prior medications	0	0	2 (4.1%)	9 (81.8%) [c]	20 (95.2%) [c]	17 (89.5%) [a,b]	35 (94.6%)
Special interest category Standardized medication name							
PDE-5i	0	0	1 (2.0%)	0	1 (4.8%)	17 (89.5%) [a,b]	35 (94.6%)
SILDENAFIL	0	0	0	0	1 (4.8%)	11 (57.9%)	27 (73.0%)
SILDENAFIL CITRATE	0	0	0	0	0	2 (10.5%)	4 (10.8%)
TADALAFIL	0	0	1 (2.0%)	0	0	4 (21.1%)	4 (10.8%)
ERA	0	0	0	9 (81.8%) [c]	20 (95.2%) [c]	0	0
AMBRISENTAN	0	0	0	3 (27.3%)	7 (33.3%)	0	0
BOSENTAN	0	0	0	2 (18.2%)	4 (19.0%)	0	0
MACITENTAN	0	0	0	4 (36.4%)	9 (42.9%)	0	0
Prostacyclin analogs/ Prostacyclin receptor agonist	0	0	1 (2.0%)	0	0	0	0
ILOPROST	0	0	1 (2.0%)	0	0	0	0
Soluble guanylate cyclase stimulator	0	0	0	0	1 (4.8%)	0	0
RIOCIGUAT	0	0	0	0	1 (4.8%)	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination.
Note: A prior medication is any treatment for which the end date is prior to the first dose of study treatment.

a. PDE5i 既治療層では，タダラフィル単剤投与群の 1 例及び本配合剤群の 2 例が治験薬初回投与日（Day 1）まで PDE5i の投与継続していたため，本帳票には含めずベースライン時点の PAH 治療を集計した帳票に含めた（5.3.5.1.1-1 CSR TSICM08B）。

b. PDE5i 既治療層では，1 例がベースライン時にタダラフィルの投与を受けていたが，タダラフィルの投与開始日が不明であったため，ベースライン時点の PAH 治療を集計した帳票（5.3.5.1.1-1 CSR TSICM08B）に含めなかった。

c. ERA 既治療層では，マシテンタン単剤投与群の 2 例及び本配合剤群の 1 例が Day 1 まで ERA の投与を継続していたため，本帳票には含めずベースライン時点の PAH 治療を集計した帳票に含めた（5.3.5.1.1-1 CSR TSICM08B）。

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PAH 治療薬を除く，PAH の症状又は合併症の治療に使用された主な前治療薬は，グルココルチコイド［本配合剤群 7.5%（8/107 例），マシテンタン単剤投与群 2.9%（1/35 例），タダラフィル単剤投与群 2.3%（1/44 例），以下同順）及びスルホンアミド［5.6%（6/107 例），14.3%（5/35 例），2.3%（1/44 例）］であった。右心カテーテル検査中に局所麻酔薬を使用した被験者は本配合剤群の 1 例のみであり，ヘパリン等の抗凝固薬を使用した被験者の割合は，本配合剤群 8.4%（9/107 例），マシテンタン単剤投与群 17.1%（6/35 例），及びタダラフィル単剤投与群 6.8%（3/44 例）であった（5.3.5.1.1-1 CSR TSICM04）。

治験薬投与開始前から継続した又は二重盲検投与期間中に投与開始した主な併用薬は，スルホンアミド［本配合剤群 60.7%（65/107 例），マシテンタン単剤投与群 57.1%（20/35 例），タダラフィル単剤投与群 47.7%（21/44 例），以下同順），アルドステロン拮抗薬［41.1%（44/107 例），51.4%（18/35 例），34.1%（15/44 例）］，及びプロトンポンプ阻害薬［36.4%（39/107 例），28.6%（10/35 例），45.5%（20/44 例）］であった（5.3.5.1.1-1 CSR TSICM01）。

前治療薬としてウイルスワクチンを使用した被験者の割合は，本配合剤群 26.2%（28/107 例），マシテンタン単剤投与群 40.0%（14/35 例），タダラフィル単剤投与群 31.8%（14/44 例）であり，使用されたウイルスワクチンはすべて COVID-19 ワクチンであった（5.3.5.1.1-1 CSR TSICM04）。

二重盲検投与期＋オープンラベル投与期①にウイルスワクチンを使用した被験者の割合は，CSS 全体で 45.4%であり，使用されたウイルスワクチンはすべて COVID-19 ワクチンであった。前治療としてウイルスワクチンを使用した被験者の割合は，二重盲検投与期と比較して二重盲検期＋オープンラベル投与期で高く，COVID-19 感染拡大の時期と一致していた（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSICMOL01）。

ウイルスワクチンの他に二重盲検投与期と比較して，二重盲検投与期＋オープンラベル投与期で使用傾向が大きく異なる併用薬はなかった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSICMOL04）。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

2.7.4.2.1.1 有害事象の概要

二重盲検投与期

本配合剤群の有害事象の発現割合は，マシテンタン単剤投与群と比較して高く，タダラフィル単剤投与群と同様であった［本配合剤群 82.2%（88/107 例），マシテンタン単剤投与群 71.4%（25/35 例），タダラフィル単剤投与群 79.5%（35/44 例），以下同順］。死亡に至った有害事象は 2 例に認められ，いずれも本配合剤群であった。重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合は，各単剤投与群と比較して本配合剤群で高かった［重篤な有害事象：14.0%（15/107 例），8.6%（3/35 例），9.1%（4/44 例），治験薬の投与中止に至った有害事象：8.4%（9/107 例），0%，4.5%（2/44 例）］（表 2.7.4-9）。

表 2.7.4-9 有害事象の概要（A DUE 試験，二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more:					
AEs	25 (71.4%)	59 (84.3%)	35 (79.5%)	72 (83.7%)	88 (82.2%)
Related AEs [a]	11 (31.4%)	33 (47.1%)	11 (25.0%)	37 (43.0%)	47 (43.9%)
AEs leading to death [b]	0	1 (1.4%)	0	1 (1.2%)	2 (1.9%)
Serious AEs	3 (8.6%)	11 (15.7%)	4 (9.1%)	12 (14.0%)	15 (14.0%)
Related serious AEs	0	3 (4.3%)	0	3 (3.5%)	3 (2.8%)
AEs leading to premature discontinuation of study treatment	0	7 (10.0%)	2 (4.5%)	8 (9.3%)	9 (8.4%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

[TSFAE01.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE01.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の有害事象の発現割合は 91.9%（170/185 例），重篤な有害事象の発現割合は 24.3%（45/185 例），治験薬の投与中止に至った有害事象の発現割合は 9.2%（17/185 例）であった。CSS 全体で死亡に至った有害事象は 3 例に認められ，いずれも DB-本配合剤群であった（表 2.7.4-10）。このうち 2 例は二重盲検投与期，1 例はオープンラベル投与期に認められた。

二重盲検投与期に各単剤投与群にランダム化された被験者では，有害事象及び重篤な有害事象の発現割合は各投与群で同程度であった［有害事象：DB-マシテンタン群 88.6%（31/35 例），DB-タダラフィル群 88.4%（38/43 例）（以下同順），重篤な有害事象：20.0%（7/35 例），20.9%（9/43 例）］。治験薬の投与を中止した被験者の割合は，DB-タダラフィル群［2.3%（1/43 例）］と比較して DB-マシテンタン群［11.4%（4/35 例）］で高かった（表 2.7.4-10）。

表 2.7.4-10 有害事象の概要（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more:				
AEs	31 (88.6%)	38 (88.4%)	101 (94.4%)	170 (91.9%)
Related AEs [a]	9 (25.7%)	10 (23.3%)	49 (45.8%)	68 (36.8%)
AEs leading to death [b]	0	0	3 (2.8%)	3 (1.6%)
Serious AEs	7 (20.0%)	9 (20.9%)	29 (27.1%)	45 (24.3%)
Related serious AEs	0	2 (4.7%)	4 (3.7%)	6 (3.2%)

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
AEs leading to premature discontinuation of study treatment	4 (11.4%)	1 (2.3%)	12 (11.2%)	17 (9.2%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
[TSFAEOL01.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL01.SAS] 02MAR2023, 08:36

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体の有害事象の発現割合は 93.5%（173/185 例），重篤な有害事象の発現割合は 26.5%（49/185 例），治験薬の投与中止に至った有害事象の発現割合は 9.2%（17/185 例）であった（表 2.7.4-11）。二重盲検投与期＋オープンラベル投与期①と比較して，新たに死亡に至った有害事象が 1 例，及び重篤な有害事象が 4 例に認められたが，いずれも治験薬と関連なしと判断された。

表 2.7.4-11 有害事象の概要（二重盲検投与期＋オープンラベル投与期②，CSS）

	M/T FDC (Total)
	D120 cut-off
Analysis set: Combination Safety Set	185
Subjects with 1 or more:	
AEs	173 (93.5%)
Related AEs [a]	69 (37.3%)
AEs leading to death [b]	4 (2.2%)
Serious AEs	49 (26.5%)
Related serious AEs	6 (3.2%)
AEs leading to premature discontinuation of study treatment	17 (9.2%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Modified from [TSFAEOL01.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/TSFAEOL01.SAS] 08JUN2023, 11:54

2.7.4.2.1.2 比較的よくみられる有害事象

二重盲検投与期

本配合剤群で 10%以上に認められた有害事象は，頭痛［本配合剤群 16.8%（18/107 例），マシテンタン単剤投与群 17.1%（6/35 例），タダラフィル単剤投与群 13.6%（6/44 例），以下同順］及び末梢性浮腫［13.1%（14/107 例），11.4%（4/35 例），11.4%（5/44 例）］であった。本配合

剤群で 10%未満 5%以上に認められた有害事象は，貧血［7.5%（8/107 例），0%，0%］，ヘモグロビン減少［7.5%（8/107 例），0%，0%］，低血圧［7.5%（8/107 例），0%，0%］，末梢腫脹［6.5%（7/107 例），2.9%（1/35 例），0%］，咳嗽［5.6%（6/107 例），2.9%（1/35 例），4.5%（2/44 例）］，筋肉痛［5.6%（6/107 例），0%，4.5%（2/44 例）］，及び悪心［5.6%（6/107 例），0%，6.8%（3/44 例）］であった（表 2.7.4-12）。

各単剤投与群と比較して本配合剤群で 5%以上発現割合が高かった有害事象は，貧血，ヘモグロビン減少，及び低血圧であった。マシテンタン単剤投与群と比較して本配合剤群で 5%以上発現割合が高かったその他の有害事象は，筋肉痛及び悪心であった。タダラフィル単剤投与群と比較して本配合剤群で 5%以上発現割合が高かったその他の有害事象は，末梢腫脹であった。本配合剤群と比較してタダラフィル単剤投与群で 5%以上発現割合が高かった有害事象は，下痢［本配合剤群 4.7%（5/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 13.6%（6/44 例），以下同順］及び関節痛［3.7%（4/107 例），5.7%（2/35 例），9.1%（4/44 例）］であった。本配合剤群と比較してマシテンタン単剤投与群で 5%以上発現割合が高かった有害事象は認められなかった（5.3.5.1.1-1 CSR TSFAE18）。

重度の有害事象の発現割合は，各単剤投与群と比較して本配合剤群で高かった［本配合剤群：14.0%（15/107 例），マシテンタン単剤投与群：5.7%（2/35 例），タダラフィル単剤投与群 6.8%（3/44 例），以下同順］。いずれかの投与群で 2 例以上に認められた重度の有害事象は，頭痛［1.9%（2/107 例），2.9%（1/35 例），0%］及び心不全［1.9%（2/107 例），0%，2.3%（1/44 例）］であった（5.3.5.1.1-1 CSR TSFAE20）。各有害事象の重症度（軽度，中等度，重度）に特定の傾向は認められなかった。

各単剤投与群と比較して本配合剤群で，血液およびリンパ系障害（SOC），心臓障害（SOC），眼障害（SOC），神経系障害（SOC），並びに血管障害（SOC）の発現割合が高かった（5.3.5.1.1-1 CSR TSFAE02）。それぞれの有害事象の発現割合等を以下に示す。

- 血液およびリンパ系障害（SOC）の発現割合は，本配合剤群 12.1%（13/107 例），マシテンタン単剤投与群 5.7%（2/35 例），タダラフィル単剤投与群 2.3%（1/44 例）であった。各単剤投与群と比較して本配合剤群で血液およびリンパ系障害（SOC）の発現割合が高かった理由は，貧血に関連する有害事象が各単剤投与群と比較して本配合剤群で高かったことが影響していた。注目すべき有害事象に「貧血」の詳細を記載した（2.7.4.2.1.7(1)2)）。

- 心臓障害（SOC）の発現割合は，本配合剤群 15.0%（16/107 例），マシテンタン単剤投与群 5.7%（2/35 例），タダラフィル単剤投与群 9.1%（4/44 例）であった（5.3.5.1.1-1 CSR TSFAE02）。その他重要な有害事象に心臓障害の詳細を記載した（2.7.4.2.1.6(3)）。

- 眼障害（SOC）の発現割合は，本配合剤群 7.5%（8/107 例），マシテンタン単剤投与群 2.9%（1/35 例），タダラフィル単剤投与群 4.5%（2/44 例）（以下同順）であった。いずれかの単剤投与群と比較して本配合剤群で 2 例以上発現例数が多かった有害事象（PT）は，眼瞼浮腫［1.9%（2/107 例），0%，0%］，眼窩周囲浮腫［1.9%（2/107 例），0%，2.3%（1/44 例）］，及び霧視［1.9%（2/107 例），2.9%（1/35 例），0%］であった（5.3.5.1.1-1 CSR TSFAE02）。これらの事象は投与開始後早期［治験薬投与開始日（Day 1）から 12 日目（Day 12）まで］に発現する傾向があった（5.3.5.1.1-1 CSR LSFAE01）。

・神経系障害（SOC）の発現割合は，本配合剤群 25.2%（27/107 例），マシテンタン単剤投与群 17.1%（6/35 例），タダラフィル単剤投与群 20.5%（9/44 例）（以下同順）であった。いずれかの単剤投与群と比較して本配合剤群で 2 例以上発現例数が多かった有害事象（PT）は，頭痛［16.8%（18/107 例），17.1%（6/35 例），13.6%（6/44 例）］，浮動性めまい［2.8%（3/107 例），2.9%（1/35 例），0%］，及び感覚鈍麻［1.9%（2/107 例），0%，0%］であった（5.3.5.1.1-1 CSR TSFAE02）。神経系障害（SOC）のうち，本配合剤群で最も発現割合が高かった有害事象（PT）の頭痛は，マシテンタン及びタダラフィルに関連する既知の事象であった。

・血管障害（SOC）の発現割合は，本配合剤群 12.1%（13/107 例），マシテンタン単剤投与群 5.7%（2/35 例），タダラフィル単剤投与群 0%（以下同順）であった。いずれかの単剤投与群と比較して本配合剤群で 2 例以上発現例数が多かった有害事象は，低血圧［7.5%（8/107 例），0%，0%］及び潮紅［2.8%（3/107 例），5.7%（2/35 例），0%］であった（5.3.5.1.1-1 CSR TSFAE02）。血管障害はマシテンタン及びタダラフィルに関連する既知の事象であった。注目すべき有害事象に「低血圧」の詳細を記載した（2.7.4.2.1.7(1)3)）。

胃腸障害（SOC），並びに筋骨格系および結合組織障害（SOC）は，タダラフィルに関連する既知の事象であり，マシテンタン単剤投与群と比較して本配合剤群及びタダラフィル単剤投与群で発現割合が高かった［胃腸障害：本配合剤群 26.2%（28/107 例），マシテンタン単剤投与群 11.4%（4/35 例），タダラフィル単剤投与群 29.5%（13/44 例）（以下同順），筋骨格系および結合組織障害：20.6%（22/107 例），8.6%（3/35 例），34.1%（15/44 例）］（5.3.5.1.1-1 CSR TSFAE02）。

表 2.7.4-12 本配合剤群で 2%以上に認められた有害事象

（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AEs	25 (71.4%)	59 (84.3%)	35 (79.5%)	72 (83.7%)	88 (82.2%)
Preferred term					
頭痛	6 (17.1%)	12 (17.1%)	6 (13.6%)	14 (16.3%)	18 (16.8%)
末梢性浮腫	4 (11.4%)	9 (12.9%)	5 (11.4%)	12 (14.0%)	14 (13.1%)
貧血	0	6 (8.6%)	0	7 (8.1%)	8 (7.5%)
ヘモグロビン減少	0	3 (4.3%)	0	8 (9.3%)	8 (7.5%)
低血圧	0	6 (8.6%)	0	5 (5.8%)	8 (7.5%)
末梢腫脹	1 (2.9%)	7 (10.0%)	0	7 (8.1%)	7 (6.5%)
咳嗽	1 (2.9%)	5 (7.1%)	2 (4.5%)	6 (7.0%)	6 (5.6%)
筋肉痛	0	5 (7.1%)	2 (4.5%)	4 (4.7%)	6 (5.6%)
悪心	0	5 (7.1%)	3 (6.8%)	4 (4.7%)	6 (5.6%)
背部痛	1 (2.9%)	5 (7.1%)	4 (9.1%)	3 (3.5%)	5 (4.7%)
下痢	0	4 (5.7%)	6 (13.6%)	5 (5.8%)	5 (4.7%)
関節痛	2 (5.7%)	2 (2.9%)	4 (9.1%)	4 (4.7%)	4 (3.7%)
心不全	0	4 (5.7%)	1 (2.3%)	3 (3.5%)	4 (3.7%)
消化不良	0	4 (5.7%)	3 (6.8%)	4 (4.7%)	4 (3.7%)
呼吸困難	0	2 (2.9%)	2 (4.5%)	4 (4.7%)	4 (3.7%)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
鼻閉	0	3 (4.3%)	0	3 (3.5%)	4 (3.7%)
動悸	1 (2.9%)	1 (1.4%)	2 (4.5%)	3 (3.5%)	4 (3.7%)
発熱	0	2 (2.9%)	0	4 (4.7%)	4 (3.7%)
嘔吐	0	3 (4.3%)	2 (4.5%)	4 (4.7%)	4 (3.7%)
狭心症	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
ＣＯＶＩＤ－１９	2 (5.7%)	2 (2.9%)	2 (4.5%)	3 (3.5%)	3 (2.8%)
浮動性めまい	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
口内乾燥	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
鼻出血	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
疲労	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	3 (2.8%)
潮紅	2 (5.7%)	3 (4.3%)	0	3 (3.5%)	3 (2.8%)
高尿酸血症	1 (2.9%)	3 (4.3%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
上咽頭炎	1 (2.9%)	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
非心臓性胸痛	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)
四肢痛	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE18.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE18.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で二重盲検投与期以降に新たな安全性の懸念は特定されなかった。CSS 全体で 10%以上に認められた有害事象は，COVID-19［21.1%（39/185 例）］，頭痛［14.1%（26/185 例）］，末梢性浮腫［10.8%（20/185 例）］，及び貧血［10.3%（19/185 例）］であった。また，CSS 全体で 5%以上 10%未満に認められた有害事象は，ヘモグロビン減少［9.2%（17/185 例）］，咳嗽［7.6%（14/185 例）］，低血圧及び上気道感染［各 6.5%（各 12/185 例）］，関節痛，呼吸困難，及び筋肉痛［各 5.9%（各 11/185 例）］，背部痛，動悸，及び発熱［各 5.4%（各 10/185 例）］であった（表 2.7.4-13）。CCO 時点で認められた有害事象は，COVID-19 及び咳嗽を除き，マシテンタン及びタダラフィルの既知の安全性プロファイルと同様であった。COVID-19 及び咳嗽は，COVID-19 感染拡大と試験実施時期が一致していたことが影響したと考えられる。

DB-マシテンタン群で 10%以上に認められた有害事象は，COVID-19［17.1%（6/35 例）］及びヘモグロビン減少［11.4%（4/35 例）］であった。DB-タダラフィル群で 10%以上に認められた有害事象は，COVID-19［18.6%（8/43 例）］，貧血，呼吸困難，及び発熱［各 11.6%（各 5/43 例）］であった（表 2.7.4-13）。

表 2.7.4-13 本配合剤群の合計で 2%以上に認められた有害事象

（A DUE 試験，二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AEs	31 (88.6%)	38 (88.4%)	101 (94.4%)	170 (91.9%)

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
Preferred term	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ＣＯＶＩＤ－１９	6 (17.1%)	8 (18.6%)	25 (23.4%)	39 (21.1%)
頭痛	3 (8.6%)	2 (4.7%)	21 (19.6%)	26 (14.1%)
末梢性浮腫	1 (2.9%)	3 (7.0%)	16 (15.0%)	20 (10.8%)
貧血	2 (5.7%)	5 (11.6%)	12 (11.2%)	19 (10.3%)
ヘモグロビン減少	4 (11.4%)	1 (2.3%)	12 (11.2%)	17 (9.2%)
咳嗽	0	4 (9.3%)	10 (9.3%)	14 (7.6%)
低血圧	1 (2.9%)	1 (2.3%)	10 (9.3%)	12 (6.5%)
上気道感染	3 (8.6%)	4 (9.3%)	5 (4.7%)	12 (6.5%)
関節痛	3 (8.6%)	2 (4.7%)	6 (5.6%)	11 (5.9%)
呼吸困難	0	5 (11.6%)	6 (5.6%)	11 (5.9%)
筋肉痛	3 (8.6%)	1 (2.3%)	7 (6.5%)	11 (5.9%)
背部痛	2 (5.7%)	1 (2.3%)	7 (6.5%)	10 (5.4%)
動悸	0	3 (7.0%)	7 (6.5%)	10 (5.4%)
発熱	0	5 (11.6%)	5 (4.7%)	10 (5.4%)
鼻閉	1 (2.9%)	2 (4.7%)	6 (5.6%)	9 (4.9%)
末梢腫脹	1 (2.9%)	0	8 (7.5%)	9 (4.9%)
尿路感染	1 (2.9%)	3 (7.0%)	5 (4.7%)	9 (4.9%)

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
嘔吐	0	2 (4.7%)	7 (6.5%)	9 (4.9%)
鉄欠乏性貧血	0	2 (4.7%)	6 (5.6%)	8 (4.3%)
悪心	0	1 (2.3%)	7 (6.5%)	8 (4.3%)
肺動脈性肺高血圧症	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
下痢	0	1 (2.3%)	6 (5.6%)	7 (3.8%)
胃炎	3 (8.6%)	0	4 (3.7%)	7 (3.8%)
上咽頭炎	1 (2.9%)	2 (4.7%)	4 (3.7%)	7 (3.8%)
四肢痛	1 (2.9%)	1 (2.3%)	5 (4.7%)	7 (3.8%)
浮動性めまい	1 (2.9%)	0	5 (4.7%)	6 (3.2%)
肺炎	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
発疹	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
右室不全	1 (2.9%)	1 (2.3%)	4 (3.7%)	6 (3.2%)
疲労	0	0	5 (4.7%)	5 (2.7%)
低カリウム血症	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
インフルエンザ	0	0	5 (4.7%)	5 (2.7%)
腹部不快感	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
腹痛	0	0	4 (3.7%)	4 (2.2%)
狭心症	0	0	4 (3.7%)	4 (2.2%)
心不全	0	0	4 (3.7%)	4 (2.2%)
白内障	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
消化不良	0	0	4 (3.7%)	4 (2.2%)
労作性呼吸困難	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
鼻出血	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
胃食道逆流性疾患	3 (8.6%)	0	1 (0.9%)	4 (2.2%)
痔出血	0	0	4 (3.7%)	4 (2.2%)
重度月経出血	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
不眠症	2 (5.7%)	0	2 (1.9%)	4 (2.2%)
鉄欠乏	0	0	4 (3.7%)	4 (2.2%)
副鼻腔炎	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
子宮ポリープ	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
ビタミンＢ１２欠乏	1 (2.9%)	0	3 (2.8%)	4 (2.2%)

KeyM/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Modified from [TSFAEOL08.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL08.SAS] 02MAR2023, 08:36

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で二重盲検投与期＋オープンラベル投与期①の CCO 後に，新たな安全性の懸念は特定されなかった。CSS 全体の有害事象の発現割合は 93.5%（173/185 例）であった。CSS 全体で 10%以上に認められた有害事象は，二重盲検投与期＋オープンラベル投与期①と同様，COVID-19［23.2%（43/185 例）］，頭痛［14.6%（27/185 例）］，末梢性浮腫［11.4%（21/185 例）］，及び貧血［10.8%（20/185 例）］であった。二重盲検投与期＋オープンラベル投与期①の CCO 後に，COVID-19 は新たに 4 例に認められ，呼吸困難，肺炎，及び上腕骨骨折は新たに 2 例に認められた（5.3.5.1.1-2 120DSU TSFAEOL08）。

2.7.4.2.1.3　タダラフィル漸増期の有害事象

二重盲検投与期に本配合剤群又はタダラフィル単剤投与群にランダム化された被験者は，治験薬投与開始後 2 週間でタダラフィルを漸増し，その後本配合剤又はタダラフィルを維持投与した（表 2.7.4-14）。

16 週間の二重盲検投与期を完了した被験者は，24 カ月間のオープンラベル投与期に移行し，全ての被験者に非盲検下で本配合剤を投与した。二重盲検投与期にマシテンタン単剤投与群にランダム化され，マシテンタン 10 mg 投与を完了した被験者は，オープンラベル投与期の治験薬初回投与日から 2 週間でタダラフィルを漸増し，その後本配合剤を維持投与した（表 2.7.4-15）。

表 2.7.4-14 二重盲検投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目*[1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠
維持投与	マシテンタンプラセボ 1 錠 タダラフィルプラセボ 2 錠 本配合剤 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠 本配合剤プラセボ 1 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠 本配合剤プラセボ 1 錠

*1. ベースライン時に，事前に規定した範囲内の PDE5i（タダラフィル 40 mg/日，シルデナフィル 60～120 mg/日，又はバルデナフィル 10 mg/日）を服用している被験者には，漸増投与せず治験薬初回投与日からタダラフィル 40 mg を投与した。

表 2.7.4-15 オープンラベル投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目[1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
維持投与	本配合剤 1 錠	本配合剤 1 錠	本配合剤 1 錠

*1. 二重盲検投与期からの盲検性を維持するために，全被験者で単剤の併用投与から開始した。二重盲検投与期に本配合剤群又はタダラフィル単剤投与群にランダム化され，タダラフィル 40 mg 投与を完了した被験者は，オープンラベル期の治験薬初回投与日からマシテンタン 10 mg 及びタダラフィル 40 mg を投与した。

<u>二重盲検投与期</u>

表 2.7.4-16 に示す期間の有害事象を集計した。

表 2.7.4-16 漸増期の有害事象の集計期間（二重盲検投与期）

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
未治療層	<u>タダラフィル 40 mg を投与した被験者</u>：治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで <u>タダラフィル 40 mg を投与しなかった被験者</u>：治験薬初回投与から治験薬投与終了日後 30 日	治験薬初回投与から Day 8 まで	<u>タダラフィル 40 mg を投与した被験者</u>：治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで <u>タダラフィル 40 mg を投与しなかった被験者</u>：治験薬初回投与から治験薬投与終了日後 30 日

	間		間
ERA 既治療層	タダラフィル 40 mg を投与した被験者：治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで タダラフィル 40 mg を投与しなかった被験者：治験薬初回投与から治験薬投与終了日後 30 日間	治験薬初回投与から Day 8 まで	－
PDE5i 既治療層	治験薬初回投与から Day 8 まで	－	治験薬初回投与から Day 8 まで

本配合剤群の 107 例のうち，漸増期にマシテンタン 10 mg 及びタダラフィル 20 mg を併用投与された被験者は 69 例であった。このうち未治療層は 48 例，ERA 既治療層は 21 例であった。タダラフィル単剤投与群の 44 例のうち，漸増期にタダラフィル 20 mg を投与された被験者は未治療層の 25 例であった（表 2.7.4-17）。

本配合剤群では，PDE5i 既治療層と比較して，未治療層及び ERA 既治療層で有害事象の発現割合が高かった［未治療層 56.3%（27/48 例），ERA 既治療層 61.9%（13/21 例），PDE5i 既治療層 32.4%（12/37 例）］。タダラフィル単剤投与群でも，PDE5i 既治療層と比較して，未治療層で有害事象の発現割合が高かった［未治療層 40.0%（10/25 例），PDE5i 既治療層 26.3%（5/19 例）］（表 2.7.4-17）。本配合剤群で，漸増期に最も発現割合が高かった有害事象は頭痛であった［未治療層 12.5%（6/48 例），ERA 既治療層 19.0%（4/21 例），PDE5i 既治療層 10.8%（4/37 例）］（M2.7.4 付録_二重盲検投与期_TSFAE02T）。

本配合剤群では，漸増期に治験薬の投与中止に至った有害事象は 5 例で認められた（表 2.7.4-17）。内訳は，未治療層が 3 例（筋肉痛，過敏症，及び血管浮腫が各 1 例），ERA 既治療層が 1 例（低血圧），PDE5i 既治療層が 1 例（末梢性浮腫）であった（5.3.5.1.1-1 CSR LSFAE01T）。また，低血圧で治験薬の投与を中止した ERA 既治療層の被験者はその後，重篤な有害事象の心不全で死亡した（2.7.4.2.1.4）。各単剤投与群では，漸増期に死亡に至った有害事象，及び治験薬の投与中止に至った有害事象は認められなかった。

上述した本配合剤群で治験薬の投与中止に至った有害事象のうち，タダラフィル漸増投与 2 週目（マシテンタン 10 mg 及びタダラフィル 40 mg の併用投与 1 週目）及び Day 15（本配合剤への切替え 1 日目）に治験薬の投与を中止した被験者は，未治療層の 2 例（Day 11 に筋肉痛により治験薬投与中止，及び Day 15 に過敏症により治験薬投与中止）で認められた（M2.7.4 付録_二重盲検投与期_LSIDS01）。

タダラフィル単剤投与群の未治療層で重篤な有害事象（肺炎）が 1 例に認められたが，治験薬の投与を変更せず回復した（5.3.5.1.1-1 CSR LSFAE01T）。

表 2.7.4-17 漸増期の有害事象の概要（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Safety	24	25	48	11	21	19	37
Subjects with 1 or more:							

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
AEs	7 (29.2%)	10 (40.0%)	27 (56.3%)	3 (27.3%)	13 (61.9%)	5 (26.3%)	12 (32.4%)
Related AEs [a]	4 (16.7%)	4 (16.0%)	16 (33.3%)	2 (18.2%)	9 (42.9%)	2 (10.5%)	8 (21.6%)
AEs leading to death [b]	0	0	0	0	1 (4.8%)	0	0
Serious AEs	0	1 (4.0%)	0	0	1 (4.8%)	0	0
Related serious AEs	0	0	0	0	0	0	0
AEs leading to premature discontinuation of study treatment	0	0	3 (6.3%)	0	1 (4.8%)	0	1 (2.7%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
[b] AEs leading to death are based on AE outcome of Fatal.
One participant was excluded from the analysis as she mistakenly took M/T FDC tablets as soon as day 1 and did not undergo titration part.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to:
- for M/T FDC and Tadalafil patients not previously treated by PDE-5i: first day (excluded) of treatment with Tadalafil 40mg (as monotherapy or FDC) for participants who uptitrate, and up to EOT-DB + 30 days for patients who do not uptitrate
- for Macitentan and M/T FDC or Tadalafil patients previously treated by PDE-5i: first intake of study + 7 days (included)

[TSFAE01T.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE01T.SAS] 21DEC2022, 13:15

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

表 2.7.4-18 に示す期間の有害事象を集計した。

表 2.7.4-18 漸増期の有害事象の集計期間（二重盲検投与期＋オープンラベル投与期）

	DB-本配合剤群	DB-マシテンタン群	DB-タダラフィル群
未治療層	タダラフィル 40 mg を投与した被験者：二重盲検投与期又はオープンラベル投与期の治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで タダラフィル 40 mg を投与しなかった被験者：二重盲検投与期又はオープンラベル投与期の治験薬初回投与から治験薬投与終了日後 30 日間	タダラフィル 40 mg を投与した被験者：オープンラベル投与期の治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで タダラフィル 40 mg を投与しなかった被験者：二重盲検投与期又はオープンラベル投与期の治験薬初回投与から治験薬投与終了日後 30 日間	二重盲検投与期又はオープンラベル投与期の治験薬初回投与から Day 7 まで
ERA 既治療層	タダラフィル 40 mg を投与した被験者：二重盲検投与期又はオープンラベル投与期の治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで タダラフィル 40 mg を投与しなかった被験者：二重盲検投与期又はオープンラベル投与期の治験薬初回投与から治験薬投与終了日後 30 日間	タダラフィル 40 mg を投与した被験者：オープンラベル投与期の治験薬初回投与からマシテンタン 10 mg 及びタダラフィル 40 mg の投与開始前まで タダラフィル 40 mg を投与しなかった被験者：オープンラベル投与期の治験薬初回投与から治験薬投与終了日後 30 日間	－
PDE5i 既治療層	二重盲検投与期又はオープンラベル投与期の治験薬初回投与から Day 7 まで	－	二重盲検投与期又はオープンラベル投与期の治験薬初回投与から Day 7 まで

DB-マシテンタン群では，35 例がオープンラベル投与期に移行し，タダラフィルを漸増投与された。DB-マシテンタン群の 12/35 例で有害事象が発現し，未治療層と比較して ERA 既治療層で有害事象の発現割合が高かった［未治療層：25.0%（6/24 例），ERA 既治療層 54.5%（6/11 例），以下同順］。また，重篤な有害事象及び治験薬の投与中止に至った有害事象は認められなかった

（表 2.7.4-19）。二重盲検投与期＋オープンラベル投与期の漸増期に DB-マシテンタン群で 2 例以上に認められた有害事象は頭痛［0%，18.2%（2/11 例）］であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02T）。

表 2.7.4-19 二重盲検投与期＋オープンラベル投与期の漸増期の有害事象の概要（CSS）

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan[a]	DB-M/T FDC[a]	DB-Tadalafil[b]	DB-M/T FDC[b]	DB-Macitentan[a]	DB-Tadalafil[b]	DB-M/T FDC[a]
Analysis set: Combination Safety Set	11	21	19	37	24	24	48
Subjects with 1 or more:							
AEs	6 (54.5%)	13 (61.9%)	2 (10.5%)	10 (27.0%)	6 (25.0%)	7 (29.2%)	27 (56.3%)
Related AEs [c]	3 (27.3%)	9 (42.9%)	1 (5.3%)	8 (21.6%)	1 (4.2%)	2 (8.3%)	16 (33.3%)
AEs leading to death [d]	0	1 (4.8%)	0	0	0	0	0
Serious AEs	0	1 (4.8%)	0	0	0	0	0
Related serious AEs	0	0	0	0	0	0	0
AEs leading to premature discontinuation of study treatment	0	1 (4.8%)	0	1 (2.7%)	0	0	3 (6.3%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] Subjects from this arms are to start on Macitentan 10mg/Tadalafil 20 mg during the first week of combination treatment. M/T FDC treatment-emergent period is defined from first intake of macitentan and tadalafil in DB or OL treatment period up to:
first day (excluded) of treatment with Tadalafil 40mg for participants who uptitrate, and up to EOT + 30 days for patients who do not uptitrate.
One subject is excluded from the analysis as she mistakenly took M/T FDC tablets from FDC Day 1 and did not undergo Tadalafil titration part.

[b] Subjects from this arms are to start on Macitentan 10mg/Tadalafil 40 mg during the first week of combination treatment. M/T FDC treatment-emergent period is defined from first intake of macitentan and tadalafil in DB or OL treatment period up to M/T FDC day 7 (included).

[c] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.

[d] AEs leading to death are based on AE outcome of Fatal.

[TSFAEOL01T.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL01T.SAS] 02MAR2023, 08:36

2.7.4.2.1.4 死亡

二重盲検投与期

二重盲検投与期に 3 例が死亡し，いずれも本配合剤群であった。死亡に至った治験治療下で発現した有害事象は 2 例（心不全及びクロストリジウム菌性胃腸炎）に認められ，いずれも治験担当医師により治験薬と関連なしと判断された（M2.7.4 付録_二重盲検投与期_LSFAE02）。死亡した 3 例のうち 1 例で認められた事象（COVID-19 肺炎）は，治験薬の投与中止から 30 日以降に発現したため，治験治療下で発現した有害事象とみなされなかった。各被験者の要約を以下に記載し，叙述は 5.3.5.1.1-1 CSR Narratives に示した。

· 本配合剤群，ERA 既治療層，死亡に至った有害事象：心不全

合併症に[redacted]を有していた。Day 4 に低血圧のため二重盲検下で治験薬投与を中止した。Day 6 に試験開始前に PAH に対して使用していたアンブリセンタンの投与を再開したが，Day 19 に心不全により死亡した。低血圧は死亡時に未回復であった。

· 本配合剤群，PDE5i 既治療層，死亡に至った有害事象：クロストリジウム菌性胃腸炎

Day 104 に下痢，低血圧，脱水及び腎不全のため入院し，クロストリジウム菌性胃腸炎と診断された。進行性腎不全，代謝性アシドーシス，及び呼吸不全と全身状態が悪化し，Day 105 にクロストリジウム菌性胃腸炎により死亡した。

· 本配合剤群，未治療層，死因：COVID-19 肺炎

Day 15 に過敏症，呼吸困難，末梢腫脹，及び顔面腫脹により治験薬の投与を中止した。Day 111 に COVID-19 肺炎により死亡した。本事象は治験薬の投与中止から 30 日以降に発現したため，治験治療下で発現した有害事象とみなされなかった。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，オープンラベル投与期に新たに 3 例が死亡し，いずれも DB-本配合剤群であった。死亡に至った有害事象は 2 例（右室不全及び呼吸不全）に認められ，いずれも治験担当医師により治験薬と関連なしと判断された。1 例で認められた事象（脳血管発作）は，治験薬の投与中止後 30 日以降に発現したため，治験治療下で発現した有害事象とみなされなかった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期②_LSFAEOL02）。各被験者の要約を以下に記載し，叙述は 5.3.5.1.1-2 120 DSU Narratives に示した。

· DB-本配合剤群，PDE5i 既治療層，死因：右室不全

Day 629 に右室不全により死亡した。関連する有害事象として，右室不全が 7 回発現していた。また，重篤な有害事象の肝硬変（発現日：Day 428），門脈圧亢進症（発現日：Day 428），食道静脈瘤（発現日：Day 428），及び急性腎障害（発現日：Day 608）が継続中であった。

· DB-本配合剤群，PDE5i 既治療層，死因：脳血管発作

Day 161 に医師判断により治験薬投与を中止し，Day 552 に脳血管発作により死亡した。本事象は治験薬投与中止から 30 日後以降に発現したため，治験治療下で発現した有害事象とみなされなかった。

· DB-本配合剤群，未治療層，死因：呼吸不全

Day 278 に呼吸不全により死亡した。

2.7.4.2.1.5　その他の重篤な有害事象

二重盲検投与期

重篤な有害事象の発現割合は本配合剤群 14.0%（15/107 例），マシテンタン単剤投与群 8.6%（3/35 例），タダラフィル単剤投与群 9.1%（4/44 例）であり，各単剤投与群と比較して，本配合剤群で高かった（表 2.7.4-20）。

2 例以上に発現した重篤な有害事象は，心不全［本配合剤群：1.9%（2/107 例），マシテンタン群：0%，タダラフィル群：2.3%（1/44 例），以下同順］及び呼吸困難［1.9%（2/107 例），0%，0%］であり，全て本配合剤群で認められた（表 2.7.4-20）。治験薬と関連ありと判断された重篤な有害事象は，本配合剤群の心不全，呼吸困難，貧血，末梢腫脹，右室不全，及び顔面腫脹（各 1 例）であった（M2.7.4 付録_二重盲検投与期_LSFAE02）。

重篤な有害事象を発現した被験者の一覧表を，M2.7.4 付録_二重盲検投与期_LSFAE02 に示す。

表 2.7.4-20 重篤な有害事象（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more SAEs	3 (8.6%)	11 (15.7%)	4 (9.1%)	12 (14.0%)	15 (14.0%)
System organ class Preferred term					
心臓障害	1 (2.9%)	5 (7.1%)	1 (2.3%)	6 (7.0%)	7 (6.5%)
心不全	0	2 (2.9%)	1 (2.3%)	1 (1.2%)	2 (1.9%)
心房粗動	0	0	0	1 (1.2%)	1 (0.9%)
冠動脈疾患	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
左室不全	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
動悸	0	0	0	1 (1.2%)	1 (0.9%)
右室不全	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
狭心症	1 (2.9%)	0	0	0	0
感染症および寄生虫症	2 (5.7%)	3 (4.3%)	1 (2.3%)	3 (3.5%)	4 (3.7%)
ＣＯＶＩＤ－１９	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
ＣＯＶＩＤ－１９肺炎	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
クロストリジウム菌性胃腸炎	0	0	0	1 (1.2%)	1 (0.9%)
インフルエンザ	0	1 (1.4%)	0	0	1 (0.9%)
肺炎	1 (2.9%)	0	1 (2.3%)	0	0
呼吸器、胸郭および縦隔障害	1 (2.9%)	2 (2.9%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
呼吸困難	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
肺静脈閉塞性疾患	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
喘息	1 (2.9%)	0	0	0	0
喀血	0	0	1 (2.3%)	0	0
一般・全身障害および投与部位の状態	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
胸痛	0	0	0	1 (1.2%)	1 (0.9%)
末梢腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
顔面腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
神経系障害	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
不全片麻痺	0	0	0	1 (1.2%)	1 (0.9%)
ホルネル症候群	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
脳梗塞	0	0	1 (2.3%)	0	0
血液およびリンパ系障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
胃腸障害	0	1 (1.4%)	1 (2.3%)	0	1 (0.9%)
舌嚢胞	0	1 (1.4%)	0	0	1 (0.9%)
食道潰瘍	0	0	1 (2.3%)	0	0
筋骨格系および結合組織障害	0	1 (1.4%)	0	0	1 (0.9%)
骨壊死	0	1 (1.4%)	0	0	1 (0.9%)
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）	0	0	0	1 (1.2%)	1 (0.9%)
卵巣粘液性嚢胞腺癌	0	0	0	1 (1.2%)	1 (0.9%)
生殖系および乳房障害	0	0	0	1 (1.2%)	1 (0.9%)
子宮内膜症	0	0	0	1 (1.2%)	1 (0.9%)
血管障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
低血圧	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; SAE = Serious adverse event; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE06.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE06.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の重篤な有害事象の発現割合は 24.3%（45/185 例）であった（表 2.7.4-21）。

DB-本配合剤群では，重篤な有害事象の発現割合は 27.1%（29/107 例）であった。DB-本配合剤群で 2 例以上に発現した重篤な有害事象は，COVID-19［4.7%（5/107 例）］，右室不全［2.8%（3/107 例）］，心不全，COVID-19 肺炎，肺炎，及び呼吸困難［各 1.9%（各 2/107 例）］であった。その他の重篤な有害事象の発現例数はいずれも 1 例であり，特定の傾向は認められなかった。

DB-マシテンタン群及び DB-タダラフィル群では，重篤な有害事象の発現割合はそれぞれ 20.0%（7/35 例）及び 20.9%（9/43 例）であった。DB-マシテンタン群及び DB-タダラフィル群の両群で発現した重篤な有害事象は右室不全であり，各群 1 例に認められた。その他の重篤な有害事象に特定の傾向は認められなかった。

表 2.7.4-21 重篤な有害事象（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more SAEs	7 (20.0%)	9 (20.9%)	29 (27.1%)	45 (24.3%)
System organ class Preferred term				
感染症および寄生虫症	2 (5.7%)	1 (2.3%)	13 (12.1%)	16 (8.6%)
ＣＯＶＩＤ－１９	0	0	5 (4.7%)	5 (2.7%)
肺炎	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
ＣＯＶＩＤ－１９肺炎	0	0	2 (1.9%)	2 (1.1%)
パラインフルエンザウイルス感染	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
憩室炎	1 (2.9%)	0	0	1 (0.5%)
胃腸炎	0	0	1 (0.9%)	1 (0.5%)
クロストリジウム菌性胃腸炎	0	0	1 (0.9%)	1 (0.5%)
インフルエンザ	0	0	1 (0.9%)	1 (0.5%)
ウイルス性肺炎	0	0	1 (0.9%)	1 (0.5%)
ウイルス性上気道感染	0	0	1 (0.9%)	1 (0.5%)
心臓障害	1 (2.9%)	4 (9.3%)	9 (8.4%)	14 (7.6%)
右室不全	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
心房粗動	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
心不全	0	0	2 (1.9%)	2 (1.1%)
心房細動	0	0	1 (0.9%)	1 (0.5%)
肺性心	0	1 (2.3%)	0	1 (0.5%)
冠動脈疾患	0	0	1 (0.9%)	1 (0.5%)
左室不全	0	0	1 (0.9%)	1 (0.5%)
動悸	0	0	1 (0.9%)	1 (0.5%)
洞結節機能不全	0	1 (2.3%)	0	1 (0.5%)
上室性頻脈	0	0	1 (0.9%)	1 (0.5%)
呼吸器、胸郭および縦隔障害	2 (5.7%)	1 (2.3%)	4 (3.7%)	7 (3.8%)
呼吸困難	0	0	2 (1.9%)	2 (1.1%)
肺動脈性肺高血圧症	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
低酸素症	1 (2.9%)	0	0	1 (0.5%)
気胸	0	1 (2.3%)	0	1 (0.5%)
肺静脈閉塞性疾患	0	0	1 (0.9%)	1 (0.5%)
胃腸障害	1 (2.9%)	1 (2.3%)	4 (3.7%)	6 (3.2%)
虚血性大腸炎	0	1 (2.3%)	0	1 (0.5%)
胃炎	0	0	1 (0.9%)	1 (0.5%)
痔出血	0	0	1 (0.9%)	1 (0.5%)
裂孔ヘルニア	0	1 (2.3%)	0	1 (0.5%)
亜イレウス	1 (2.9%)	0	0	1 (0.5%)
舌嚢胞	0	0	1 (0.9%)	1 (0.5%)
上部消化管出血	0	0	1 (0.9%)	1 (0.5%)
食道静脈瘤	0	0	1 (0.9%)	1 (0.5%)
生殖系および乳房障害	0	2 (4.7%)	3 (2.8%)	5 (2.7%)
子宮ポリープ	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
子宮内膜症	0	0	1 (0.9%)	1 (0.5%)
月経中間期出血	0	0	1 (0.9%)	1 (0.5%)
卵巣嚢胞破裂	0	1 (2.3%)	0	1 (0.5%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
基底細胞癌	0	1 (2.3%)	0	1 (0.5%)
乳癌	1 (2.9%)	0	0	1 (0.5%)

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
卵巣粘液性嚢胞腺癌	0	0	1 (0.9%)	1 (0.5%)
前立腺癌	0	0	1 (0.9%)	1 (0.5%)
筋骨格系および結合組織障害	2 (5.7%)	0	1 (0.9%)	3 (1.6%)
椎間板突出	1 (2.9%)	0	0	1 (0.5%)
骨壊死	0	0	1 (0.9%)	1 (0.5%)
全身性強皮症	1 (2.9%)	0	0	1 (0.5%)
血液およびリンパ系障害	0	0	2 (1.9%)	2 (1.1%)
貧血	0	0	1 (0.9%)	1 (0.5%)
正色素性貧血	0	0	1 (0.9%)	1 (0.5%)
一般・全身障害および投与部位の状態	0	0	2 (1.9%)	2 (1.1%)
胸痛	0	0	1 (0.9%)	1 (0.5%)
末梢腫脹	0	0	1 (0.9%)	1 (0.5%)
顔面腫脹	0	0	1 (0.9%)	1 (0.5%)
傷害、中毒および処置合併症	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
過量投与	0	1 (2.3%)	0	1 (0.5%)
硬膜下血腫	0	0	1 (0.9%)	1 (0.5%)
神経系障害	0	0	2 (1.9%)	2 (1.1%)
不全片麻痺	0	0	1 (0.9%)	1 (0.5%)
ホルネル症候群	0	0	1 (0.9%)	1 (0.5%)
腎および尿路障害	0	0	2 (1.9%)	2 (1.1%)
急性腎障害	0	0	1 (0.9%)	1 (0.5%)
膜性糸球体腎炎	0	0	1 (0.9%)	1 (0.5%)
眼障害	0	1 (2.3%)	0	1 (0.5%)
網膜静脈閉塞	0	1 (2.3%)	0	1 (0.5%)
肝胆道系障害	0	0	1 (0.9%)	1 (0.5%)
肝硬変	0	0	1 (0.9%)	1 (0.5%)
門脈圧亢進症	0	0	1 (0.9%)	1 (0.5%)
血管障害	0	0	1 (0.9%)	1 (0.5%)
低血圧	0	0	1 (0.9%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; SAE = Serious adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Modified from [TSFAEOL03.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL03.SAS] 02MAR2023, 08:36

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体の重篤な有害事象の発現割合は 26.5%（49/185 例）であった。二重盲検投与期＋オープンラベル投与期①の CCO 後に発現した重篤な有害事象は，肺炎，ウイルス性肺炎，呼吸困難，低酸素症，前立腺癌，大腿骨骨折，及び上腕骨骨折（各 1 例）であり，いずれも治験薬と関連なしと判断された（5.3.5.1.1-2 120DSU TSFAEOL03）。

重篤な有害事象を発現した被験者の一覧表を，M2.7.4 付録_二重盲検投与期＋オープンラベル投与期②_LSFAEOL02 に示す。

2.7.4.2.1.6 その他の重要な有害事象

(1) 治験薬の投与中止に至った有害事象

二重盲検投与期

治験薬の投与中止に至った有害事象の発現割合は本配合剤群 8.4%（9/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 4.5%（2/44 例）であった（表 2.7.4-22）。治験薬の投与中止に至った有害事象のうち，本配合剤群の 5 件（3 例）が重篤な有害事象と判断された。治験薬の投与中止に至った有害事象が認められた 3 例は未治療層であり，有害事象の内訳は，肺静脈閉塞性疾患 1 例，貧血 1 例，並びに呼吸困難，末梢腫脹，及び顔面腫脹 1 例であった（5.3.5.1.1-1 CSR LSFAE03）。

治験薬の投与中止に至った有害事象の発現割合は本配合剤群で高かったものの，2 例以上で認められた事象はなく，発現した有害事象に特定の傾向は認められなかった。

表 2.7.4-22 治験薬の投与中止に至った有害事象（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AEs leading to discontinuation of double-blind study treatment	0	7 (10.0%)	2 (4.5%)	8 (9.3%)	9 (8.4%)
System organ class Preferred term					
一般・全身障害および投与部位の状態	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
末梢性浮腫	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
末梢腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
顔面腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
臨床検査	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
ヘモグロビン減少	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
トランスアミナーゼ上昇	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
呼吸器、胸郭および縦隔障害	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
呼吸困難	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
肺静脈閉塞性疾患	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
血液およびリンパ系障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
免疫系障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
過敏症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
筋骨格系および結合組織障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
筋肉痛	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
皮膚および皮下組織障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
血管浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
血管障害	0	1 (1.4%)	0	0	1 (0.9%)
低血圧	0	1 (1.4%)	0	0	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE07.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE07.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の治験薬の投与中止に至った有害事象の発現割合は 9.2%（17/185 例）であった。

二重盲検投与期の群別の治験薬の投与中止に至った有害事象の発現割合は，DB-本配合剤群 11.2%（12/107 例），DB-マシテンタン群 11.4%（4/35 例），DB-タダラフィル群 2.3%（1/43 例）であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL04）。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

二重盲検投与期＋オープンラベル投与期①の CCO 後に，新たな治験薬の投与中止に至った有害事象は認められなかった（5.3.5.1.1-2 120DSU TSFAEOL04）。

(2) タダラフィルの減量に至った有害事象

二重盲検投与期に腎障害又は肝障害が発現した場合，タダラフィルの用量を 40 mg/日から 20 mg/日に減量した。また，安全性の面で治験担当医師がタダラフィルの減量が必要と判断した場合は，タダラフィルの用量を 40 mg/日から 20 mg/日に減量可能であった。また，オープンラベル投与期の用量調節は不可であった。

二重盲検投与期にタダラフィルの減量に至った有害事象は，本配合剤群の 2 例に認められ，その内訳は末梢性浮腫 1 例（ERA 既治療層，Day 13 にタダラフィルを減量），及び心不全 1 例（未治療層，Day 19 にタダラフィルを減量）であった（5.3.5.1.1-1 CSR LSFAE01）。心不全は日本人被験者で認められ，その要約は 2.7.4.6.1.7 に示した。

(3) 心臓障害

心臓障害（SOC）の発現割合が各単剤投与群と比較して本配合剤群で高かったことから，その他の重要な有害事象として評価した。

二重盲検投与期

心臓障害（SOC）の発現割合は，本配合剤群 15.0%（16/107 例），マシテンタン単剤投与群 5.7%（2/35 例），タダラフィル単剤投与群 9.1%（4/44 例）であった（5.3.5.1.1-1 CSR TSFAE02）。心不全の発現割合は各単剤投与群と比較して本配合剤群で高く［本配合剤群 3.7%（4/107 例），マシテンタン単剤投与群 0%，タダラフィル単剤投与群 2.3%（1/44 例），以下同順］，左室不全及び右室不全は本配合剤群の各 1 例でのみ認められた。慢性心不全はタダラフィル単剤投与群の 1 例でのみ認められた。

重篤な心臓障害に関連する有害事象は 5 例に認められ，その内訳は，心不全（本配合剤群 2 例，タダラフィル群 1 例），右室不全及び左室不全（本配合剤群各 1 例）であった。心不全の 1 例（本配合剤群）は死亡に至った。当該被験者の要約は 2.7.4.2.1.4 に示した。心不全及び右室不全（本配合剤群各 1 例）は日本人被験者で認められ，その要約は 2.7.4.6.1.7 に示した。その他の各被験者の要約を以下に記載し，叙述は 5.3.5.1.1-1 CSR Narratives に示した。

・ 本配合剤群，未治療層，重篤な有害事象：左室不全

合併症に[redacted]，[redacted]，及び[redacted]を有していた。Day 18 に中等度の左室不全が発現した。治験薬の投与は変更せず，Day 23 に左室不全は回復した。

・ タダラフィル単剤投与群，PDE5i 既治療層，重篤な有害事象：心不全

合併症に[redacted]，[redacted]，[redacted]，既往歴に[redacted]を有していた。Day 89 に重度の心不全が発現した。治験薬の投与は変更せず，Day 169 に回復した。

本配合剤群で心不全（4 例），左室不全及び右室不全（各 1 例）が認められた被験者は，未治療層 5 例，及び ERA 既治療層 1 例であった。タダラフィル単剤投与群で心不全及び慢性心不全が認められた被験者（各 1 例）はいずれも PDE5i 既治療層であった（5.3.5.1.1-1 CSR TSFAE02F）。

本配合剤群で心不全（2 例），左室不全及び右室不全（各 1 例）が認められた被験者，並びにタダラフィル単剤投与群で慢性心不全（1 例）が認められた被験者のベースライン時の年齢は 65 歳以上であった（5.3.5.1.1-1 CSR TSFAE02C）。

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の心臓障害（SOC）の発現割合は 17.3%（32/185 例）であった。DB-本配合剤群では，右室不全が 3.7%（4/107 例）に認められ，このうち 1 例は二重盲検投与期に，3 例はオープンラベル投与期に認められた（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02）。オープンラベル投与期に認められた右室不全のうち 1 例は死亡に至った

（2.7.4.2.1.4）。また，DB-マシテンタン群及び DB-タダラフィル群では各 1 例で右室不全が認められ，いずれも本配合剤投与開始から 4 週間以上経過していた（5.3.5.1.1-2 120DSU LSFAEOL01）。CSS 全体でオープンラベル投与期に新たな心不全又は左室不全は認められなかった。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体の心臓障害（SOC）の発現割合は，17.8%（33/185 例）であった。二重盲検投与期＋オープンラベル投与期①の CCO 後に右室不全が 1 例（DB-本配合剤群）に認められた（5.3.5.1.1-2 120DSU TSFAEOL02）。本事象は中等度，非重篤，治験薬の投与は変更せず，CCO 時点で未回復であった（5.3.5.1.1-2 120DSU LSFAEOL01）。

(4) 月経出血

マシテンタンの潜在的リスクであり，タダラフィルの一般的な副作用である月経出血を評価した（macitentan EU-RMP; ADCIRCA SmPC）。

二重盲検投与期

女性被験者の生殖系及び乳房障害（SOC）の発現割合は本配合剤群 6.1%（5/82 例），マシテンタン単剤投与群 3.4%（1/29 例），タダラフィル単剤投与群 2.9%（1/34 例）であった（5.3.5.1.1-1 CSR TSFAE02D）。本配合剤群で生殖系及び乳房障害（SOC）の発現が認められた女性被験者は，いずれも PDE5i 既治療層であった（5.3.5.1.1-1 CSR TSFAE02F）。月経出血に関連する有害事象は本配合剤群でのみ認められ，重度月経出血［2.4%（2/82 例）］，月経中間期出血及び膣出血［各 1.2%（各 1/82 例）］であった（5.3.5.1.1-1 CSR TSFAE02D）。

重度月経出血及び月経中間出血を発現した 3 例でヘモグロビン減少が認められた。2 例は出血の発現前からヘモグロビン減少が継続していた（1 例は出血の発現日の 8 日前，1 例は 76 日前にヘモグロビン減少が発現した）。1 例は出血の回復日の 2 日後にヘモグロビン減少が発現した。

月経出血に関連する事象では治験薬の投与中止に至った有害事象は認められず，臨床的に管理可能であった。

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体の女性被験者で認められた月経出血に関連する有害事象は，重度月経出血［2.8%（4/144 例）］，月経中間期出血，及び膣出血［各 1.4%（各 2/144 例）］，並びに頻発過多月経［0.7%（1/144 例）］であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02E）。

DB-本配合剤群の女性被験者 82 例のうち，3 例でオープンラベル投与期に月経出血に関連する有害事象が認められた。その内訳は，月経中間期出血及び膣出血（1 例），重度月経出血及び頻発過多月経（1 例），並びに重度月経出血（1 例）であった。また，DB-マシテンタン群の女性被験者 29 例のうち 1 例で月経出血に関連する有害事象（重度月経出血）が認められた。月経出血に関連する有害事象は，いずれも治験薬の投与を変更せず回復した（5.3.5.1.1-2 120DSU

LSFAEOL01）。DB-タダラフィル群では，オープンラベル投与期に月経出血に関連する有害事象は認められなかった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02E）。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

二重盲検投与期＋オープンラベル投与期①の CCO 後に新たな月経出血に関連する有害事象は認められなかった（5.3.5.1.1-2 120DSU TSFAEOL02）。

2.7.4.2.1.7 器官別又は症候群別有害事象の解析

(1) 注目すべき有害事象

1) 肝障害

二重盲検投与期

「肝障害」の発現割合は，本配合剤群 0.9%（1/107 例），マシテンタン単剤投与群 2.9%（1/35 例），タダラフィル単剤投与群 9.1%（4/44 例）であった。重篤な「肝障害」はいずれの投与群でも認められず，本配合剤群の 1 例を除き，いずれも軽度又は中等度であった。治験薬の投与中止に至った「肝障害」は，本配合剤群及びタダラフィル単剤投与群の各 1 例で認められた（表 2.7.4-23）。

治験薬の投与中止に至った「肝障害」の各被験者の要約を以下に記載する。

- 本配合剤群，PDE5i 既治療層：Day 113 に重度のトランスアミナーゼ上昇が認められ，治験薬の投与を中止した。本事象は Day 170 に回復した。
- タダラフィル単剤投与群，未治療層：Day 58 に軽度のトランスアミナーゼ上昇が認められ，Day 77 に治験薬の投与を中止した。本事象は試験完了時点で未回復であった。

表 2.7.4-23 「肝障害」の発現状況（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AESIs	1 (2.9%)	0	4 (9.1%)	1 (1.2%)	1 (0.9%)
Severity[a]					
Mild	1 (2.9%)	0	3 (6.8%)	0	0
Moderate	0	0	1 (2.3%)	0	0
Severe	0	0	0	1 (1.2%)	1 (0.9%)
Preferred term					
トランスアミナーゼ上昇	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
アラニンアミノトランスフェラーゼ増加	1 (2.9%)	0	1 (2.3%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.9%)	0	2 (4.5%)	0	0
血中アルカリホスファターゼ増加	1 (2.9%)	0	0	0	0
脂肪肝	0	0	1 (2.3%)	0	0

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Total number of recurrent AESIs	3	0	5	1	1
AESI outcome[b]					
Fatal	0	0	0	0	0
Not Recovered or Not Resolved	1 (33.3%)	0	2 (40.0%)	0	0
Recovered or Resolved	2 (66.7%)	0	2 (40.0%)	1 (100.0%)	1 (100.0%)
Recovered or Resolved with Sequelae	0	0	0	0	0
Recovering or Resolving	0	0	0	0	0
Unknown	0	0	1 (20.0%)	0	0
Subjects with 1 or more serious AESIs	0	0	0	0	0
No data to report	-	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0	0
No data to report	-	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
トランスアミナーゼ上昇	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; EOT-DB = End of treatment in double-blind treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

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二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「肝障害」の発現件数は 4.082 件であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEEAIR02）。CCO 時点までの「肝障害」の発現割合は 4.9%（9/185 例）であった（表 2.7.4-24）。

DB-本配合剤群では，「肝障害」は 5.6%（6/107 例）に認められた。このうち 1 例は二重盲検投与期，5 例はオープンラベル投与期に認められた。DB-マシテンタン群及び DB-タダラフィル群では，オープンラベル投与期に「肝障害」がそれぞれ 2.9%（1/35 例），及び 4.7%（2/43 例）に認められた。オープンラベル投与期に発現した「肝障害」はいずれも軽度又は中等度であった（表 2.7.4-24）。

表 2.7.4-24 「肝障害」の発現状況
（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs	1 (2.9%)	2 (4.7%)	6 (5.6%)	9 (4.9%)
Severity[a]				
Mild	1 (2.9%)	2 (4.7%)	2 (1.9%)	5 (2.7%)
Moderate	0	0	3 (2.8%)	3 (1.6%)
Severe	0	0	1 (0.9%)	1 (0.5%)
Preferred term				
アラニンアミノトランスフェラーゼ増加	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
Ｂ型肝炎	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
トランスアミナーゼ上昇	0	0	2 (1.9%)	2 (1.1%)
食道静脈瘤	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
血中アルカリホスファターゼ増加	0	0	1 (0.9%)	1 (0.5%)
血中ビリルビン増加	0	0	1 (0.9%)	1 (0.5%)
薬物性肝障害	0	0	1 (0.9%)	1 (0.5%)
肝硬変	0	0	1 (0.9%)	1 (0.5%)
脂肪肝	0	0	1 (0.9%)	1 (0.5%)
Ｂ型肝炎抗体異常	0	1 (2.3%)	0	1 (0.5%)
Ｃ型肝炎	0	1 (2.3%)	0	1 (0.5%)
黄疸眼	0	0	1 (0.9%)	1 (0.5%)
門脈圧亢進症	0	0	1 (0.9%)	1 (0.5%)
Total number of recurrent AESIs	2	4	15	21
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (25.0%)	10 (66.7%)	11 (52.4%)
Recovered or Resolved	2 (100.0%)	3 (75.0%)	4 (26.7%)	9 (42.9%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (6.7%)	1 (4.8%)
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (0.9%)	1 (0.5%)
肝硬変	0	0	1 (0.9%)	1 (0.5%)
門脈圧亢進症	0	0	1 (0.9%)	1 (0.5%)
食道静脈瘤	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (0.9%)	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (0.9%)	1 (0.5%)
薬物性肝障害	0	0	1 (0.9%)	1 (0.5%)
Ｂ型肝炎	1 (2.9%)	0	0	1 (0.5%)
トランスアミナーゼ上昇	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Adverse events are coded using MedDRA Version 25.1.
Modified from [TSFAEOL16.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL16.SAS] 02MAR2023, 10:29

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「肝障害」の発現件数は 3.923 件であり，二重盲検投与期＋オープンラベル投与期①と比較して同程度であった（5.3.5.1.1-2 120DSU TSFAEEAIR02）。二重盲検投与期＋オープンラベル投与期①の CCO 後に，軽度，非重篤な AST 増加が 1 例（DB-タダラフィル群）に認められた。治験薬の投与を中断し，その後回復した（5.3.5.1.1-2 120DSU TSFAEOL16，LSFAEOL07）。

2) 貧血

二重盲検投与期

「貧血」の発現割合は，各単剤投与群と比較して本配合剤群で高かった［本配合剤群 18.7%（20/107 例），マシテンタン単剤投与群 2.9%（1/35 例），タダラフィル単剤投与群 2.3%（1/44 例）］。重篤，及び治験薬の中止に至った「貧血」は本配合剤群で 0.9%（1/107 例）に認められ，各単剤投与群では認められなかった（表 2.7.4-25）。

「貧血」が認められた被験者の大半が未治療層であり，本配合剤群 11/20 例，マシテンタン単剤投与群及びタダラフィル単剤投与群各 1/1 例であった（5.3.5.1.1-1 Post hoc TSFAE24E）。

本配合剤群の「貧血」の発現割合は，未治療層と PDE5i 既治療層の間で同程度であり，ERA 既治療層で低かった［未治療層 22.4%（11/49 例），ERA 既治療層 4.8%（1/21 例），PDE5i 既治療層 21.6%（8/37）］（5.3.5.1.1-1 Post hoc TSFAE24E）。

重篤な「貧血」は日本人被験者で認められ，当該被験者の要約を 2.7.4.6.1.7 に記載した。その他の治験薬投与中止に至った「貧血」の要約を以下に記載する。

- 本配合剤群，未治療層：Day 57 に中等度，非重篤なヘモグロビン減少が発現した。Day 60～66 に治験薬の投与を中断し，Day 67 に治験薬の投与を再開した。治験薬の投与を再開した時点でヘモグロビン減少は未回復であった。Day 115 にヘモグロビン減少により治験薬の投与を中止した。二重盲検投与期の CCO 時点で，本事象は未回復であった。

表 2.7.4-25 「貧血」の発現状況（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AESIs	1 (2.9%)	12 (17.1%)	1 (2.3%)	19 (22.1%)	20 (18.7%)
Severity[a]					
Mild	1 (2.9%)	7 (10.0%)	1 (2.3%)	11 (12.8%)	12 (11.2%)
Moderate	0	5 (7.1%)	0	7 (8.1%)	7 (6.5%)
Severe	0	0	0	1 (1.2%)	1 (0.9%)
Preferred term					
貧血	0	6 (8.6%)	0	7 (8.1%)	8 (7.5%)
ヘモグロビン減少	0	3 (4.3%)	0	8 (9.3%)	8 (7.5%)
鉄欠乏性貧血	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
慢性疾患の貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
正色素性貧血	0	0	0	1 (1.2%)	1 (0.9%)
汎血球減少症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Total number of recurrent AESIs	1	15	1	22	23
AESI outcome[b]					
Fatal	0	0	0	0	0
Not Recovered or Not Resolved	1 (100.0%)	7 (46.7%)	1 (100.0%)	8 (36.4%)	9 (39.1%)
Recovered or Resolved	0	5 (33.3%)	0	6 (27.3%)	6 (26.1%)
Recovered or Resolved with Sequelae	0	0	0	0	0
Recovering or Resolving	0	1 (6.7%)	0	1 (4.5%)	1 (4.3%)
Unknown	0	2 (13.3%)	0	7 (31.8%)	7 (30.4%)
Subjects with 1 or more serious AESIs	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Subjects with 1 or more fatal AESIs	0	0	0	0	0
No data to report	-	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
ヘモグロビン減少	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; EOT-DB = End of treatment in double-blind treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE24.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE24.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「貧血」の発現件数は 23.27 件であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEEAIR02）。CCO 時点までの「貧血」の発現割合は 22.2%（41/185 例）であった（表 2.7.4-26）。

DB-本配合剤群では，「貧血」は 27.1%（29/107 例）に認められた。このうち 20 例は二重盲検投与期，9 例はオープンラベル投与期に認められた。DB-マシテンタン群及び DB-タダラフィル群では，オープンラベル投与期に「貧血」がそれぞれ 14.3%（5/35 例），及び 16.3%（7/43 例）に認められた。オープンラベル投与期に発現した「貧血」はいずれも軽度又は中等度であった（表 2.7.4-26）。

オープンラベル投与期に重篤な「貧血」は，DB-本配合剤群で 1 例に認められ（正色素性貧血），DB-マシテンタン群及び DB-タダラフィル群では認められなかった。オープンラベル投与期に治験薬の投与中止に至った「貧血」は，DB-マシテンタン群で 1 例に認められ（ヘモグロビン減少），DB-本配合剤群及び DB-タダラフィル群では認められなかった（表 2.7.4-26）。

表 2.7.4-26 「貧血」の発現状況
（二重盲検投与期+オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AESIs	5 (14.3%)	7 (16.3%)	29 (27.1%)	41 (22.2%)
Severity[a]				
Mild	3 (8.6%)	5 (11.6%)	18 (16.8%)	26 (14.1%)
Moderate	2 (5.7%)	2 (4.7%)	10 (9.3%)	14 (7.6%)
Severe	0	0	1 (0.9%)	1 (0.5%)
Preferred term				
貧血	2 (5.7%)	5 (11.6%)	12 (11.2%)	19 (10.3%)
ヘモグロビン減少	4 (11.4%)	1 (2.3%)	12 (11.2%)	17 (9.2%)
鉄欠乏性貧血	0	2 (4.7%)	6 (5.6%)	8 (4.3%)
慢性疾患の貧血	0	0	1 (0.9%)	1 (0.5%)
失血性貧血	0	0	1 (0.9%)	1 (0.5%)
骨髄線維症	0	1 (2.3%)	0	1 (0.5%)
正色素性貧血	0	0	1 (0.9%)	1 (0.5%)
汎血球減少症	0	0	1 (0.9%)	1 (0.5%)
Total number of recurrent AESIs	6	9	39	54
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	2 (33.3%)	6 (66.7%)	13 (33.3%)	21 (38.9%)
Recovered or Resolved	3 (50.0%)	3 (33.3%)	25 (64.1%)	31 (57.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (2.6%)	1 (1.9%)
Unknown	1 (16.7%)	0	0	1 (1.9%)
Subjects with 1 or more serious AESIs	0	0	2 (1.9%)	2 (1.1%)
貧血	0	0	1 (0.9%)	1 (0.5%)
正色素性貧血	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
ヘモグロビン減少	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
貧血	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
ヘモグロビン減少	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
貧血	0	0	1 (0.9%)	1 (0.5%)
正色素性貧血	0	0	1 (0.9%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Adverse events are coded using MedDRA Version 25.1.
Modified from [TSFAEOL14.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL14.SAS] 02MAR2023, 10:29

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「貧血」の発現件数は 20.90 件であり，二重盲検投与期＋オープンラベル投与期①と比較して同程度であった（5.3.5.1.1-2 120DSU TSFAEEAIR02）。二重盲検投与期＋オープンラベル投与期①の CCO 後に，汎血球減少症が 1 例（DB-マシテンタン群）に発現したが，軽度，非重篤であり治験薬の投与は変更せず回復した（5.3.5.1.1-2 120DSU TSFAEOL14, LSFAEOL05）。

3) 低血圧

二重盲検投与期

「低血圧」の発現割合は，本配合剤群では 7.5%（8/107 例）であり，各単剤投与群では認められなかった。「低血圧」はいずれも軽度又は中等度であり，重篤，及び治験薬の投与中止に至った「低血圧」は各 1 例であった（表 2.7.4-27）。

「低血圧」が認められた被験者は，未治療層 3 例，ERA 既治療層 3 例，PDE5i 既治療層 2 例であった（5.3.5.1.1-1 Post hoc TSFAE23E）。「低血圧」の発現時期は，5 例が治験薬投与開始から 4 週間以内であり，3 例が治験薬投与開始から 4 週間より後であった（5.3.5.1.1-1 CSR LSFAE08）。

重篤な「低血圧」の要約を以下に記載した。低血圧により治験薬の投与を中止し，その後，心不全により死亡に至った被験者の要約は 2.7.4.2.1.4 に記載した。

・ 本配合剤群，未治療層：Day 125 に低酸素血症を伴う COVID-19 肺炎のために入院し，Day 126 に中等度，重篤な低血圧が発現した。Day 137 から Day 138 まで治験薬の投与を中

断し，Day 138 に低血圧は回復した。治験担当医師により，低血圧は「COVID-19 肺炎に関連する自律神経機能障害」であり，治験薬と関連なしと判断された。

表 2.7.4-27 「低血圧」の発現状況（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AESIs	0	6 (8.6%)	0	5 (5.8%)	8 (7.5%)
Severity[a]					
Mild	0	4 (5.7%)	0	4 (4.7%)	6 (5.6%)
Moderate	0	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
Severe	0	0	0	0	0
Preferred term					
低血圧	0	6 (8.6%)	0	5 (5.8%)	8 (7.5%)
Total number of recurrent AESIs	0	6	0	5	8
AESI outcome[b]					
Fatal	0	0	0	0	0
Not Recovered or Not Resolved	0	1 (16.7%)	0	0	1 (12.5%)
Recovered or Resolved	0	4 (66.7%)	0	4 (80.0%)	6 (75.0%)
Recovered or Resolved with Sequelae	0	0	0	0	0
Recovering or Resolving	0	0	0	0	0
Unknown	0	1 (16.7%)	0	1 (20.0%)	1 (12.5%)
Subjects with 1 or more serious AESIs	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
低血圧	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Subjects with 1 or more fatal AESIs	0	0	0	0	0
No data to report	-	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	1 (1.4%)	0	0	1 (0.9%)
低血圧	0	1 (1.4%)	0	0	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; EOT-DB = End of treatment in double-blind treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).

Note: Adverse events are coded using MedDRA Version 25.0.

Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE23.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE23.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「低血圧」の発現件数は 5.568 件であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEEAIR02）。CCO 時点までの「低血圧」の発現割合は 6.5%（12/185 例）であった（表 2.7.4-28）。

DB-本配合剤群では，「低血圧」は 9.3%（10/107 例）に認められた。このうち 8 例は二重盲検投与期間，2 例はオープンラベル投与期に認められた。オープンラベル投与期に発現した「低血圧」はいずれも中等度，非重篤であり，治験薬の投与中止には至らなかった（表 2.7.4-28）。

DB-マシテンタン群及び DB-タダラフィル群では，オープンラベル投与期に「低血圧」がそれぞれ 1 例に認められ，いずれも軽度であった。重篤，及び治験薬の投与中止に至った「低血圧」は認められなかった（表 2.7.4-28）。

表 2.7.4-28 「低血圧」の発現状況（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AESIs	1 (2.9%)	1 (2.3%)	10 (9.3%)	12 (6.5%)
Severity[a]				
Mild	1 (2.9%)	1 (2.3%)	6 (5.6%)	8 (4.3%)
Moderate	0	0	4 (3.7%)	4 (2.2%)
Severe	0	0	0	0
Preferred term				
低血圧	1 (2.9%)	1 (2.3%)	10 (9.3%)	12 (6.5%)
Total number of recurrent AESIs	1	1	11	13
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	1 (9.1%)	1 (7.7%)
Recovered or Resolved	1 (100.0%)	1 (100.0%)	9 (81.8%)	11 (84.6%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (9.1%)	1 (7.7%)
Subjects with 1 or more serious AESIs	0	0	1 (0.9%)	1 (0.5%)
低血圧	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (0.9%)	1 (0.5%)
低血圧	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	2 (1.9%)	2 (1.1%)
低血圧	0	0	2 (1.9%)	2 (1.1%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

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二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「低血圧」の発現件数は 4.815 件であり，二重盲検投与期＋オープンラベル投与期①と比較して同程度であった（5.3.5.1.1-2 120DSU TSFAEEAIR02）。二重盲検投与期＋オープンラベル投与期①の CCO 後に，新たな「低血圧」は認められなかった（5.3.5.1.1-2 120DSU TSFAEOL13）。

4）浮腫及び体液貯留

二重盲検投与期

「浮腫及び体液貯留」の発現割合は，本配合剤群で 20.6%（22/107 例），マシテンタン単剤投与群で 14.3%（5/35 例），タダラフィル単剤投与群で 15.9%（7/44 例）であった。重篤な「浮腫及び体液貯留」は，本配合剤群で 0.9%（1/107 例）に認められ，各単剤投与群では認められなかった。治験薬の投与中止に至った「浮腫及び体液貯留」は，本配合剤群で 1.9%（2/107 例），タダラフィル単剤投与群で 2.3%（1/44 例）に認められ，マシテンタン単剤投与群では認められなかった。重度の「浮腫及び体液貯留」は本配合剤群の 1 例に認められ，その他は全て軽度又は中等度であった（表 2.7.4-29）。

「浮腫及び体液貯留」が認められた被験者大半が未治療層であり，本配合剤群 15/22 例，マシテンタン単剤投与群 5/5 例，タダラフィル単剤投与群 4/7 例であった（5.3.5.1.1-1 Post hoc TSFAE25E）。「浮腫及び体液貯留」の発現時期は，本配合剤群では 22 例のうち，18 例が治験薬投与後 4 週間以内であり，4 例が治験薬投与開始から 4 週間より後であった（5.3.5.1.1-1 CSR LSFAE10）。

重篤な「浮腫及び体液貯留」及び治験薬の投与中止に至った「浮腫及び体液貯留」の要約を以下に記載する。

- 本配合剤群，未治療層：Day 14 に重度，重篤な末梢腫脹及び顔面腫脹が発現し，フロセミドが投与された。Day 15 に治験薬の投与を中止し，Day 23 に本事象は回復した。Day 111 に COVID-19 肺炎により死亡した（2.7.4.2.1.4）。
- 本配合剤群，PDE5i 既治療層：Day 6 に中等度，非重篤な末梢性浮腫が発現し，治験薬の投与を中止した。本事象は Day 10 に回復した。
- タダラフィル単剤投与群，未治療層：Day 78 に中等度，非重篤な末梢性浮腫が発現した。オープンラベル投与期移行後に治験薬の投与を中止した。

表 2.7.4-29「浮腫及び体液貯留」の発現状況

（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Subjects with 1 or more AESIs	5 (14.3%)	17 (24.3%)	7 (15.9%)	20 (23.3%)	22 (20.6%)
Severity[a]					
Mild	4 (11.4%)	13 (18.6%)	5 (11.4%)	16 (18.6%)	16 (15.0%)
Moderate	1 (2.9%)	3 (4.3%)	2 (4.5%)	3 (3.5%)	5 (4.7%)
Severe	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Preferred term					
末梢性浮腫	4 (11.4%)	9 (12.9%)	5 (11.4%)	12 (14.0%)	14 (13.1%)
末梢腫脹	1 (2.9%)	7 (10.0%)	0	7 (8.1%)	7 (6.5%)
骨髄浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
全身性浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
体液貯留	0	0	1 (2.3%)	0	0
関節腫脹	0	0	1 (2.3%)	0	0
Total number of recurrent AESIs	6	20	8	25	27
AESI outcome[b]					
Fatal	0	0	0	0	0
Not Recovered or Not Resolved	1 (16.7%)	7 (35.0%)	4 (50.0%)	8 (32.0%)	9 (33.3%)
Recovered or Resolved	5 (83.3%)	11 (55.0%)	3 (37.5%)	13 (52.0%)	14 (51.9%)
Recovered or Resolved with Sequelae	0	0	0	0	0
Recovering or Resolving	0	0	0	0	0
Unknown	0	2 (10.0%)	1 (12.5%)	4 (16.0%)	4 (14.8%)
Subjects with 1 or more serious AESIs	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
末梢腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Subjects with 1 or more fatal AESIs	0	0	0	0	0
No data to report	-	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
末梢性浮腫	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
末梢腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; EOT-DB = End of treatment in double-blind treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFAE25.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE25.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「浮腫及び体液貯留」の発現件数は 17.21 件であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEEAIR02）。CCO 時点までの「浮腫及び体液貯留」の発現割合は 17.3%（32/185 例）であった（表 2.7.4-30）。

DB-本配合剤群では，「浮腫及び体液貯留」は，22.4%（24/107 例）に認められた。このうち 22 例は二重盲検投与期間，2 例はオープンラベル投与期に認められた。DB-マシテンタン群及び DB-タダラフィル群では，オープンラベル投与期にそれぞれ 8.6%（3/35 例）及び 11.6%（5/43 例）に認められた。これらの事象はいずれも軽度又は中等度であった。また，重篤，及び治験薬の投与中止に至った「浮腫及び体液貯留」は認められなかった（表 2.7.4-30）。

表 2.7.4-30 「浮腫及び体液貯留」の発現状況
（二重盲検投与期＋オープンラベル投与期①，CSS）

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AESIs	3 (8.6%)	5 (11.6%)	24 (22.4%)	32 (17.3%)
Severity[a]				
Mild	3 (8.6%)	4 (9.3%)	16 (15.0%)	23 (12.4%)
Moderate	0	1 (2.3%)	7 (6.5%)	8 (4.3%)
Severe	0	0	1 (0.9%)	1 (0.5%)
Preferred term				
末梢性浮腫	1 (2.9%)	3 (7.0%)	16 (15.0%)	20 (10.8%)
末梢腫脹	1 (2.9%)	0	8 (7.5%)	9 (4.9%)
浮腫	0	2 (4.7%)	0	2 (1.1%)
骨髄浮腫	0	0	1 (0.9%)	1 (0.5%)
全身性浮腫	0	0	1 (0.9%)	1 (0.5%)
血液量増加症	1 (2.9%)	0	0	1 (0.5%)
心嚢液貯留	0	0	1 (0.9%)	1 (0.5%)
腫脹	0	0	1 (0.9%)	1 (0.5%)
Total number of recurrent AESIs	3	8	32	43
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (12.5%)	9 (28.1%)	10 (23.3%)
Recovered or Resolved	3 (100.0%)	7 (87.5%)	22 (68.8%)	32 (74.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (3.1%)	1 (2.3%)
Subjects with 1 or more serious AESIs	0	0	1 (0.9%)	1 (0.5%)
末梢腫脹	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	2 (1.9%)	2 (1.1%)
末梢性浮腫	0	0	1 (0.9%)	1 (0.5%)
末梢腫脹	0	0	1 (0.9%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.
[b] Percentages are counted with respect to the total number of recurrent AESIs.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Adverse events are coded using MedDRA Version 25.1.
Modified from [TSFAEOL15.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL15.SAS] 02MAR2023, 10:29

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，本配合剤の投与期間で標準化した 100 人年あたりの「浮腫及び体液貯留」の発現件数は 15.74 件であり，二重盲検投与期＋オープンラベル投与期①と比較して同程度であった（5.3.5.1.1-2 120DSU TSFAEEAIR02）。二重盲検投与期＋オープンラベル投与期①の CCO 後，末梢性浮腫及び肺水腫が各 1 例に認められた。これらの事象はいずれも軽度であり，治験薬の投与中止に至らなかった（5.3.5.1.1-2 120DSU TSFAEOL15）。

2.7.4.2.2 個別有害事象の文章による説明

二重盲検投与期に認められた死亡，その他の重篤な有害事象，及び治験薬の投与中止に至った有害事象の叙述は治験総括報告書に記載し（5.3.5.1.1-1 CSR Narratives），二重盲検投与期＋オープンラベル投与期に認められた死亡，その他の重篤な有害事象，及び治験薬の投与中止に至った有害事象の叙述は 120 day safety update に記載した（5.3.5.1.1-2 120DSU Narratives）。日本人で認められた重篤な有害事象の要約は，2.7.4.6.1.7 に記載した。

2.7.4.3 臨床検査値の評価

本項では，二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の結果を示す。

2.7.4.3.1 血液学的検査及び血液生化学検査

2.7.4.3.1.1 血液学的検査

(1) 肝機能検査値

二重盲検投与期

ALT 又は AST の検査値異常（ULN の 3 倍以上）が認められた被験者の割合は，本配合剤群で 1.0%（1/107 例），タダラフィル単剤投与群で 4.5%（2/44 例）であり，マシテンタン単剤投与群では認められなかった（表 2.7.4-31）。ALT 又は AST が ULN の 3 倍以上であった被験者は，いずれも注目すべき有害事象の「肝障害」と判断された。当該被験者の要約を 2.7.4.2.1.7(1)1)に記載した。

表 2.7.4-31 肝機能検査値異常（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
ALT (U/L) or AST (U/L)					
N	35	63	44	82	100
ALT or AST >= 3 x ULN	0	0	2 (4.5%)	1 (1.2%)	1 (1.0%)
ALT or AST >= 5 x ULN	0	0	1 (2.3%)	1 (1.2%)	1 (1.0%)
ALT or AST >= 8 x ULN	0	0	0	1 (1.2%)	1 (1.0%)
ALT (U/L) or AST (U/L) and BILI (umol/L)[a]					
N	35	63	44	82	100
ALT or AST >= 3xULN and BILI >= 2xULN[b]	0	0	0	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BILI = Bilirubin; ULN = Upper limit of normal; EOT-DB = End of treatment in double-blind treatment period.
[a] Blood sample for ALT or AST and bilirubin collected on the same day .
[b] ALT or AST and concomitant bilirubin increased compared to baseline.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: N is the number of subjects with at least 1 postbaseline value for the specified lab tests. Subject is counted in all categories which satisfied the abnormality criteria.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

Modified from [TSFLAB11.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFLAB11.SAS] 13DEC2022, 16:53

肝機能検査値（ALT，AST，ALP 及びビリルビン）のベースラインから 16 週までの平均変化量は，以下に示すとおり，各単剤投与群と比較して本配合剤群で減少した（5.3.5.1.1-1 CSR TSFLAB01B）。

- ALT のベースラインから 16 週までの平均変化量は，本配合剤群（78 例）が-4.0 U/L，マシテンタン単剤投与群（28 例）が 0.0 U/L，タダラフィル単剤投与群（35 例）が-0.7 U/L であった。
- AST のベースラインから 16 週までの平均変化量は，本配合剤群（77 例）が-1.6 U/L，マシテンタン単剤投与群（28 例）が 0.6 U/L，タダラフィル単剤投与群（35 例）が 1.1 U/L であった。
- ALP のベースラインから 16 週までの平均変化量は，本配合剤群（80 例）が-13.3 U/L，マシテンタン単剤投与群（29 例）が-6.5 U/L，タダラフィル単剤投与群（35 例）が 5.6 U/L であった。
- ビリルビンのベースラインから 16 週までの平均変化量は，本配合剤群（81 例）が -3.486 μmol/L，マシテンタン単剤投与群（29 例）が-0.060 μmol/L，タダラフィル単剤投与群（35 例）が 1.417 μmol/L であった。

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，ALT 及び/又は AST が ULN の 8 倍以上であった被験者の割合は 1.7%（3/178 例），ALT 及び/又は AST が ULN の 5 倍以上 8 倍未満であった被験者の割合は 1.1%（2/178 例），ALT

及び/又は AST が ULN の 3 倍以上 5 倍未満であった被験者の割合は 1.1%（2/178 例）であった。Potential Hy's Law（ALT 及び／又は AST が ULN の 3 倍以上かつ総ビリルビンが ULN の 2 倍以上）に該当した被験者はいなかった（5.3.5.1.1-2 120DSU TSFLABOL03）。

(2) ヘモグロビン

二重盲検投与期

ヘモグロビン低値及びヘモグロビン減少は，各単剤投与群と比較して本配合剤群で発現割合が高かった（表 2.7.4-32）。「貧血」も各単剤投与群と比較して本配合剤群で発現割合が高く，同様の傾向であった（2.7.4.2.1.7(1)2)）。本配合剤群では，ベースラインと比較して臨床的に意味のある減少（50 g/L 以上）が 3.0%（3/100 例）に認められ，ヘモグロビン低値（80 g/L 未満）が 2.0%（2/100 例）に認められた（表 2.7.4-32）。

ヘモグロビンのベースラインから 16 週までの平均変化量は，各単剤投与群と比較して本配合剤群で大きく減少した（本配合剤群-13.9 g/L，マシテンタン単剤投与群-6.8 g/L，タダラフィル単剤投与群-0.8 g/L）（5.3.5.1.1-1 CSR TSFLAB01A）。

表 2.7.4-32 ヘモグロビン値異常（二重盲検投与期，安全性解析対象集団）

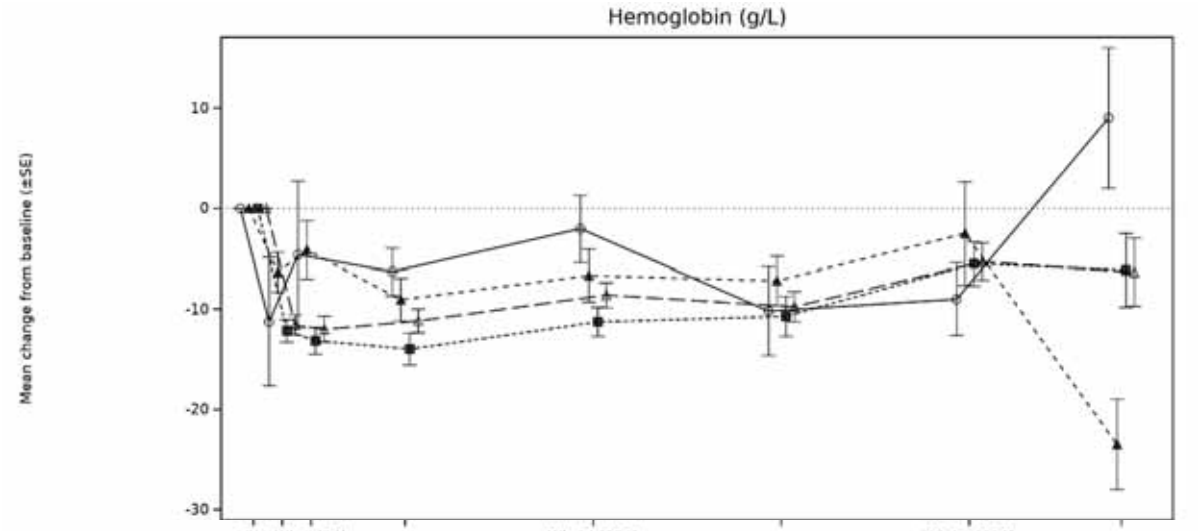
	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Hemoglobin (g/L), N	35	63	44	82	100
HGB < 100	1 (2.9%)	6 (9.5%)	0	10 (12.2%)	11 (11.0%)
HGB < 80	0	2 (3.2%)	0	2 (2.4%)	2 (2.0%)
HGB decrease from baseline >= 20 g/L	8 (22.9%)	22 (34.9%)	4 (9.1%)	40 (48.8%)	42 (42.0%)
HGB decrease from baseline >= 50 g/L	0	3 (4.8%)	0	3 (3.7%)	3 (3.0%)

Key: EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: N is the number of subjects with at least 1 postbaseline value for the hemoglobin tests. Subject is counted in all categories which satisfied the abnormality criteria.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

[TSFLAB12.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFLAB12.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，ヘモグロビン減少（ベースラインから 50 g/L 以上の減少）は 2.8%（5/177 例）に認められた。5 例のうち 3 例は二重盲検投与期，2 例はオープンラベル投与期に認められた。ヘモグロビン低値（80 g/L 未満）は，2.3%（4/177 例）に認められた。4 例のうち 2 例は二重盲検投与期，2 例はオープンラベル投与期に認められた（5.3.5.1.1-2 120DSU TSFLABOL04）。ヘモグロビン値は本配合剤の初回投与後に減少する傾向が認められた（図 2.7.4-1）。



Key: M/T FDC = Macitentan/tadalafil fixed dose combination; SE = Standard error; DB = Double-blind; OL = Open-label; EOT = End of treatment.
Note: Baseline and treatment-emergent assessments are included. Under treatment period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. Under treatment period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Baseline for DB-macitentan and DB-tadalafil is the last assessment during the DB period prior to OL M/T-FDC start.
Note: N for measured value is the number of subjects with a non-missing value for the lab test at the specified time point and at baseline. Laboratory data provided by the central laboratory are included in the table.

[GSFLABOL06.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/GSFLABOL06.SAS] 08JUN2023, 11:54

図 2.7.4-1 ヘモグロビンのベースラインからの平均変化量
（二重盲検投与期＋オープンラベル投与期②，CSS）

(3) 腎機能検査値

二重盲検投与期

eGFR の検査値異常（60 mL/min/1.73m^2 未満）が認められた被験者の割合は，投与群間で同程度であった（表 2.7.4-33）。本配合剤群の 2 例で eGFR が 30 mL/min/1.73m^2 未満であったが，いずれも治験薬の投与中止に至らなかった（5.3.5.1.1-1 CSR LSFLAB02）。このうち 1 例で，血中クレアチニン増加の有害事象が認められた。

eGFR のベースラインからの最大変化量の分布に，投与群間で大きな差はなかった（5.3.5.1.1-1 Post hoc GSFLAB05）。

本配合剤群では，腎機能障害及び血中クレアチニン増加が各 1 例，マシテンタン単剤投与群では，血中クレアチニン値増加及び糸球体濾過率減少が各 1 例に認められた。タダラフィル単剤投与群ではこれらの有害事象は認められなかった（5.3.5.1.1-1 CSR TSFAE02）。

表 2.7.4-33 腎機能検査値異常（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Creatinine (umol/L)					
N	35	63	44	82	100
CREAT > 1.5 x ULN	0	1 (1.6%)	0	1 (1.2%)	1 (1.0%)
CREAT > 3 x ULN	0	0	0	0	0
GFR from Creatinine Adjusted for BSA (mL/min/1.73m2)					
N	35	63	43	82	100
eGFR < 60 ml/min/1.73m2	4 (11.4%)	10 (15.9%)	5 (11.6%)	10 (12.2%)	11 (11.0%)
eGFR < 30 ml/min/1.73m2	0	1 (1.6%)	0	2 (2.4%)	2 (2.0%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; ULN = Upper limit of normal; EOT-DB = End of treatment in double-blind treatment period.
Note: A postbaseline marked abnormality is considered treatment-emergent if it is worse than the baseline abnormality or if baseline is missing. Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: N is the number of subjects with at least 1 postbaseline value for the specified lab test. Subject is counted in all categories which satisfied the marked abnormality criteria.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display
Modified from [TSFLAB09.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFLAB09.SAS] 13DEC2022, 16:53

二重盲検投与期＋オープンラベル投与期②（CCO：2023 年 4 月 28 日）

CSS 全体で，eGFR が 60 mL/min/1.73m^2 未満の割合は 13.8%（24/174 例）であり，30 mL/min/1.73m^2 未満の割合は 1.7%（3/174 例）であった（5.3.5.1.1-2 120DSU TSFLABOL02）。

2.7.4.4 バイタルサイン，身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1 バイタルサイン

二重盲検投与期間＋オープンラベル投与期間②までの時点で，血圧については本配合剤群の一部の被験者で顕著な拡張期血圧の低下及び注目すべき有害事象の「低血圧」が認められたものの，安全性解析対象集団及び CSS 全体としては，血圧を含むバイタルサイン，身体所見及び安全性に関連する他の観察項目の検査値及びベースラインからの変化に臨床的に意味のある所見は認められなかった（5.3.5.1.1-1 CSR TSFVIT01，5.3.5.1.1-2 120DSU TSFVITOL02）。

2.7.4.4.1.1 血圧

二重盲検投与期で，本配合剤群の 3 例で顕著な拡張期血圧の低下（拡張期血圧が 50 mmHg 未満かつベースラインから 20 mmHg 超の低下）が認められたが，治験担当医師により有害事象と判断されなかった（表 2.7.4-34）。有害事象と判断された「低血圧」は 2.7.4.2.1.7(1)3)に記載した。

血圧のベースラインから 16 週までの変化（平均値及び中央値）はいずれの投与群もわずかであった（5.3.5.1.1-1 CSR TSFVIT01）。

二重盲検投与期間＋オープンラベル投与期間②の CCO 時点で，オープンラベル投与期に新たに顕著な拡張期血圧の低下（拡張期血圧が 50 mmHg 未満かつベースラインから 20 mmHg 超の低下）は認められなかった（5.3.5.1.1-2 120DSU TSFVITOL02）。

表 2.7.4-34 血圧異常（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Systolic Blood Pressure, N	35	63	44	82	100
<90 mm Hg	3 (8.6%)	1 (1.6%)	0	2 (2.4%)	2 (2.0%)
<90 mm Hg and with >40 mm Hg decrease from baseline	0	0	0	0	0
>160 mm Hg	0	1 (1.6%)	2 (4.5%)	1 (1.2%)	1 (1.0%)
>160 mm Hg and with >20 mm Hg increase from baseline	0	1 (1.6%)	1 (2.3%)	1 (1.2%)	1 (1.0%)
Diastolic Blood Pressure, N	35	63	44	82	100
<50 mm Hg	0	2 (3.2%)	1 (2.3%)	4 (4.9%)	4 (4.0%)
<50 mm Hg and with >20 mm Hg decrease from baseline	0	2 (3.2%)	0	3 (3.7%)	3 (3.0%)
>100 mm Hg	0	0	3 (6.8%)	0	0
>100 mm Hg and with >20 mm Hg increase from baseline	0	0	3 (6.8%)	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: N is the number of subjects with at least 1 postbaseline value for the specified vital sign parameter.
Note: Abnormality categories are not mutually exclusive
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display.

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2.7.4.5 発現時期別の有害事象

CSS 全体で認められた有害事象を，本配合剤の投与開始から 12 カ月まで 3 カ月ごとに区切って集計した。CSS 全体の有害事象及び重篤な有害事象の発現割合は，12 カ月までおおむね減少する傾向が認められた。13 カ月以降の有害事象及び重篤な有害事象の発現割合が高かったのは，0～12 カ月は有害事象の集計期間が 3 カ月であるのに対し，13 カ月以降は有害事象の集計期間が 3 カ月以上であり，他の期間より長かったことが原因と考えられる（表 2.7.4-6）。治験薬の投与中止に至った有害事象は本配合剤の投与開始から 9 カ月まで減少傾向が認められ，10 カ月以降は 0 例であった。死亡に至った有害事象は発現例数が少なかったため，明確な傾向は認められなかった（表 2.7.4-35）。

12 カ月まで一貫して発現割合が増加傾向であった有害事象は認められなかった（M274 付録_二重盲検投与期＋オープンラベル投与期②_TSFAE02A）。

表 2.7.4-35 発現時期別の有害事象の概要（CSS）

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Analysis set: Combination Safety Set	185	185	180	174	161	138
Subjects with 1 or more:						
AEs	173 (93.5%)	142 (76.8%)	70 (38.9%)	60 (34.5%)	48 (29.8%)	57 (41.3%)
Related AEs [a]	69 (37.3%)	63 (34.1%)	10 (5.6%)	2 (1.1%)	1 (0.6%)	5 (3.6%)
AEs leading to death [b]	4 (2.2%)	2 (1.1%)	0	1 (0.6%)	0	1 (0.7%)
Serious AEs	49 (26.5%)	22 (11.9%)	11 (6.1%)	10 (5.7%)	6 (3.7%)	16 (11.6%)
Related serious AEs	6 (3.2%)	4 (2.2%)	1 (0.6%)	0	0	1 (0.7%)
AEs leading to premature discontinuation of study treatment	17 (9.2%)	13 (7.0%)	2 (1.1%)	2 (1.1%)	0	0

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.

[b] AEs leading to death are based on AE outcome of Fatal.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

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2.7.4.6　特別な患者集団及び状況下における安全性

2.7.4.6.1　日本人集団

本項では二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の結果を示す。

2.7.4.6.1.1　被験者の内訳，全体的な曝露，及び投与状況

二重盲検投与期に，計 8 例の日本人患者を組み入れ，本配合剤群に 6 例，マシテンタン単剤投与群に 1 例，タダラフィル単剤投与群に 1 例がランダム化された。本配合剤群の 2 例が重篤な有害事象により治験薬の投与を中止した（5.3.5.1.1-1 Japan analysis TSIDS04J）。

6 例（本配合剤群 4 例，マシテンタン単剤投与群 1 例，タダラフィル単剤投与群 1 例）が 16 週間の治験薬の投与を完了し，オープンラベル投与期に移行した。オープンラベル投与期に 3 例（DB-本配合剤群 2 例，DB-タダラフィル群 1 例）が治験薬の投与を中止し，二重盲検期＋オープンラベル投与期②の CCO 時点で 1 例が治験薬の投与を完了し，2 例が治験薬の投与を継続していた（5.3.5.1.1-2 Japan analysis TSIDSOL02CJPN，5.3.5.1.1-2 120DSU LSIDSOL01）。治験薬の投与中止理由は，1 例が有害事象（COVID-19），2 例が「その他」であった。「その他」の内訳は，1 例は治験実施計画書に規定された中止の基準である腎機能障害に合致したためであり，1 例は eGFR が 60 mL/min/1.73m^{2}未満となったためであった（5.3.5.1.1-2 120DSU LSIDSOL01）。

二重盲検期＋オープンラベル投与期②の治験薬の投与期間の中央値（範囲）は，日本人集団の CSS 全体で 28.29（1.0～105.3）週であった。二重盲検投与期の投与群別では，DB-本配合剤群 28.29（3.1～58.3）週，DB-マシテンタン群の 1 例は 105.29 週，及び DB-タダラフィル群の 1 例は 1.00 週であった（5.3.5.1.1-2 Japan analysis TSIEXOL01CJPN）。

2.7.4.6.1.2　人口統計学的特性

本配合剤群の年齢の中央値（範囲）は，75.5（5[redacted]～7[redacted]）歳，マシテンタン単剤投与群の 1 例は [redacted] 歳，タダラフィル単剤投与群の 1 例は [redacted] 歳であった。各単剤投与群の WHO FC はいずれも class III であり，本配合剤群では class II の割合が 66.7%（4/6 例），class III が 33.3%（2/6 例）であった（5.3.5.1.1-1 Japan analysis TSIDEM01J）。

2.7.4.6.1.3　前治療及び併用療法

PAH に対する前治療で分けた治療層ごとの被験者数は，本配合剤群では未治療層が 5 例，ERA 既治療層が 1 例であった。マシテンタン単剤投与群の 1 例は ERA 既治療層，タダラフィル単剤投与群の 1 例は PDE5i 既治療層であった。ERA 既治療層の 2 例が使用していた前治療薬はいずれもマシテンタンであり，PDE5i 既治療層の 1 例が使用していた前治療薬はタダラフィルであった（5.3.5.1.1-1 Japan analysis TSICM06BJ）。

2.7.4.6.1.4 有害事象の概要

二重盲検投与期の有害事象の発現割合は本配合剤群 66.7%（4/6 例），マシテンタン単剤投与群 100.0%（1/1 例），タダラフィル単剤投与群 100.0%（1/1 例）であった（5.3.5.1.1-1 Japan analysis TSFAE01J）。重篤な有害事象及び治験薬の投与中止に至った有害事象は本配合剤群で 33.3%（2/6 例）に認められ，各単剤投与群では認められなかった。死亡に至った有害事象はいずれの投与群でも認められなかった（表 2.7.4-36）。

二重盲検投与期＋オープンラベル投与期②の有害事象の発現割合は，日本人集団の CSS 全体で 100.0%（8/8 例）であった。オープンラベル投与期に新たに重篤な有害事象が 3 例，治験薬の投与中止に至った有害事象が 1 例に認められ，死亡に至った有害事象は認められなかった（5.3.5.1.1-2 Japan analysis TSFAEOL01JPN）。

表 2.7.4-36 日本人の有害事象の概要（二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	1	6	1	5	6
Subjects with 1 or more:					
AEs	1 (100.0%)	4 (66.7%)	1 (100.0%)	3 (60.0%)	4 (66.7%)
Related AEs	0	4 (66.7%)	0	3 (60.0%)	4 (66.7%)
AEs leading to death	0	0	0	0	0
Serious AEs	0	2 (33.3%)	0	2 (40.0%)	2 (33.3%)
Related serious AEs	0	2 (33.3%)	0	2 (40.0%)	2 (33.3%)
AEs leading to premature discontinuation of study treatment	0	2 (33.3%)	0	2 (40.0%)	2 (33.3%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Modified from [TSFAE01J.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TSFAE01J.SAS] 10JAN2023, 09:03

2.7.4.6.1.5 比較的よくみられる有害事象

二重盲検投与期に本配合剤群で 2 例以上に認められた有害事象は，肺炎，貧血，及び末梢性浮腫［各 33.3%（各 2/6 例）］であった。これらの事象はいずれも各単剤投与群では認められなかった（5.3.5.1.1-1 Japan analysis TSFAE02J）。

二重盲検投与期＋オープンラベル投与期②に日本人集団の CSS 全体で 2 例以上に認められた有害事象は，貧血［37.5%（3/8 例）］，肺炎，末梢性浮腫，及び不眠症［各 25.0%（各 2/8 例）］であった（5.3.5.1.1-2 Japan analysis TSFAEOL02JPN）。

2.7.4.6.1.6 死亡

二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の全期間を通して，死亡及び死亡に至った有害事象はいずれの投与群でも認められなかった。

2.7.4.6.1.7 その他の重篤な有害事象

二重盲検投与期に重篤な有害事象は本配合剤群で 33.3%（2/6 例）に認められ，各単剤投与群では認められなかった（5.3.5.1.1-1 Japan analysis TSFAE06J）。内訳は，右室不全及び肺静脈閉塞性疾患 1 例，貧血及び心不全 1 例であった。これらの要約を以下に示す。

右室不全及び肺静脈閉塞性疾患を認めた被験者（未治療層）

Day 29 に右室不全が認められ，Day 30 に入院した。同日，利尿剤（トルバプタン，フロセミド，トラセミド）及び酸素療法を開始した。右室不全は重度の重篤な有害事象と判断された。また，Day 29 に実施した胸部 CT 検査にて肺炎像が認められたことから，肺炎（非重篤な有害事象）を併発していると判断され，Day 30 から抗菌剤（セフトリアキソンナトリウム）の投与を開始した。Day 34 に肺炎は回復した。Day 40 に気管支肺胞洗浄を伴う気管支鏡検査を実施した。Day 47 に検査結果が判明し，肺静脈性閉塞疾患が強く疑われたため，同日治験薬の投与を中止し，盲検を解除した。肺静脈性閉塞疾患は重度の重篤な有害事象と判断された。PAH 治療薬（マシテンタン及びタダラフィル）の急な中止，及びマシテンタン 10 mg／タダラフィル 40 mg 併用による過度の血管拡張のいずれも患者にとって好ましくないため，Day 48 から，マシテンタンを 10 mg/日，タダラフィルを 20 mg/日の用量で投与を継続した。病状が安定したため，Day 56 に退院した。Day 82 時点で引き続き病状は安定していたため追跡調査を終了した。転帰は，右室不全が軽快，肺静脈閉塞性疾患が未回復であった。

治験担当医師により，右室不全は治験薬と関連あり，肺静脈閉塞性疾患は治験薬と関連なしと判断された。右室不全は，主な原因は原疾患悪化に伴うものであり併発した肺炎も原因の一つと考えられるが，治験薬投与中であり因果関係は否定できない，との治験担当医師見解であった。

貧血及び心不全を認めた被験者（未治療層）

Day 15 に心不全が認められ，重度の重篤な有害事象と判断された。同日，経口利尿剤（アゾセミド及びスピロノラクトン）の投与を開始した。Day 18 に呼吸不全及び酸素飽和度の悪化が認められ，心不全の治療のため入院した。また，同日経口利尿剤（アゾセミド）を静注利尿剤（フロセミド）に切り替えた。Day 19 に肺炎（中等度の非重篤な有害事象）が認められ，抗生剤（アンピシリン／スルバクタム）の投与を開始した。Day 19 から Day 22 まで治験薬をマシテンタン 10 mg/日及びタダラフィル 20 mg/日の併用投与に減量した。Day 22 に貧血（ヘモグロビン値：75 g/L，正常範囲：120～160 g/L）が認められ，中等度の重篤な有害事象と判断された。同日，本事象（貧血）のため治験薬の投与を中止した。Day 28 に浮腫症状の改善が認められ，静注利尿剤（フロセミド）の投与を終了した。Day 30 に肺炎は回復し，Day 33 に心不全は回復した。貧血は，Day 30 で改善が認められなかったため，クエン酸第一鉄ナトリウムの投与を開始し，Day 33 及び Day 40 に赤血球輸血を実施した。Day 42 に貧血の改善が認められ，Day 43 に退院した。Day 193 に貧血は回復した（ヘモグロビン値：109 g/L）。貧血及び心不全は，いずれも治験薬投与開始後に発現しており，治験責任医師により治験薬と関連ありと判断された。

二重盲検投与期＋オープンラベル投与期②に重篤な有害事象は，日本人集団の CSS 全体で 62.5%（5/8 例）に認められた（5.3.5.1.1-2 Japan analysis TSFAEOL03JPN）。このうち，3 例がオ

ープンラベル投与期に新たに発現した。これらの要約を以下に示す（5.3.5.1.1-2 Japan analysis LSFAEOL01JPN）。

- DB-本配合剤群，未治療層，重篤な有害事象：硬膜下血腫

  Day 218 に中等度の重篤な硬膜下血腫が発現した。治験薬の投与を変更することなく，本事象は Day 231 に回復した。治験担当医師により，本事象は治験薬と関連なしと判断された。

- DB-本配合剤群，ERA 既治療層，重篤な有害事象：COVID-19

  Day 267 に重度の重篤な COVID-19 が発現し，同日に治験薬の投与を中止した。本事象は Day 296 に回復した。治験担当医師により，本事象は治験薬と関連なしと判断された。

- DB-マシテンタン群：ERA 既治療層，重篤な有害事象：椎間板突出

  Day 428 に重度の重篤な椎間板突出が発現した。治験薬の投与を変更することなく，本事象は Day 488 に回復した。治験担当医師により，本事象は治験薬と関連なしと判断された。

2.7.4.6.1.8 その他の重要な有害事象

二重盲検投与期に治験薬の投与中止に至った有害事象は本配合剤群の 33.3%（2/6 例）に認められ，各単剤投与群では認められなかった（5.3.5.1.1-1 Japan analysis TSFAE07J）。内訳は肺静脈閉塞性疾患 1 例，貧血 1 例であり，いずれも重篤な有害事象と同一事象であった。

二重盲検投与期＋オープンラベル投与期②の新たな治験薬の投与中止に至った有害事象は COVID-19 であり，重篤な有害事象と同一事象であった（5.3.5.1.1-2 Japan analysis TSFAEOL04JPN）。

二重盲検投与期に心臓障害（SOC）は本配合剤群の 33.3%（2/6 例），タダラフィル単剤投与群 100%（1/1 例）に認められ，マシテンタン投与群では認められなかった。本配合剤群の 2 例の内訳は心不全及び右室不全各 1 例であり，いずれも重篤な有害事象と同一事象であった。タダラフィル単剤投与群の 1 例は慢性心不全であった（5.3.5.1.1-1 Japan analysis TSFAE02J）。

二重盲検投与期＋オープンラベル投与期②に新たな心臓障害（SOC）は認められなかった（5.3.5.1.1-2 Japan analysis TSFAEOL02JPN）。

二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の全期間を通して月経出血に関連する有害事象はいずれの投与群でも認められなかった（5.3.5.1.1-1 Japan analysis TSFAE02J, 5.3.5.1.1-2 Japan analysis TSFAEOL02JPN）。

2.7.4.6.1.9 器官別又は症候群別有害事象の解析

(1) 注目すべき有害事象

二重盲検投与期に「貧血」は本配合剤群で 33.3%（2/6 例）に認められた。このうち 1 例は未治療層であり，重篤な「貧血」であった。残りの 1 例は ERA 既治療層であり，非重篤な「貧血」

であった。各単剤投与群で「貧血」は認められなかった（5.3.5.1.1-1 Japan analysis TSFAE24AJ, TSFAE24J）。

二重盲検投与期＋オープンラベル投与期②に，「貧血」は 37.5%（3/8 例）に認められた。オープンラベル投与期に認められた新たな「貧血」は，DB-マシテンタン群の 1 例で認められ，軽度，非重篤であった（5.3.5.1.1-2 Japan analysis TSFAEOL14JPN）。

二重盲検投与期に「浮腫及び体液貯留」は本配合剤群で 33.3%（2/6 例）に認められ，未治療層及び ERA 既治療層各 1 例であった。「浮腫及び体液貯留」は各単剤投与群では認められなかった。重篤な「浮腫及び体液貯留」はいずれの投与群でも認められなかった（5.3.5.1.1-1 Japan analysis TSFAE25AJ，TSFAE25J）。

二重盲検投与期＋オープンラベル投与期②に，新たな「浮腫及び体液貯留」は認められなかった（5.3.5.1.1-2 Japan analysis TSFAEOL15JPN）。

二重盲検投与期に「低血圧」はいずれの投与群でも認められなかった（5.3.5.1.1-1 Japan analysis TSFAE23AJ，TSFAE23J）。

二重盲検投与期＋オープンラベル投与期②に，中等度，非重篤な「低血圧」が DB-本配合剤群の 1 例に認められ，治験薬投与を変更することなく回復した（5.3.5.1.1-2 Japan analysis TSFAEOL13JPN）。

二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の全期間を通して「肝障害」はいずれの投与群でも認められなかった（5.3.5.1.1-1 Japan analysis TSFAE26AJ，TSFAE26J, 5.3.5.1.1-2 Japan analysis TSFAEOL16JPN）。

2.7.4.6.1.10 PAH に対する前治療別の有害事象

二重盲検投与期に有害事象が発現した被験者は，本配合剤群では未治療層が 3 例，ERA 既治療層が 1 例であった。また，マシテンタン単剤投与群の 1 例は ERA 既治療層，タダラフィル単剤投与群の 1 例は PDE5i 既治療層であった。重篤な有害事象及び治験薬の投与中止に至った有害事象は，本配合剤群の未治療層のみに認められた［各 40.0%（2/5 例）］（5.3.5.1.1-1 Japan analysis TSFAE01AJ）。

2.7.4.6.1.11 血液学的検査及び血液生化学検査

二重盲検投与期に AST 及び／又は ALT 異常が認められた被験者はいなかった（5.3.5.1.1-1 Japan analysis TSFLAB11J）。

二重盲検投与期＋オープンラベル投与期②に AST 異常は認められなかった。ALT が ULN の 3 倍以上となった被験者が 1 例認められたが，有害事象と判断されなかった（5.3.5.1.1-2 Japan analysis TSFAEOL02JPN，TSFLABOL03JPN）。

二重盲検投与期にベースラインと比較して臨床的に意味のあるヘモグロビン減少（50 g/L 以上減少）及びヘモグロビン低値（80 g/L 未満）はそれぞれ本配合剤群の 16.7%（1/6 例）で認められ，各単剤投与群では認められなかった（5.3.5.1.1-1 Japan analysis TSFLAB12J）。

二重盲検投与期＋オープンラベル投与期②にベースラインと比較して臨床的に意味のあるヘモグロビン減少は新たに認められなかった（5.3.5.1.1-2 Japan analysis TSFLABOL04JPN）。

二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の全期間を通してビリルビン及びクレアチニン値に異常が認められた被験者はいなかった（5.3.5.1.1-1 Japan analysis TSFLAB09J, 5.3.5.1.1-2 Japan analysis TSFLABOL02JPN）。

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

二重盲検投与期＋オープンラベル投与期②の CCO 時点で，拡張期血圧が 90 mmHg 未満（1 例）が認められたものの，治験担当医師により有害事象と判断されなかった。二重盲検投与期及び二重盲検投与期＋オープンラベル投与期②の全期間を通して，バイタルサイン，身体所見及び安全性に関連する他の観察項目で日本人集団特有の所見は認められなかった（5.3.5.1.1-2 Japan analysis TSFVITOL02JPN）。

2.7.4.6.2 内因性要因

年齢，性別，及び人種は二重盲検投与期及び二重盲検投与期＋オープンラベル投与期①の結果を示す。腎機能は二重盲検投与期＋オープンラベル投与期①の結果を示す。

2.7.4.6.2.1 年齢

<u>二重盲検投与期</u>

本配合剤群及び各単剤投与群では，いずれも 18～64 歳と比較して 65 歳以上が少なかった（18～64 歳：本配合剤群 87 例，マシテンタン単剤投与群 27 例，タダラフィル単剤投与群 34 例，65 歳以上：本配合剤群 20 例，マシテンタン単剤投与群 8 例，タダラフィル単剤投与群 10 例）（5.3.5.1.1-1 CSR TSFAE02C）。

本配合剤群では，18～64 歳と比較して 65 歳以上で有害事象の発現割合が高かった［18～64 歳：80.5%（70/87 例），65 歳以上：90.0%（18/20 例）］。本配合剤群では，心臓障害（SOC）及び筋骨格系および結合組織障害（SOC）の有害事象は，18～64 歳［それぞれ 12.6%（11/87 例）及び 19.5%（17/87 例）］と比較して 65 歳以上［各 25.0%（5/20 例）］で発現割合が高かった（5.3.5.1.1-1 CSR TSFAE02C）。また，「貧血」及び「浮腫及び体液貯留」も 18～64 歳［それぞれ 16.1%（14/87 例）及び 17.2%（15/87 例）］と比較して 65 歳以上［それぞれ 30.0%（6/20 例）及び 35.0%（7/20 例）］で発現割合が高かった（5.3.5.1.1-1 post-hoc TSFAE24C，TSFAE25C）。このように，65 歳以上で発現割合の高い有害事象が認められたものの，一般的な加齢で認められる所見と同様であると考えられ，いずれの部分集団でも新たな安全性の懸念は認められなかった。

本配合剤群の 18～64 歳で，発現割合が 25%超の有害事象（SOC）は，胃腸障害，及び神経系障害［各 26.4%（23/87 例）］，並びに一般・全身障害および投与部位の状態［25.3%（22/87 例）］であった。本配合剤群の 18～64 歳で，発現割合が 10%超の有害事象（PT）は，頭痛（17.2%）であった（5.3.5.1.1-1 CSR TSFAE02C）。

本配合剤群の 65 歳以上で，発現割合が 25%超の有害事象（SOC）は，一般・全身障害および投与部位の状態［40.0%（8/20 例）］，感染症および寄生虫症［35.0%（7/20 例）］，血液およびリンパ系障害［30.0%（6/20 例）］であった。本配合剤群の 65 歳以上で，発現割合が 10%超の有害事象（PT）は，末梢性浮腫（30.0%），貧血（25.0%），及び頭痛（15.0%）であった。これら

の有害事象の本配合剤群の 18～64 歳での発現割合は，それぞれ 9.2%，3.4%，及び 17.2%であった（5.3.5.1.1-1 CSR TSFAE02C）。

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で年齢別の部分集団で新たな安全性の懸念は特定されなかった。年齢ごとに集計した有害事象の表を 2.7.4 付録に含めた（有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02D，重篤な有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL03D，「肝障害」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL16D，「貧血」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL14D，「低血圧」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL13D，「浮腫及び体液貯留」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL15D）。

2.7.4.6.2.2 性別

二重盲検投与期

本配合剤群及び各単剤投与群では，いずれも女性と比較して男性は少なかった（女性：本配合剤群 82 例，マシテンタン単剤投与群 29 例，タダラフィル単剤投与群 34 例，男性：本配合剤群 25 例，マシテンタン単剤投与群 6 例，タダラフィル単剤投与群 10 例）（5.3.5.1.1-1 CSR TSFAE02D）。

本配合剤群の有害事象の発現割合は，女性と男性で同程度であった［女性 82.9%（68/82 例），男性 80.0%（20/25 例）］（5.3.5.1.1-1 CSR TSFAE02D）。いずれの部分集団でも新たな安全性の懸念は認められなかった。

本配合剤群の女性で，発現割合が 25%超の有害事象（SOC）は，一般・全身障害および投与部位の状態［29.3%（24/68 例）］，並びに胃腸障害［26.8%（22/68 例）］であった。本配合剤群の女性で，発現割合が 10%超の有害事象（PT）は，頭痛（17.1%）及び末梢性浮腫（14.6%）であった。これらの有害事象（PT）の本配合剤群の男性での発現割合は，それぞれ 16.0%及び 8.0%であった。

本配合剤群の男性で，発現割合が 25%超の有害事象（SOC）は，感染症および寄生虫症，神経系障害，並びに呼吸器，胸郭および縦隔障害であった［各 28.0%（各 7/20 例）］。本配合剤群の男性で，発現割合が 10%超の有害事象（PT）は，頭痛（16.0%），COVID-19（12.0%），浮動性めまい（12.0%）及び発熱（12.0%）であった。これらの有害事象（PT）の本配合剤群の女性での発現割合は，それぞれ 17.1%，0%，0%及び 1.2%であった。

本配合剤群の「貧血」の発現割合は，女性 19.5%（16/82 例）及び男性 16.0%（4/25 例）であった（5.3.5.1.1-1 post-hoc TSFAE24B）。

本配合剤群の「浮腫及び体液貯留」の発現割合は，男性 16.0%（4/25 例）と比較して女性 22.0%（18/82 例）で高かった（5.3.5.1.1-1 post-hoc TSFAE25B）。

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で性別の部分集団で新たな安全性の懸念は認められなかった。性別ごとに集計した有害事象の表を 2.7.4 付録に含めた（有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02E，重篤な有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL03E，「肝障害」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL16E，「貧血」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL14E，「低血圧」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL13E，「浮腫及び体液貯留」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL15E）。

2.7.4.6.2.3 人種

二重盲検投与期

本配合剤群及び各単剤投与群では，いずれも白人が最も多く，次にアジア人が多かった［白人：本配合剤群 66 例，マシテンタン単剤投与群 20 例，タダラフィル単剤投与群 29 例（以下同順），アジア人：36 例，12 例，11 例，黒人又はアフリカ系アメリカ人：2 例，1 例，2 例，その他：1 例，0 例，0 例］（5.3.5.1.1-1 CSR TSFAE02E）。被験者数の多かった白人とアジア人の結果について要約した。黒人又はアフリカ系アメリカ人，その他の人種については，被験者数が 10 例未満であったため結論を出すことはできなかった。

本配合剤群の白人とアジア人での有害事象の発現割合は同程度であった［白人：84.8%（56/66 例），アジア人：75.0%（27/36 例）］（5.3.5.1.1-1 CSR TSFAE02E）。いずれの部分集団でも新たな安全性の懸念は認められなかった。

本配合剤群の白人で，発現割合が 25%超の有害事象（SOC）は，胃腸障害，一般・全身障害および投与部位の状態［各 28.8%（19/66 例）］，及び神経系障害［27.3%（18/66 例）］であった。本配合剤群の白人で，発現割合が 10%超の有害事象（PT）は，頭痛（21.2%），末梢性浮腫（15.2%）及び低血圧（12.1%）であった。

本配合剤群のアジア人で，発現割合が 25%超の有害事象（SOC）は，一般・全身障害および投与部位の状態［30.6%（11/36 例）］，並びに呼吸器，胸郭および縦隔障害［27.8%（10/36 例）］であった。本配合剤群のアジア人で，発現割合が 10%超の有害事象（PT）は，貧血（11.1%），末梢性浮腫及び筋肉痛（各 11.1%）であった。

本配合剤群の「貧血」の発現割合は，白人［15.2%（10/66 例）］と比較してアジア人［25.0%（9/36 例）］で高かった（5.3.5.1.1-1 post-hoc TSFAE24D）。

本配合剤群の「浮腫及び体液貯留」の発現割合は，白人［24.2%（16/66 例）］と比較してアジア人［16.7%（6/36 例）］で低かった（5.3.5.1.1-1 post-hoc TSFAE25D）。

二重盲検投与期＋オープンラベル投与期①（CCO：2022 年 12 月 31 日）

CSS 全体で人種別の部分集団で新たな安全性の懸念は特定されなかった。人種ごとに集計した有害事象の表を 2.7.4 付録に含めた（有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02F，重篤な有害事象：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL03F，「肝障害」：M274 付録_二重盲検投与期＋オープンラベル投与期①

_TSFAEOL16F，「貧血」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL14F，「低血圧」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL13F，「浮腫及び体液貯留」：M274 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL15F）。

2.7.4.6.2.4 腎機能

CSS について，ベースライン時の腎機能障害別に事後解析した。本解析での腎機能障害の定義は，障害なし（eGFR：90 mL/min/1.73 m^2 以上），軽度障害（eGFR：60 mL/min/1.73 m^2 以上 90 mL/min/1.73 m^2 未満），中等度障害（eGFR：30 mL/min/1.73 m^2 以上 60 mL/min/1.73 m^2 未満），重度障害（eGFR：30 mL/min/1.73 m^2 未満）とした。CSS（185 例）のベースライン時の腎機能障害の内訳は，障害なし 77 例，軽度障害 81 例，中等度障害 26 例であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL01R）。治験実施計画書の規定に従い，ベースライン時に重度の腎障害を有する被験者は組み入れられなかった。

中等度障害［96.2%（25/26 例）］及び障害なし［90.9%（70/77 例）］の間で，有害事象の発現割合に 5%以上の差が認められた。有害事象を SOC 別，PT 別に検討した結果，各部分集団で有害事象の発現に特定の傾向は認められなかった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL02R）。

重篤な有害事象の発現割合は，障害なしと比較して，軽度障害及び中等度障害で高かった［障害なし：14.3%（11/77 例），軽度障害：32.1%（26/81 例），中等度：30.8%（8/26 例）］（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL07R）。各部分集団で重篤な有害事象の発現割合に明確な差は認められなかった。治験薬の投与中止に至った有害事象の発現割合は，各部分集団で同様であった（M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL09R）。

腎機能障害の程度別の注目すべき有害事象の発現割合は，「肝機能障害」，「貧血」，「低血圧」，及び「浮腫及び体液貯留」をそれぞれ，M2.7.4 付録_二重盲検投与期＋オープンラベル投与期①_TSFAEOL16R，TSFAEOL14R，TSFAEOL13R，及び TSFAEOL15R に示した。

2.7.4.6.3 外因性要因

本配合剤の安全性プロファイルに対する喫煙及び飲酒の影響を評価する臨床試験は実施していない。

2.7.4.6.3.1 PAH に対する前治療

本項では二重盲検投与期の結果を示す。

(1) 治療層別の有害事象

PAH に対する前治療で分けた治療層ごとの被験者数は，未治療層では本配合剤群 49 例，マシテンタン単剤投与群 24 例，タダラフィル単剤投与群 25 例，ERA 既治療層では本配合剤群 21 例，マシテンタン単剤投与群 11 例，PDE5i 既治療層では本配合剤群 37 例，タダラフィル単剤投与群 19 例であった（5.3.5.1.1-1 CSR TSIDEM02a）。有害事象の発現割合は，未治療層では本配合剤群

87.8%（43/49 例），マシテンタン単剤投与群 70.8%（17/24 例），タダラフィル単剤投与群 80.0%（20/25 例）であった。ERA 既治療層では本配合剤群 76.2%（16/21 例），マシテンタン単剤投与群 72.7%（8/11 例）であった。PDE5i 既治療層では本配合剤群 78.4%（29/37 例），タダラフィル単剤投与群 78.9%（15/19 例）であった（表 2.7.4-37）。

本配合剤群では，ERA 及び PDE5i 既治療層と比較して未治療層で，有害事象，重篤な有害事象，及び治験薬の投与中止に至った有害事象の発現割合が高かった［有害事象：未治療層 87.8%（43/49 例），ERA 既治療層 76.2%（16/21 例），PDE5i 既治療層 78.4%（29/37 例），以下同順，重篤な有害事象：16.3%（8/49 例），14.3%（3/21 例），10.8%（4/37 例），治験薬の投与中止に至った有害事象：12.2%（6/49 例），4.8%（1/21 例），5.4%（2/37 例）］。死亡に至った有害事象は，ERA 及び PDE5i 既治療層の各 1 例で認められた（表 2.7.4-37）。

表 2.7.4-37 PAH に対する前治療別の有害事象の概要

（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Safety	24	25	49	11	21	19	37
Subjects with 1 or more:							
AEs	17 (70.8%)	20 (80.0%)	43 (87.8%)	8 (72.7%)	16 (76.2%)	15 (78.9%)	29 (78.4%)
Related AEs [a]	8 (33.3%)	8 (32.0%)	23 (46.9%)	3 (27.3%)	10 (47.6%)	3 (15.8%)	14 (37.8%)
AEs leading to death [b]	0	0	0	0	1 (4.8%)	0	1 (2.7%)
Serious AEs	2 (8.3%)	3 (12.0%)	8 (16.3%)	1 (9.1%)	3 (14.3%)	1 (5.3%)	4 (10.8%)
Related serious AEs	0	0	3 (6.1%)	0	0	0	0
AEs leading to premature discontinuation of study treatment	0	2 (8.0%)	6 (12.2%)	0	1 (4.8%)	0	2 (5.4%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.

[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.

[b] AEs leading to death are based on AE outcome of Fatal.

Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).

[TSFAE01A.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_JAPAN/PROD/TSFAE01A.SAS] 03FEB2023, 01:30

本配合剤群の未治療層の治験薬の投与中止に至った有害事象は，5/6 例が二重盲検投与期の治験薬投与開始から 4 週間以内に発現した（5.3.5.1.1-1 CSR LSFAE01）。

本配合剤群の未治療層で発現割合が 10%以上の有害事象は，頭痛［16.3%（8/49 例）］，末梢性浮腫及び末梢腫脹［各 14.3%（各 7/49 例）］，貧血及び咳嗽［各 10.2%（各 5/49 例）］であった。発現割合が 5%以上 10%未満の有害事象は，下痢［8.2%（4/49 例）］，消化不良［8.2%（4/49 例）］，並びに背部痛，心不全，潮紅，ヘモグロビン減少，高尿酸血症，低血圧，筋肉痛，悪心，及び嘔吐［各 6.1%（各 3/49 例）］であった（5.3.5.1.1-1 CSR TSFAE02F）。

本配合剤群の ERA 既治療層で発現割合が 10%以上の有害事象は，頭痛（19.0%［4/21 例］）及び低血圧（14.3%［3/21 例］）であった。本配合剤群の PDE5i 既治療層で発現割合が 10%以上の有害事象は，頭痛［16.2%（6/37 例）］，ヘモグロビン減少及び末梢性浮腫［各 13.5%（各 5/37 例）］であった（5.3.5.1.1-1 CSR TSFAE02F）。

本配合剤群での注目すべき有害事象の発現状況について以下に示す。

- 「肝障害」は PDE5i 既治療層で治験薬の投与中止に至った事象が 1 例に認められた（2.7.4.2.1.7(1)1)）。
- 「貧血」の発現割合は，未治療層及び PDE5i 既治療層で同程度であり，ERA 既治療層で低かった［未治療層 22.4%（11/49 例），ERA 既治療層 4.8%（1/21 例），PDE5i 既治療層 21.6%（8/37 例）］（5.3.5.1.1-1 post hoc TSFAE24E）。
- 「低血圧」の発現割合は，未治療層及び PDE5i 既治療層と比較して ERA 既治療層で高かった［未治療層 6.1%（3/49 例），ERA 既治療層 14.3%（3/21 例），PDE5i 既治療層 5.4%（2/37 例）］（5.3.5.1.1-1 post hoc TSFAE23E）。
- 「浮腫及び体液貯留」の発現割合は，ERA 及び PDE5i 既治療層と比較して未治療層で高かった［未治療層 30.6%（15/49 例），ERA 既治療層 9.5%（2/21 例），PDE5i 既治療層は 13.5%（5/37 例）］（5.3.5.1.1-1 post hoc TSFAE25E）。

(2) 薬剤別の有害事象

層別因子となる PAH に対する前治療の薬剤の内訳は，ERA 既治療層では，ボセンタン 4 例，マシテンタン 9 例，及びアンブリセンタン 7 例であり，PDE5i 既治療層では，シルデナフィル 31 例及びタダラフィル 4 例であった。本配合剤群の PAH に対する前治療の薬剤別の有害事象の発現割合は，ERA 既治療層では，ボセンタン 50.0%（2/4 例），マシテンタン 88.9%（8/9 例），及びアンブリセンタン 85.7%（6/7 例）であり，PDE5i 既治療層では，シルデナフィル 74.2%（23/31 例），及びタダラフィル 100.0%（4/4 例）であった。死亡に至った有害事象の 2 例の PAH に対する前治療の内訳は，アンブリセンタン 1 例及びシルデナフィル 1 例であり，いずれも治験薬との因果関係はなしと判断された。本配合剤群の PAH に対する前治療の薬剤別の重篤な有害事象の発現割合は，ERA 既治療層では，ボセンタン 25.0%（1/4 例），マシテンタン 0%，及びアンブリセンタン 28.6%（2/7 例），PDE5i 既治療層では，シルデナフィル 12.9%（4/31 例）及びタダラフィル 0%であり，いずれも治験薬との因果関係はなしと判断された。治験薬の投与中止に至った有害事象は，ERA 既治療層では，アンブリセンタン 14.3%（1/7 例），ボセンタン及

びマシテンタン 0%であり，PDE5i 既治療層では，シルデナフィル 6.5%（2/31 例）及びタダラフィル 0%であった（表 2.7.4-38）。

各薬剤で有害事象の発現割合にばらつきが認められたものの，各薬剤の被験者数が少ないことに起因すると考えられる。また，マシテンタン及びタダラフィルを投与していた患者では，死亡に至った有害事象，重篤な有害事象，及び治験薬の投与中止に至った有害事象は認められなかったものの，その他のいずれの薬剤も 1～4 例と少数であったため，これらの有害事象の発現割合に明確な傾向は認められず，PAH に対する前治療について薬剤別の安全性の懸念は認められなかった。

表 2.7.4-38 PAH に対する前治療（薬剤別）の有害事象の概要（二重盲検投与期，安全性解析対象集団）

	Treatment-naïve			Prior ERA strata						Prior PDE-5i strata			
				Macitentan			M/T FDC			Tadalafil		M/T FDC	
	Macitentan	Tadalafil	M/T FDC	Bosentan	Macitentan	Ambrisentan	Bosentan	Macitentan	Ambrisentan	Sildenafil	Tadalafil	Sildenafil	Tadalafil
Analysis set: Safety	24	25	49	2	4	3	4	9	7	13	4	31	4
Subjects with 1 or more:													
AEs	17 (70.8%)	20 (80.0%)	43 (87.8%)	1 (50.0%)	3 (75.0%)	2 (66.7%)	2 (50.0%)	8 (88.9%)	6 (85.7%)	9 (69.2%)	4 (100.0%)	23 (74.2%)	4 (100.0%)
Related AEs [a]	8 (33.3%)	8 (32.0%)	23 (46.9%)	0	1 (25.0%)	2 (66.7%)	1 (25.0%)	5 (55.6%)	4 (57.1%)	2 (15.4%)	1 (25.0%)	12 (38.7%)	1 (25.0%)
AEs leading to death [b]	0	0	0	0	0	0	0	0	1 (14.3%)	0	0	1 (3.2%)	0
Serious AEs	2 (8.3%)	3 (12.0%)	8 (16.3%)	0	0	0	1 (25.0%)	0	2 (28.6%)	1 (7.7%)	0	4 (12.9%)	0
Related serious AEs	0	0	3 (6.1%)	0	0	0	0	0	0	0	0	0	0
AEs leading to premature discontinuation of study treatment	0	2 (8.0%)	6 (12.2%)	0	0	0	0	0	1 (14.3%)	0	0	2 (6.5%)	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.

[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.

[b] AEs leading to death are based on AE outcome of Fatal.

Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).

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2.7.4.6.3.2 地理的地域

アジアを除き，地域別の各部分集団の本配合剤群の被験者数は 20 例未満であった（アジア：49 例，北米：14 例，ラテンアメリカ：10 例，東ヨーロッパ：19 例，南西ヨーロッパ：14 例，及びアフリカ 1 例）（5.3.5.1.1-1 CSR TSFAE02A）。いずれの部分集団でも新たな安全性の懸念は認められなかった。

2.7.4.6.4 薬物相互作用

本配合剤の薬物相互作用の評価については【2.7.2】に示した。

2.7.4.6.5 妊娠及び授乳時の使用

マシテンタンは妊婦に対して禁忌である。A DUE 試験では妊娠中，授乳中又は妊娠を予定している女性は試験の対象から除外した。また，妊娠する可能性のある女性は，スクリーニングから治験薬投与中止 30 日後まで有効な避妊方法を用いることに同意していた。しかし，A DUE 試験で 1 例の妊娠が認められた。当該被験者はオープンラベル投与期の本配合剤投与中に妊娠し，妊娠のため Day 278 に治験薬の投与を中止した。Day 293 に人工妊娠中絶手術を受け，Day 320 に試験を中止した（5.3.5.1.1-2 120DSU Narratives）。

2.7.4.6.6 過量投与

A DUE 試験では，過量投与は認められなかった。

2.7.4.6.7 薬物乱用

A DUE 試験では，薬物乱用及び依存性の可能性に関連した有害事象は認められなかった。

2.7.4.6.8 離脱症状及び反跳現象

A DUE 試験では，離脱症状及び反跳現象を検討しなかった。

2.7.4.6.9 自動車運転及び機械操作に対する影響又は精神機能の障害

自動車運転及び機械操作に対する影響に関する試験は実施していないものの，A DUE 試験では，本配合剤群で疲労，浮動性めまい，無力症及び霧視といった自動車運転及び機械操作に対する影響を及ぼす可能性がある有害事象が認められた（5.3.5.1.1-1 CSR TSFAE18）。本配合剤の国内添付文書（案）の重要な基本的注意で，高所作業，自動車の運転等危険を伴う機械操作について注意喚起する予定である。

2.7.4.7 市販後データ

2021 年 9 月 11 日（国際誕生日：2021 年 10 月 14 日）から 2022 年 9 月 10 日までの Periodic Benefit Risk Evaluation Report を M5.3.6.1 に含めた。

2022 年 9 月 10 日までに本配合剤は，カナダ及びアルゼンチンで，マシテンタン 10 mg 及びタダラフィル 40 mg の各単剤を併用投与している PAH 患者を対象として承認されている。

カナダでは，2021 年 9 月 11 日から 2022 年 9 月 10 日までに 9 例の患者が市販品の本配合剤を投与された。アルゼンチンでは，2022 年 9 月 10 日時点で本配合剤を投与された患者はいない。

2022 年 9 月 10 日までに重篤な有害事象は認められなかった。また，本配合剤の市販後の安全性データを検討した結果，新たな安全性の懸念は認められなかった。本配合剤の安全性プロファイルは，各単剤の臨床試験で確立されたプロファイルと同様であった。

参考文献

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OPSUMIT®(macitentan) European Union Risk Management Plan (EU-RMP) 22 Nov 2021. Version number 13.1

2.7.4　付録

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LSFAE02: Listing of Serious Adverse Events in the Double-blind Period; Safety Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last DB Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
Treatment-naive/ Macitentan 10mg			/ M/	NA/10mg/34	狭心症/ Paroxygenic Cardiac Chest Pain	37		/ 19	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/	NA/10mg/45	COVID-19肺炎/ Covid Pneumonia	45		/ 6	Recovered/ Resolved/ Drug Interrupted	Severe/ Not Related	Y
				NA/10mg/79	喘息/ Asthma Exacerbation	79		/ 7	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
Treatment-naive/ Tadalafil 40 mg			/ M/	40mg/NA/58	食道潰瘍/ Esophageal Ulcer	58		/ 10	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	Y
				40mg/NA/59	脳梗塞/ Cerebral Infarction	59			Recovering/ Resolving/ Dose Not Changed	Severe/ Not Related	Y
			/ M/	40mg/NA/29	喀血/ Haemoptysis Worsening	29		/ 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/		/ (No Further Information)			/ 6	Recovered/ Resolved/ Not Applicable	Moderate/ Not Related	
			/ F/	20mg/NA/5	肺炎/ Pneumonia	5		/ 5	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/		/			/ 5	Recovered/ Resolved/ Not Applicable	Mild/ Not Related	
Treatment-naive/ M/T FDC			/ M/	40mg/10mg/ 104	COVID-19肺炎/ Covid 19 Pneumonia	104		/ 39	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 126	低血圧/ Hypotension	126		/ 13	Recovered/ Resolved/ Drug Interrupted	Moderate/ Not Related	Y
			/ M/	40mg/10mg/ 95	COVID-19/ Covid-19	95		/ 29	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/	40mg/10mg/ 118	ホルネル症候群/ Horner Syndrome	118			Not Recovered/ Not Resolved/ Dose Not Changed	Mild/ Not Related	Y

LSFAE02: Listing of Serious Adverse Events in the Double-blind Period; Safety Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last DB Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
	[redacted]	[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 18	左室不全/ Mild Decompensation Of The Left Heart	18	[redacted]	[redacted] / 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted] /	40mg/10mg/ 51	冠動脈疾患/ Single Vessel Disease	51	[redacted]	[redacted] / 3	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted] /	40mg/10mg/ 29	右室不全/ Right Heart Failure	29	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Related	Y
				40mg/10mg/ 47	肺静脈閉塞性疾患/ Pulmonary Veno-Occlusive Disease	47	[redacted]		Not Recovered/ Not Resolved/ Drug Withdrawn	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 15	心不全/ Heart Failure	15	[redacted]	[redacted] / 19	Recovered/ Resolved/ Dose Reduced	Severe/ Related	Y
				20mg/10mg/ 22	貧血/ Anemia	22	[redacted]	[redacted] / 172	Recovered/ Resolved/ Drug Withdrawn	Moderate/ Related	Y
		[redacted]	[redacted] / F/ [redacted] /		[redacted]	[redacted]	[redacted]	[redacted] / 76	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 14	呼吸困難/ Dyspnoe	14	[redacted]	[redacted] / 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	末梢腫脹/ Swelling Of The Limbs	14	[redacted]	[redacted] / 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	顔面腫脹/ Swelling Of The Face	14	[redacted]	[redacted] / 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	心不全/ Heart Failure	86	[redacted]	[redacted] / 14	Recovered/ Resolved/ Not Applicable	Severe/ Not Related	
				40mg/10mg/ 14	COVID-19肺炎/ Pneumonia Due To Covid-19	100	[redacted]		Fatal/ Not Applicable	Severe/ Not Related	
				40mg/10mg/ 14	急性呼吸不全/ Acute Respiratory Failure	111	[redacted]		Not Recovered/ Not Resolved/ Not Applicable	Severe/ Not Related	
		[redacted]	[redacted] / F/ [redacted] /		[redacted] / [redacted]	[redacted]	[redacted]	[redacted] / 4	Recovered/ Resolved/ Not Applicable	Moderate/ Not Related	
Prior ERA/ Macitentan 10mg		[redacted]	[redacted] / M/ [redacted] /	NA/10mg/24	肺炎/ Bronchopneumonia	24	[redacted]	[redacted] / 15	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	Y

LSFAE02: Listing of Serious Adverse Events in the Double-blind Period; Safety Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last DB Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
Prior ERA/ M/T FDC	[redacted]	[redacted]	[redacted] / F/ [redacted] /	20mg/10mg/ 4	心不全/ Worsening Of Hf	19	[redacted]		Fatal/ Not Applicable	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 77	インフルエンザ/ Flu Syndrome	77	[redacted]	[redacted] / 13	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 79	骨壊死/ Ostonecrosis	79	[redacted]		---/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 86	舌嚢胞/ Tongue Root Cyst	86	[redacted]	[redacted] / 3	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
Prior PDE-5i/ Tadalafil 40 mg		[redacted]	[redacted] / F/ [redacted] /	40mg/NA/89	心不全/ Heart Failure Exacerbation	89	[redacted]		---/ Dose Not Changed	Severe/ Not Related	Y
Prior PDE-5i/ M/T FDC		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/ 104	クロストリジウム菌性胃腸炎/ Gastoenteritis C. Difficile	104	[redacted]		Fatal/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 53	心房粗動/ Atrial Flutter	53*	[redacted]*		---/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 76	胸痛/ Acute Episode Of Chest Pain (No Further Information)	76	[redacted]	[redacted] / 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	呼吸困難/ Acute Episode Of Dyspnoea	76	[redacted]	[redacted] / 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	不全片麻痺/ Transient Hemiparesis Of Uncertain Mechanism	76	[redacted]	[redacted] / 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	動悸/ Acute Episode Of Palpitation	76	[redacted]	[redacted] / 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 27	子宮内膜症/ Endometriosis	27	[redacted]	[redacted] / 6	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 42	卵巣粘液性嚢胞腺癌/ Ovarian Mucinous Carcinoma G2	42	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted] /	40mg/10mg/ 6	心房中隔欠損症/ Confirmed Patent Foramen Ovale 2.0 Mm With Left-Right Reset.	85	[redacted]	[redacted] / 6	Recovered/ Resolved/ Not Applicable	Mild/ Not Related	

LSFAE02: Listing of Serious Adverse Events in the Double-blind Period; Safety Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last DB Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; EOT-DB = End of treatment in double-blind treatment period; * = imputed date, day, or duration.
[a] Day of last administration of study treatment prior to AE onset.
[b] Day of last administration of study treatment (prior to the AE) and Day of AE Onset are in reference to the first study treatment administration.
[c] Relationship to study treatment is assessed by the investigator.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: Adverse events are coded using MedDRA Version 25.0.

[LSFAE02.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PREPROD/LSFAE02.SAS] 16DEC2022, 14:26

LSIDS01: Listing of Subjects Who Discontinued Double-blind Study Treatment Prematurely; All Randomized Analysis Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race	Last Visit[a]	Study Day[b] of Last DB Study Treatment Administered	Date of Treatment Discontinuation	Primary Reason for Treatment Discontinuation	Preferred Term	Stage
Treatment-naive/ Tadalafil 40 mg			/F/	Premature EDBT Unscheduled Visit 1	78		Adverse Event	Elevated Transaminases	2
Treatment-naive/ M/T FDC			34/F/White	Visit 4 - Week 2 - Day 15	24		Lack of Efficacy		1
			/F/	Visit 4 - Week 2 - Day 15	23		Withdrawal by Subject: Study Treatment Contains Too Much Pills		1
			/F/	Premature EDBT Unscheduled Visit 1	11		Adverse Event	Myalgia	1
			/M/	Visit 5 - Week 4 - Day 29 Unscheduled Visit 1	47		Adverse Event	Pulmonary Veno-Occlusive Disease	2
			/F/	Visit 5 - Week 4 - Day 29 Unscheduled Visit 3	36		Adverse Event	Anemia	2
			/F/	Visit 4 - Week 2 - Day 15	15		Adverse Event	Swelling of The Face	1
			61/F/	Visit 4 - Week 2 - Day 15	15		Non-Compliance with Study Drug		1
			/F/	Premature EDBT Unscheduled Visit 1	5		Adverse Event	Angioedema	1
			/F/	Visit 7 - Week 12	115		Adverse Event	Decreased Hgb	1
Prior ERA/ M/T FDC			/F/	Visit 2 - Day 1	4		Adverse Event	Hypotension	1
			58/F/White	Visit 5 - Week 4 - Day 29	45		Withdrawal by Subject: Lack of Transportation		1
			54/F/	Visit 2 - Day 1	7		Withdrawal by Subject: Due to Adverse Event (Back Pain). Death		1
Prior PDE-5i/ M/T FDC			/M/	Survival Follow-Up	105				2
			/F/	Visit 3 - Week 1 - Day 8	6		Adverse Event	Edema of The Lower Extremities	1
			/F/	Visit 7 - Week 12	113		Adverse Event	Liver Tramsaminase Elevation	2
			34/F/White	Visit 6 - Week 8	77		Other: Relocation of Patient to Turkey Due to Regional Crisis		2

Listing Page 1 of 2

LSIDS01: Listing of Subjects Who Discontinued Double-blind Study Treatment Prematurely; All Randomized Analysis Set (Study AC-077A301)

Stratum/ Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race	Last Visit[a]	Study Day[b] of Last DB Study Treatment Administered	Date of Treatment Discontinuation	Primary Reason for Treatment Discontinuation	Preferred Term	Stage

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; DB = Double-blind.
[a] Last visit is the last visit which the subject attended before discontinuing DB study treatment.
[b] Study day is relative to the first study treatment administration.
Note: A subject will be considered as discontinuing the double-blind study treatment prematurely if the subject discontinues treatment prior to Visit 8/Week 16.

[LSIDS01.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/LSIDS01.SAS] 13DEC2022, 16:45

TSFAE02T: Number of Subjects With Treatment-emergent Adverse Events in the Double-blind Period by System Organ Class and Preferred Term, during the first part of titration phase; Safety Set (Study AC-077A301)

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Safety	24	25	48	11	21	19	37
Subjects with 1 or more AEs	7 (29.2%)	10 (40.0%)	27 (56.3%)	3 (27.3%)	13 (61.9%)	5 (26.3%)	12 (32.4%)
System organ class Preferred term							
筋骨格系および結合組織障害	1 (4.2%)	4 (16.0%)	4 (8.3%)	0	5 (23.8%)	1 (5.3%)	0
関節痛	1 (4.2%)	2 (8.0%)	0	0	0	0	0
背部痛	0	1 (4.0%)	0	0	2 (9.5%)	0	0
四肢痛	0	1 (4.0%)	0	0	1 (4.8%)	0	0
筋力低下	0	0	0	0	1 (4.8%)	0	0
筋骨格系胸痛	0	0	0	0	0	1 (5.3%)	0
筋骨格痛	0	0	0	0	1 (4.8%)	0	0
筋肉痛	0	0	3 (6.3%)	0	2 (9.5%)	0	0
顎痛	0	0	1 (2.1%)	0	0	0	0

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
One participant was excluded from the analysis as she mistakenly took M/T FDC tablets as soon as day 1 and did not undergo titration part.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to:
- for M/T FDC and Tadalafil patients not previously treated by PDE-5i: first day (excluded) of treatment with Tadalafil 40mg (as monotherapy or FDC) for participants who uptitrate, and up to EOT-DB + 30 days for patients who do not uptitrate
- for Macitentan and M/T FDC or Tadalafil patients previously treated by PDE-5i: first intake of study + 7 days (included)
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

TSFAE02T: Number of Subjects With Treatment-emergent Adverse Events in the Double-blind Period by System Organ Class and Preferred Term, during the first part of titration phase; Safety Set (Study AC-077A301)

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
一般・全身障害および投与部位の状態	3 (12.5%)	2 (8.0%)	10 (20.8%)	0	1 (4.8%)	0	1 (2.7%)
非心臓性胸痛	0	1 (4.0%)	0	0	0	0	0
末梢性浮腫	1 (4.2%)	1 (4.0%)	4 (8.3%)	0	0	0	1 (2.7%)
無力症	0	0	1 (2.1%)	0	0	0	0
疲労	1 (4.2%)	0	0	0	1 (4.8%)	0	0
疼痛	0	0	1 (2.1%)	0	0	0	0
末梢腫脹	1 (4.2%)	0	2 (4.2%)	0	0	0	0
発熱	0	0	1 (2.1%)	0	0	0	0
腫脹	0	0	1 (2.1%)	0	0	0	0
顔面腫脹	0	0	1 (2.1%)	0	0	0	0
口渇	0	0	0	0	0	0	1 (2.7%)
神経系障害	2 (8.3%)	2 (8.0%)	8 (16.7%)	2 (18.2%)	4 (19.0%)	1 (5.3%)	5 (13.5%)
頭痛	2 (8.3%)	2 (8.0%)	6 (12.5%)	2 (18.2%)	4 (19.0%)	1 (5.3%)	4 (10.8%)
浮動性めまい	0	0	1 (2.1%)	0	0	0	1 (2.7%)
労作性めまい	0	0	1 (2.1%)	0	0	0	0
労作性頭痛	0	0	1 (2.1%)	0	0	0	0
耳および迷路障害	0	1 (4.0%)	0	0	0	0	0
回転性めまい	0	1 (4.0%)	0	0	0	0	0

TSFAE02T: Number of Subjects With Treatment-emergent Adverse Events in the Double-blind Period by System Organ Class and Preferred Term, during the first part of titration phase; Safety Set (Study AC-077A301)

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
胃腸障害	1 (4.2%)	1 (4.0%)	7 (14.6%)	1 (9.1%)	4 (19.0%)	1 (5.3%)	4 (10.8%)
下痢	0	1 (4.0%)	1 (2.1%)	0	0	0	0
消化不良	0	1 (4.0%)	3 (6.3%)	0	0	0	0
嘔吐	0	1 (4.0%)	1 (2.1%)	0	0	0	1 (2.7%)
腹部不快感	1 (4.2%)	0	0	0	0	0	0
便秘	0	0	1 (2.1%)	1 (9.1%)	0	0	0
口内乾燥	0	0	0	0	0	0	2 (5.4%)
鼓腸	0	0	1 (2.1%)	0	0	0	0
胃炎	0	0	0	0	0	0	1 (2.7%)
胃腸障害	0	0	1 (2.1%)	0	0	0	0
痔核	0	0	0	0	1 (4.8%)	0	0
腰ヘルニア	0	0	0	0	1 (4.8%)	0	0
悪心	0	0	0	0	2 (9.5%)	1 (5.3%)	1 (2.7%)
食道炎	0	0	0	0	0	0	1 (2.7%)
肝胆道系障害	0	1 (4.0%)	0	0	0	0	0
脂肪肝	0	1 (4.0%)	0	0	0	0	0
感染症および寄生虫症	0	1 (4.0%)	1 (2.1%)	0	0	1 (5.3%)	1 (2.7%)
肺炎	0	1 (4.0%)	0	0	0	0	0
上咽頭炎	0	0	0	0	0	0	1 (2.7%)
咽頭炎	0	0	0	0	0	1 (5.3%)	0
歯膿瘍	0	0	1 (2.1%)	0	0	0	0
生殖系および乳房障害	0	1 (4.0%)	0	1 (9.1%)	0	0	0
卵巣嚢胞	0	1 (4.0%)	0	0	0	0	0
閉経期症状	0	0	0	1 (9.1%)	0	0	0

TSFAE02T: Number of Subjects With Treatment-emergent Adverse Events in the Double-blind Period by System Organ Class and Preferred Term, during the first part of titration phase; Safety Set (Study AC-077A301)

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
心臓障害	0	0	2 (4.2%)	1 (9.1%)	1 (4.8%)	0	0
心不全	0	0	1 (2.1%)	0	1 (4.8%)	0	0
動悸	0	0	0	1 (9.1%)	0	0	0
頻脈	0	0	1 (2.1%)	0	0	0	0
眼障害	1 (4.2%)	0	1 (2.1%)	0	0	1 (5.3%)	2 (5.4%)
眼瞼痙攣	0	0	0	0	0	1 (5.3%)	0
眼瞼浮腫	0	0	1 (2.1%)	0	0	0	1 (2.7%)
眼窩周囲浮腫	0	0	0	0	0	0	2 (5.4%)
霧視	1 (4.2%)	0	0	0	0	0	0
免疫系障害	0	0	1 (2.1%)	0	0	0	0
過敏症	0	0	1 (2.1%)	0	0	0	0
傷害、中毒および処置合併症	1 (4.2%)	0	1 (2.1%)	1 (9.1%)	0	0	0
節足動物刺傷	1 (4.2%)	0	0	0	0	0	0
皮膚創傷	0	0	0	1 (9.1%)	0	0	0
歯牙破折	0	0	1 (2.1%)	0	0	0	0
臨床検査	3 (12.5%)	0	1 (2.1%)	0	1 (4.8%)	0	0
血中アルカリホスファターゼ増加	1 (4.2%)	0	0	0	0	0	0
血中鉄減少	1 (4.2%)	0	0	0	0	0	0
血中尿酸異常	0	0	0	0	1 (4.8%)	0	0
心雑音	0	0	1 (2.1%)	0	0	0	0
体重増加	1 (4.2%)	0	0	0	0	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (4.2%)	0	0	0	0	0	0
扁平上皮癌	1 (4.2%)	0	0	0	0	0	0

TSFAE02T: Number of Subjects With Treatment-emergent Adverse Events in the Double-blind Period by System Organ Class and Preferred Term, during the first part of titration phase; Safety Set (Study AC-077A301)

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
精神障害	0	0	0	0	0	1 (5.3%)	0
不安	0	0	0	0	0	1 (5.3%)	0
呼吸器、胸郭および縦隔障害	1 (4.2%)	0	2 (4.2%)	0	2 (9.5%)	2 (10.5%)	2 (5.4%)
咳嗽	0	0	0	0	0	1 (5.3%)	0
咽喉乾燥	0	0	0	0	0	1 (5.3%)	0
呼吸困難	0	0	1 (2.1%)	0	0	1 (5.3%)	0
労作性呼吸困難	1 (4.2%)	0	0	0	0	0	1 (2.7%)
鼻閉	0	0	1 (2.1%)	0	1 (4.8%)	0	1 (2.7%)
アレルギー性鼻炎	0	0	0	0	1 (4.8%)	0	0
皮膚および皮下組織障害	1 (4.2%)	0	1 (2.1%)	0	1 (4.8%)	0	0
血管浮腫	0	0	1 (2.1%)	0	0	0	0
発疹	1 (4.2%)	0	0	0	1 (4.8%)	0	0
血管障害	2 (8.3%)	0	2 (4.2%)	0	2 (9.5%)	0	1 (2.7%)
潮紅	2 (8.3%)	0	2 (4.2%)	0	0	0	0
低血圧	0	0	0	0	2 (9.5%)	0	1 (2.7%)

[TSFAE02T.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSFAE02T.SAS] 21DEC2022, 13:15

TSFAEEAIR02: Overall Summary of Treatment-emergent Adverse Events of Special Interest adjusted for observation time; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata			
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	DB/OL M/T FDC (Total)
Analysis set: Combination Safety Set	35	43	107	185
Hypotension AESI				
Subjects with at least one AE	1 (2.9%)	1 (2.3%)	10 (9.3%)	12 (6.5%)
Subject-Years of Exposure (SYE)[a]	38.2	49.5	127.7	215.5
Exposure Adjusted Incidence Rate (EAIR) per 100 SYE[b]	2.615	2.019	7.829	5.568
95% CL[c]	(0.37, 18.56)	(0.28, 14.33)	(4.21, 14.55)	(3.16, 9.80)
Anemia AESI				
Subjects with at least one AE	5 (14.3%)	7 (16.3%)	29 (27.1%)	41 (22.2%)
Subject-Years of Exposure (SYE)[a]	36.2	41.5	98.5	176.2
Exposure Adjusted Incidence Rate (EAIR) per 100 SYE[b]	13.80	16.87	29.44	23.27
95% CL[c]	(5.75, 33.16)	(8.04, 35.38)	(20.46, 42.37)	(17.13, 31.60)
Edema and Fluid Retention AESI				
Subjects with at least one AE	3 (8.6%)	5 (11.6%)	24 (22.4%)	32 (17.3%)
Subject-Years of Exposure (SYE)[a]	36.2	43.1	106.7	186.0
Exposure Adjusted Incidence Rate (EAIR) per 100 SYE[b]	8.290	11.61	22.49	17.21
95% CL[c]	(2.67, 25.71)	(4.83, 27.89)	(15.08, 33.56)	(12.17, 24.33)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period; SYE = Subject-years of exposure; CL = Confidence Limit.

[a] Subject-years of exposure is calculated as (sum of subject-observation time for all subjects / 365.25 days). The subject-observation time is calculated by considering the study treatment duration for participants without event or by considering the study treatment duration up to the date of first event (or up to the study treatment end date, if earlier) for participants with event.

[b] Exposure adjusted incidence rate is calculated as 100 * (number of participants with at least a treatment-emergent event/ subject-years of exposure).

[c] Confidence limits are based on Poisson regression model.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

TSFAEEAIR02: Overall Summary of Treatment-emergent Adverse Events of Special Interest adjusted for observation time; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	All strata			
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	DB/OL M/T FDC (Total)
Hepatic Disorders AESI				
Subjects with at least one AE	1 (2.9%)	2 (4.7%)	6 (5.6%)	9 (4.9%)
Subject-Years of Exposure (SYE)[a]	39.1	47.9	133.5	220.5
Exposure Adjusted Incidence Rate (EAIR) per 100 SYE[b]	2.556	4.179	4.494	4.082
95% CL[c]	(0.36, 18.14)	(1.05, 16.71)	(2.02, 10.00)	(2.12, 7.84)

[TSFAEEAIR02.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEEAIR02.SAS] 02MAR2023, 08:36

TSFAEOL01R: Overall Summary of Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more:				
AEs	70 (90.9%)	74 (91.4%)	25 (96.2%)	170 (91.9%)
Related AEs [a]	28 (36.4%)	27 (33.3%)	12 (46.2%)	68 (36.8%)
AEs leading to death [b]	1 (1.3%)	0	2 (7.7%)	3 (1.6%)
Serious AEs	11 (14.3%)	26 (32.1%)	8 (30.8%)	45 (24.3%)
Related serious AEs	1 (1.3%)	4 (4.9%)	1 (3.8%)	6 (3.2%)
AEs leading to premature discontinuation of study treatment	8 (10.4%)	7 (8.6%)	2 (7.7%)	17 (9.2%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.

[b] AEs leading to death are based on AE outcome of Fatal.

Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.

Note: One subject with missing baseline eGFR is only included in the Total column.

Note: Renal impairment is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

[TSFAEOL01R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL01R.SAS] 20APR2023, 11:09

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AEs	31 (88.6%)	38 (88.4%)	101 (94.4%)	170 (91.9%)
System organ class				
Preferred term				

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	19 (54.3%)	20 (46.5%)	50 (46.7%)	89 (48.1%)
ＣＯＶＩＤ－１９	6 (17.1%)	8 (18.6%)	25 (23.4%)	39 (21.1%)
上気道感染	3 (8.6%)	4 (9.3%)	5 (4.7%)	12 (6.5%)
尿路感染	1 (2.9%)	3 (7.0%)	5 (4.7%)	9 (4.9%)
上咽頭炎	1 (2.9%)	2 (4.7%)	4 (3.7%)	7 (3.8%)
肺炎	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
インフルエンザ	0	0	5 (4.7%)	5 (2.7%)
副鼻腔炎	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
ＣＯＶＩＤ－１９肺炎	0	0	3 (2.8%)	3 (1.6%)
蜂巣炎	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
口腔ヘルペス	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
気管支炎	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
結膜炎	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
Ｂ型肝炎	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
限局性感染	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
パラインフルエンザウイルス感染	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
鼻炎	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
ＣＯＶＩＤ－１９の疑い	2 (5.7%)	0	0	2 (1.1%)
急性副鼻腔炎	0	0	1 (0.9%)	1 (0.5%)
真菌性肛門感染	0	0	1 (0.9%)	1 (0.5%)
細菌感染	0	0	1 (0.9%)	1 (0.5%)
体部白癬	1 (2.9%)	0	0	1 (0.5%)
細菌性気管支炎	0	0	1 (0.9%)	1 (0.5%)
カンジダ感染	0	1 (2.3%)	0	1 (0.5%)
子宮頚管炎	0	0	1 (0.9%)	1 (0.5%)
慢性扁桃炎	0	0	1 (0.9%)	1 (0.5%)
サイトメガロウイルス性脈絡網膜炎	0	0	1 (0.9%)	1 (0.5%)
憩室炎	1 (2.9%)	0	0	1 (0.5%)
子宮内膜炎	0	0	1 (0.9%)	1 (0.5%)
胃腸炎	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
クロストリジウム菌性胃腸炎	0	0	1 (0.9%)	1 (0.5%)
消化管感染	0	0	1 (0.9%)	1 (0.5%)
陰部ヘルペス	0	0	1 (0.9%)	1 (0.5%)
歯肉炎	0	0	1 (0.9%)	1 (0.5%)
血液学的感染	0	0	1 (0.9%)	1 (0.5%)
Ｃ型肝炎	0	1 (2.3%)	0	1 (0.5%)
帯状疱疹	0	0	1 (0.9%)	1 (0.5%)
食道カンジダ症	0	0	1 (0.9%)	1 (0.5%)
中耳炎	0	1 (2.3%)	0	1 (0.5%)
耳管炎	0	0	1 (0.9%)	1 (0.5%)
歯冠周囲炎	0	0	1 (0.9%)	1 (0.5%)
咽頭炎	0	1 (2.3%)	0	1 (0.5%)
細菌性咽頭炎	1 (2.9%)	0	0	1 (0.5%)
咽頭扁桃炎	0	1 (2.3%)	0	1 (0.5%)
細菌性肺炎	0	0	1 (0.9%)	1 (0.5%)
シュードモナス性肺炎	0	1 (2.3%)	0	1 (0.5%)
ブドウ球菌性肺炎	0	1 (2.3%)	0	1 (0.5%)
ウイルス性肺炎	0	0	1 (0.9%)	1 (0.5%)
急性ＣＯＶＩＤ－１９後症候群	0	0	1 (0.9%)	1 (0.5%)
気道感染	0	0	1 (0.9%)	1 (0.5%)
ウイルス性気道感染	1 (2.9%)	0	0	1 (0.5%)
卵管卵巣炎	0	0	1 (0.9%)	1 (0.5%)
歯膿瘍	0	0	1 (0.9%)	1 (0.5%)
腟感染	0	1 (2.3%)	0	1 (0.5%)
ウイルス感染	0	0	1 (0.9%)	1 (0.5%)
ウイルス性上気道感染	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	8 (22.9%)	8 (18.6%)	37 (34.6%)	53 (28.6%)
嘔吐	0	2 (4.7%)	7 (6.5%)	9 (4.9%)
悪心	0	1 (2.3%)	7 (6.5%)	8 (4.3%)
下痢	0	1 (2.3%)	6 (5.6%)	7 (3.8%)
胃炎	3 (8.6%)	0	4 (3.7%)	7 (3.8%)
腹部不快感	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
腹痛	0	0	4 (3.7%)	4 (2.2%)
消化不良	0	0	4 (3.7%)	4 (2.2%)
胃食道逆流性疾患	3 (8.6%)	0	1 (0.9%)	4 (2.2%)
痔出血	0	0	4 (3.7%)	4 (2.2%)
便秘	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
口内乾燥	0	0	3 (2.8%)	3 (1.6%)
痔核	0	0	3 (2.8%)	3 (1.6%)
上腹部痛	0	0	2 (1.9%)	2 (1.1%)
小腸炎	0	0	2 (1.9%)	2 (1.1%)
鼓腸	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
食道炎	0	0	2 (1.9%)	2 (1.1%)
歯痛	0	0	2 (1.9%)	2 (1.1%)
食道静脈瘤	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
腹部膨満	0	0	1 (0.9%)	1 (0.5%)
肛門出血	0	1 (2.3%)	0	1 (0.5%)
慢性胃炎	1 (2.9%)	0	0	1 (0.5%)
大腸炎	0	0	1 (0.9%)	1 (0.5%)
虚血性大腸炎	0	1 (2.3%)	0	1 (0.5%)
排便回数増加	1 (2.9%)	0	0	1 (0.5%)
胃障害	0	1 (2.3%)	0	1 (0.5%)
胃腸障害	0	0	1 (0.9%)	1 (0.5%)
裂孔ヘルニア	0	1 (2.3%)	0	1 (0.5%)
腰ヘルニア	0	0	1 (0.9%)	1 (0.5%)
口腔内潰瘍形成	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
亜イレウス	1 (2.9%)	0	0	1 (0.5%)
舌嚢胞	0	0	1 (0.9%)	1 (0.5%)
上部消化管出血	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	13 (37.1%)	7 (16.3%)	31 (29.0%)	51 (27.6%)
関節痛	3 (8.6%)	2 (4.7%)	6 (5.6%)	11 (5.9%)
筋肉痛	3 (8.6%)	1 (2.3%)	7 (6.5%)	11 (5.9%)
背部痛	2 (5.7%)	1 (2.3%)	7 (6.5%)	10 (5.4%)
四肢痛	1 (2.9%)	1 (2.3%)	5 (4.7%)	7 (3.8%)
椎間板突出	2 (5.7%)	0	1 (0.9%)	3 (1.6%)
変形性関節症	0	0	3 (2.8%)	3 (1.6%)
筋骨格系胸痛	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
筋骨格痛	0	0	2 (1.9%)	2 (1.1%)
全身性強皮症	2 (5.7%)	0	0	2 (1.1%)
滑液包炎	0	1 (2.3%)	0	1 (0.5%)
四肢不快感	0	0	1 (0.9%)	1 (0.5%)
筋力低下	0	0	1 (0.9%)	1 (0.5%)
筋骨格不快感	0	1 (2.3%)	0	1 (0.5%)
骨軟骨炎	0	0	1 (0.9%)	1 (0.5%)
骨壊死	0	0	1 (0.9%)	1 (0.5%)
骨減少症	0	0	1 (0.9%)	1 (0.5%)
骨粗鬆症	1 (2.9%)	0	0	1 (0.5%)
顎痛	0	0	1 (0.9%)	1 (0.5%)
足底筋膜炎	0	1 (2.3%)	0	1 (0.5%)
仙腸骨炎	0	0	1 (0.9%)	1 (0.5%)
シェーグレン症候群	0	0	1 (0.9%)	1 (0.5%)
全身性エリテマトーデス	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
呼吸器、胸郭および縦隔障害	6 (17.1%)	14 (32.6%)	31 (29.0%)	51 (27.6%)
咳嗽	0	4 (9.3%)	10 (9.3%)	14 (7.6%)
呼吸困難	0	5 (11.6%)	6 (5.6%)	11 (5.9%)
鼻閉	1 (2.9%)	2 (4.7%)	6 (5.6%)	9 (4.9%)
肺動脈性肺高血圧症	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
労作性呼吸困難	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
鼻出血	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
低酸素症	2 (5.7%)	0	0	2 (1.1%)
口腔咽頭痛	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
アレルギー性鼻炎	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
鼻漏	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
アレルギー性副鼻腔炎	0	1 (2.3%)	0	1 (0.5%)
喘息	0	0	1 (0.9%)	1 (0.5%)
気管支反応性亢進	0	0	1 (0.9%)	1 (0.5%)
気管支分泌物貯留	0	1 (2.3%)	0	1 (0.5%)
喀血	0	0	1 (0.9%)	1 (0.5%)
鼻中隔弯曲	0	0	1 (0.9%)	1 (0.5%)
起坐呼吸	0	0	1 (0.9%)	1 (0.5%)
咽頭腫脹	0	0	1 (0.9%)	1 (0.5%)
気胸	0	1 (2.3%)	0	1 (0.5%)
湿性咳嗽	1 (2.9%)	0	0	1 (0.5%)
肺塞栓症	1 (2.9%)	0	0	1 (0.5%)
肺静脈閉塞性疾患	0	0	1 (0.9%)	1 (0.5%)
睡眠時無呼吸症候群	0	0	1 (0.9%)	1 (0.5%)
咽喉刺激感	0	0	1 (0.9%)	1 (0.5%)
気管の炎症	0	1 (2.3%)	0	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	2 (5.7%)	11 (25.6%)	34 (31.8%)	47 (25.4%)
末梢性浮腫	1 (2.9%)	3 (7.0%)	16 (15.0%)	20 (10.8%)
発熱	0	5 (11.6%)	5 (4.7%)	10 (5.4%)
末梢腫脹	1 (2.9%)	0	8 (7.5%)	9 (4.9%)
疲労	0	0	5 (4.7%)	5 (2.7%)
胸部不快感	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
非心臓性胸痛	0	0	3 (2.8%)	3 (1.6%)
胸痛	0	0	2 (1.9%)	2 (1.1%)
悪寒	0	0	2 (1.9%)	2 (1.1%)
浮腫	0	2 (4.7%)	0	2 (1.1%)
疼痛	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
顔面腫脹	0	0	2 (1.9%)	2 (1.1%)
無力症	0	0	1 (0.9%)	1 (0.5%)
顔面浮腫	0	1 (2.3%)	0	1 (0.5%)
全身性浮腫	0	0	1 (0.9%)	1 (0.5%)
倦怠感	0	0	1 (0.9%)	1 (0.5%)
ポリープ	0	0	1 (0.9%)	1 (0.5%)
腫脹	0	0	1 (0.9%)	1 (0.5%)
口渇	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	9 (25.7%)	6 (14.0%)	26 (24.3%)	41 (22.2%)
ヘモグロビン減少	4 (11.4%)	1 (2.3%)	12 (11.2%)	17 (9.2%)
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 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
体重減少	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
体重増加	0	0	3 (2.8%)	3 (1.6%)
アラニンアミノトランスフェラーゼ増加	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
血中ブドウ糖増加	2 (5.7%)	0	0	2 (1.1%)
トランスアミナーゼ上昇	0	0	2 (1.9%)	2 (1.1%)
血中アルカリホスファターゼ増加	0	0	1 (0.9%)	1 (0.5%)
血中ビリルビン増加	0	0	1 (0.9%)	1 (0.5%)
血中クレアチニン増加	0	0	1 (0.9%)	1 (0.5%)
血圧上昇	0	0	1 (0.9%)	1 (0.5%)
血中尿酸異常	0	0	1 (0.9%)	1 (0.5%)
血中尿酸増加	0	1 (2.3%)	0	1 (0.5%)
体温上昇	1 (2.9%)	0	0	1 (0.5%)
脳性ナトリウム利尿ペプチド増加	1 (2.9%)	0	0	1 (0.5%)
心雑音	0	0	1 (0.9%)	1 (0.5%)
心拍数増加	1 (2.9%)	0	0	1 (0.5%)
Ｂ型肝炎抗体異常	0	1 (2.3%)	0	1 (0.5%)
好中球数減少	0	0	1 (0.9%)	1 (0.5%)
酸素飽和度低下	0	0	1 (0.9%)	1 (0.5%)
血小板数減少	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
神経系障害	6 (17.1%)	2 (4.7%)	33 (30.8%)	41 (22.2%)
頭痛	3 (8.6%)	2 (4.7%)	21 (19.6%)	26 (14.1%)
浮動性めまい	1 (2.9%)	0	5 (4.7%)	6 (3.2%)
感覚鈍麻	0	0	3 (2.8%)	3 (1.6%)
失神	0	0	3 (2.8%)	3 (1.6%)
労作性めまい	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
体位性めまい	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
労作性頭痛	0	0	1 (0.9%)	1 (0.5%)
顔面麻痺	0	0	1 (0.9%)	1 (0.5%)
不全片麻痺	0	0	1 (0.9%)	1 (0.5%)
ホルネル症候群	0	0	1 (0.9%)	1 (0.5%)
嗜眠	0	0	1 (0.9%)	1 (0.5%)
片頭痛	0	0	1 (0.9%)	1 (0.5%)
ヘルペス後神経痛	0	0	1 (0.9%)	1 (0.5%)
失神寸前の状態	0	0	1 (0.9%)	1 (0.5%)
傾眠	1 (2.9%)	0	0	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
血液およびリンパ系障害	4 (11.4%)	7 (16.3%)	22 (20.6%)	33 (17.8%)
貧血	2 (5.7%)	5 (11.6%)	12 (11.2%)	19 (10.3%)
鉄欠乏性貧血	0	2 (4.7%)	6 (5.6%)	8 (4.3%)
白血球減少症	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
好中球減少症	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
白血球増加症	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
リンパ球減少症	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
血小板減少症	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
慢性疾患の貧血	0	0	1 (0.9%)	1 (0.5%)
失血性貧血	0	0	1 (0.9%)	1 (0.5%)
骨髄浮腫	0	0	1 (0.9%)	1 (0.5%)
脾機能亢進	0	0	1 (0.9%)	1 (0.5%)
単球減少症	0	0	1 (0.9%)	1 (0.5%)
正色素性貧血	0	0	1 (0.9%)	1 (0.5%)
汎血球減少症	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
心臓障害	2 (5.7%)	8 (18.6%)	22 (20.6%)	32 (17.3%)
動悸	0	3 (7.0%)	7 (6.5%)	10 (5.4%)
右室不全	1 (2.9%)	1 (2.3%)	4 (3.7%)	6 (3.2%)
狭心症	0	0	4 (3.7%)	4 (2.2%)
心不全	0	0	4 (3.7%)	4 (2.2%)
心房粗動	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
頻脈	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
冠動脈疾患	0	0	2 (1.9%)	2 (1.1%)
心房細動	0	0	1 (0.9%)	1 (0.5%)
徐脈	0	0	1 (0.9%)	1 (0.5%)
心血管障害	0	0	1 (0.9%)	1 (0.5%)
肺性心	0	1 (2.3%)	0	1 (0.5%)
左室不全	0	0	1 (0.9%)	1 (0.5%)
心嚢液貯留	0	0	1 (0.9%)	1 (0.5%)
洞結節機能不全	0	1 (2.3%)	0	1 (0.5%)
上室性頻脈	0	0	1 (0.9%)	1 (0.5%)
心室性不整脈	0	0	1 (0.9%)	1 (0.5%)
心室性期外収縮	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	4 (11.4%)	6 (14.0%)	19 (17.8%)	29 (15.7%)
低カリウム血症	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
鉄欠乏	0	0	4 (3.7%)	4 (2.2%)
ビタミンＢ１２欠乏	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
高尿酸血症	0	0	3 (2.8%)	3 (1.6%)
食欲減退	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
痛風	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
高脂血症	0	0	2 (1.9%)	2 (1.1%)
低ナトリウム血症	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
脱水	0	1 (2.3%)	0	1 (0.5%)
糖尿病	0	0	1 (0.9%)	1 (0.5%)
脂質異常症	0	1 (2.3%)	0	1 (0.5%)
高血糖	0	0	1 (0.9%)	1 (0.5%)
高カリウム血症	0	0	1 (0.9%)	1 (0.5%)
血液量増加症	1 (2.9%)	0	0	1 (0.5%)
空腹時血中ブドウ糖不良	0	1 (2.3%)	0	1 (0.5%)
２型糖尿病	1 (2.9%)	0	0	1 (0.5%)
ビタミンＤ欠乏	1 (2.9%)	0	0	1 (0.5%)
血管障害	2 (5.7%)	4 (9.3%)	14 (13.1%)	20 (10.8%)
低血圧	1 (2.9%)	1 (2.3%)	10 (9.3%)	12 (6.5%)
潮紅	0	0	3 (2.8%)	3 (1.6%)
ほてり	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
血腫	1 (2.9%)	0	0	1 (0.5%)
高血圧	0	1 (2.3%)	0	1 (0.5%)
末梢静脈疾患	0	0	1 (0.9%)	1 (0.5%)
静脈瘤	0	1 (2.3%)	0	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
眼障害	2 (5.7%)	6 (14.0%)	11 (10.3%)	19 (10.3%)
白内障	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
霧視	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
眼瞼浮腫	0	0	2 (1.9%)	2 (1.1%)
眼充血	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
眼窩周囲浮腫	0	0	2 (1.9%)	2 (1.1%)
眼刺激	0	1 (2.3%)	0	1 (0.5%)
眼痛	0	1 (2.3%)	0	1 (0.5%)
眼部腫脹	0	0	1 (0.9%)	1 (0.5%)
遠視	0	0	1 (0.9%)	1 (0.5%)
網膜出血	1 (2.9%)	0	0	1 (0.5%)
網膜静脈閉塞	0	1 (2.3%)	0	1 (0.5%)
視力障害	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
皮膚および皮下組織障害	0	4 (9.3%)	15 (14.0%)	19 (10.3%)
発疹	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
皮膚色素過剰	0	0	3 (2.8%)	3 (1.6%)
血管浮腫	0	0	2 (1.9%)	2 (1.1%)
紅斑	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
そう痒症	0	0	2 (1.9%)	2 (1.1%)
ざ瘡	0	0	1 (0.9%)	1 (0.5%)
脱毛症	0	0	1 (0.9%)	1 (0.5%)
冷汗	0	0	1 (0.9%)	1 (0.5%)
接触皮膚炎	0	0	1 (0.9%)	1 (0.5%)
皮膚乾燥	0	0	1 (0.9%)	1 (0.5%)
斑状出血	0	0	1 (0.9%)	1 (0.5%)
過剰肉芽組織	0	0	1 (0.9%)	1 (0.5%)
過角化	0	0	1 (0.9%)	1 (0.5%)
爪甲剥離症	0	0	1 (0.9%)	1 (0.5%)
丘疹	0	0	1 (0.9%)	1 (0.5%)
丘疹性皮疹	0	0	1 (0.9%)	1 (0.5%)
皮膚色素減少	0	0	1 (0.9%)	1 (0.5%)
皮膚病変	0	1 (2.3%)	0	1 (0.5%)
皮膚潰瘍	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
傷害、中毒および処置合併症	2 (5.7%)	3 (7.0%)	10 (9.3%)	15 (8.1%)
処置による疼痛	0	0	2 (1.9%)	2 (1.1%)
挫傷	0	0	1 (0.9%)	1 (0.5%)
上顆炎	0	1 (2.3%)	0	1 (0.5%)
転倒	0	0	1 (0.9%)	1 (0.5%)
足骨折	0	1 (2.3%)	0	1 (0.5%)
靭帯断裂	0	0	1 (0.9%)	1 (0.5%)
靭帯捻挫	0	0	1 (0.9%)	1 (0.5%)
過量投与	0	1 (2.3%)	0	1 (0.5%)
ワクチン接種後症候群	1 (2.9%)	0	0	1 (0.5%)
放射線肺線維症	1 (2.9%)	0	0	1 (0.5%)
肋骨骨折	0	0	1 (0.9%)	1 (0.5%)
硬膜下血腫	0	0	1 (0.9%)	1 (0.5%)
熱傷	0	0	1 (0.9%)	1 (0.5%)
歯牙破折	0	0	1 (0.9%)	1 (0.5%)
外傷性血腫	0	0	1 (0.9%)	1 (0.5%)
創傷	0	0	1 (0.9%)	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
生殖系および乳房障害	1 (2.9%)	2 (4.7%)	9 (8.4%)	12 (6.5%)
重度月経出血	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
子宮ポリープ	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
腺筋症	0	0	2 (1.9%)	2 (1.1%)
月経中間期出血	0	0	2 (1.9%)	2 (1.1%)
卵巣嚢胞	0	0	2 (1.9%)	2 (1.1%)
腟出血	0	0	2 (1.9%)	2 (1.1%)
乳房腫瘤	0	0	1 (0.9%)	1 (0.5%)
子宮頚部嚢胞	0	0	1 (0.9%)	1 (0.5%)
子宮頚外反	0	0	1 (0.9%)	1 (0.5%)
子宮内膜増殖症	0	0	1 (0.9%)	1 (0.5%)
子宮内膜症	0	0	1 (0.9%)	1 (0.5%)
女性化乳房	0	0	1 (0.9%)	1 (0.5%)
卵巣嚢胞破裂	0	1 (2.3%)	0	1 (0.5%)
骨盤癒着症	0	0	1 (0.9%)	1 (0.5%)
頻発過多月経	0	0	1 (0.9%)	1 (0.5%)
腎および尿路障害	2 (5.7%)	2 (4.7%)	7 (6.5%)	11 (5.9%)
腎機能障害	0	0	3 (2.8%)	3 (1.6%)
急性腎障害	0	0	2 (1.9%)	2 (1.1%)
慢性腎臓病	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
排尿困難	0	1 (2.3%)	0	1 (0.5%)
膜性糸球体腎炎	0	0	1 (0.9%)	1 (0.5%)
血尿	1 (2.9%)	0	0	1 (0.5%)
ループス腎炎	0	0	1 (0.9%)	1 (0.5%)
蛋白尿	0	0	1 (0.9%)	1 (0.5%)
尿閉	1 (2.9%)	0	0	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
乳癌	2 (5.7%)	0	0	2 (1.1%)
基底細胞癌	0	1 (2.3%)	0	1 (0.5%)
線維腫	0	0	1 (0.9%)	1 (0.5%)
卵巣粘液性嚢胞腺癌	0	0	1 (0.9%)	1 (0.5%)
骨髄線維症	0	1 (2.3%)	0	1 (0.5%)
前立腺癌	0	0	1 (0.9%)	1 (0.5%)
子宮平滑筋腫	0	0	1 (0.9%)	1 (0.5%)
精神障害	2 (5.7%)	1 (2.3%)	2 (1.9%)	5 (2.7%)
不眠症	2 (5.7%)	0	2 (1.9%)	4 (2.2%)
不安	0	1 (2.3%)	0	1 (0.5%)
肝胆道系障害	0	0	4 (3.7%)	4 (2.2%)
薬物性肝障害	0	0	1 (0.9%)	1 (0.5%)
肝硬変	0	0	1 (0.9%)	1 (0.5%)
脂肪肝	0	0	1 (0.9%)	1 (0.5%)
黄疸眼	0	0	1 (0.9%)	1 (0.5%)
門脈圧亢進症	0	0	1 (0.9%)	1 (0.5%)
免疫系障害	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
節足動物刺傷アレルギー	1 (2.9%)	0	0	1 (0.5%)
過敏症	0	0	1 (0.9%)	1 (0.5%)
耳および迷路障害	1 (2.9%)	0	0	1 (0.5%)
聴覚過敏	1 (2.9%)	0	0	1 (0.5%)

TSFAEOL02: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
内分泌障害	1 (2.9%)	0	0	1 (0.5%)
甲状腺腫	1 (2.9%)	0	0	1 (0.5%)

[TSFAEOL02.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02.SAS] 02MAR2023, 08:36

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age at baseline: 18-64 years	27	33	87	147
Subjects with 1 or more AEs	23 (85.2%)	29 (87.9%)	82 (94.3%)	134 (91.2%)
System organ class Preferred term				

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	15 (55.6%)	17 (51.5%)	41 (47.1%)	73 (49.7%)
ＣＯＶＩＤ－１９	5 (18.5%)	6 (18.2%)	21 (24.1%)	32 (21.8%)
上気道感染	2 (7.4%)	4 (12.1%)	5 (5.7%)	11 (7.5%)
尿路感染	1 (3.7%)	2 (6.1%)	4 (4.6%)	7 (4.8%)
インフルエンザ	0	0	5 (5.7%)	5 (3.4%)
上咽頭炎	0	2 (6.1%)	3 (3.4%)	5 (3.4%)
副鼻腔炎	1 (3.7%)	1 (3.0%)	2 (2.3%)	4 (2.7%)
ＣＯＶＩＤ－１９肺炎	0	0	3 (3.4%)	3 (2.0%)
肺炎	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
気管支炎	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
蜂巣炎	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
結膜炎	1 (3.7%)	1 (3.0%)	0	2 (1.4%)
Ｂ型肝炎	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
口腔ヘルペス	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
鼻炎	1 (3.7%)	1 (3.0%)	0	2 (1.4%)
ＣＯＶＩＤ－１９の疑い	2 (7.4%)	0	0	2 (1.4%)
急性副鼻腔炎	0	0	1 (1.1%)	1 (0.7%)
細菌感染	0	0	1 (1.1%)	1 (0.7%)
体部白癬	1 (3.7%)	0	0	1 (0.7%)
細菌性気管支炎	0	0	1 (1.1%)	1 (0.7%)
カンジダ感染	0	1 (3.0%)	0	1 (0.7%)
子宮頚管炎	0	0	1 (1.1%)	1 (0.7%)
慢性扁桃炎	0	0	1 (1.1%)	1 (0.7%)
憩室炎	1 (3.7%)	0	0	1 (0.7%)
子宮内膜炎	0	0	1 (1.1%)	1 (0.7%)
胃腸炎	0	0	1 (1.1%)	1 (0.7%)
消化管感染	0	0	1 (1.1%)	1 (0.7%)
歯肉炎	0	0	1 (1.1%)	1 (0.7%)
血液学的感染	0	0	1 (1.1%)	1 (0.7%)
Ｃ型肝炎	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
帯状疱疹	0	0	1 (1.1%)	1 (0.7%)
限局性感染	0	0	1 (1.1%)	1 (0.7%)
食道カンジダ症	0	0	1 (1.1%)	1 (0.7%)
中耳炎	0	1 (3.0%)	0	1 (0.7%)
耳管炎	0	0	1 (1.1%)	1 (0.7%)
パラインフルエンザウイルス感染	1 (3.7%)	0	0	1 (0.7%)
歯冠周囲炎	0	0	1 (1.1%)	1 (0.7%)
咽頭炎	0	1 (3.0%)	0	1 (0.7%)
細菌性咽頭炎	1 (3.7%)	0	0	1 (0.7%)
咽頭扁桃炎	0	1 (3.0%)	0	1 (0.7%)
細菌性肺炎	0	0	1 (1.1%)	1 (0.7%)
ウイルス性肺炎	0	0	1 (1.1%)	1 (0.7%)
急性ＣＯＶＩＤ－１９後症候群	0	0	1 (1.1%)	1 (0.7%)
気道感染	0	0	1 (1.1%)	1 (0.7%)
ウイルス性気道感染	1 (3.7%)	0	0	1 (0.7%)
卵管卵巣炎	0	0	1 (1.1%)	1 (0.7%)
腟感染	0	1 (3.0%)	0	1 (0.7%)
ウイルス感染	0	0	1 (1.1%)	1 (0.7%)
ウイルス性上気道感染	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	5 (18.5%)	5 (15.2%)	29 (33.3%)	39 (26.5%)
嘔吐	0	2 (6.1%)	5 (5.7%)	7 (4.8%)
下痢	0	1 (3.0%)	5 (5.7%)	6 (4.1%)
悪心	0	0	5 (5.7%)	5 (3.4%)
胃炎	2 (7.4%)	0	2 (2.3%)	4 (2.7%)
痔出血	0	0	4 (4.6%)	4 (2.7%)
腹部不快感	1 (3.7%)	0	2 (2.3%)	3 (2.0%)
腹痛	0	0	3 (3.4%)	3 (2.0%)
胃食道逆流性疾患	2 (7.4%)	0	1 (1.1%)	3 (2.0%)
痔核	0	0	3 (3.4%)	3 (2.0%)
上腹部痛	0	0	2 (2.3%)	2 (1.4%)
口内乾燥	0	0	2 (2.3%)	2 (1.4%)
消化不良	0	0	2 (2.3%)	2 (1.4%)
小腸炎	0	0	2 (2.3%)	2 (1.4%)
歯痛	0	0	2 (2.3%)	2 (1.4%)
食道静脈瘤	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
腹部膨満	0	0	1 (1.1%)	1 (0.7%)
肛門出血	0	1 (3.0%)	0	1 (0.7%)
慢性胃炎	1 (3.7%)	0	0	1 (0.7%)
大腸炎	0	0	1 (1.1%)	1 (0.7%)
便秘	0	1 (3.0%)	0	1 (0.7%)
鼓腸	0	0	1 (1.1%)	1 (0.7%)
排便回数増加	1 (3.7%)	0	0	1 (0.7%)
胃障害	0	1 (3.0%)	0	1 (0.7%)
腰ヘルニア	0	0	1 (1.1%)	1 (0.7%)
食道炎	0	0	1 (1.1%)	1 (0.7%)
舌嚢胞	0	0	1 (1.1%)	1 (0.7%)
上部消化管出血	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
呼吸器、胸郭および縦隔障害	3 (11.1%)	10 (30.3%)	26 (29.9%)	39 (26.5%)
咳嗽	0	4 (12.1%)	9 (10.3%)	13 (8.8%)
鼻閉	1 (3.7%)	2 (6.1%)	6 (6.9%)	9 (6.1%)
呼吸困難	0	3 (9.1%)	5 (5.7%)	8 (5.4%)
肺動脈性肺高血圧症	1 (3.7%)	1 (3.0%)	4 (4.6%)	6 (4.1%)
労作性呼吸困難	0	1 (3.0%)	3 (3.4%)	4 (2.7%)
鼻出血	0	0	3 (3.4%)	3 (2.0%)
アレルギー性鼻炎	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
鼻漏	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
アレルギー性副鼻腔炎	0	1 (3.0%)	0	1 (0.7%)
喘息	0	0	1 (1.1%)	1 (0.7%)
気管支反応性亢進	0	0	1 (1.1%)	1 (0.7%)
喀血	0	0	1 (1.1%)	1 (0.7%)
鼻中隔弯曲	0	0	1 (1.1%)	1 (0.7%)
口腔咽頭痛	0	1 (3.0%)	0	1 (0.7%)
咽頭腫脹	0	0	1 (1.1%)	1 (0.7%)
湿性咳嗽	1 (3.7%)	0	0	1 (0.7%)
肺塞栓症	1 (3.7%)	0	0	1 (0.7%)
睡眠時無呼吸症候群	0	0	1 (1.1%)	1 (0.7%)
咽喉刺激感	0	0	1 (1.1%)	1 (0.7%)
気管の炎症	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	9 (33.3%)	6 (18.2%)	22 (25.3%)	37 (25.2%)
筋肉痛	3 (11.1%)	1 (3.0%)	6 (6.9%)	10 (6.8%)
関節痛	2 (7.4%)	1 (3.0%)	4 (4.6%)	7 (4.8%)
背部痛	1 (3.7%)	1 (3.0%)	4 (4.6%)	6 (4.1%)
四肢痛	1 (3.7%)	1 (3.0%)	4 (4.6%)	6 (4.1%)
変形性関節症	0	0	3 (3.4%)	3 (2.0%)
全身性強皮症	2 (7.4%)	0	0	2 (1.4%)
滑液包炎	0	1 (3.0%)	0	1 (0.7%)
椎間板突出	0	0	1 (1.1%)	1 (0.7%)
筋力低下	0	0	1 (1.1%)	1 (0.7%)
筋骨格系胸痛	1 (3.7%)	0	0	1 (0.7%)
筋骨格不快感	0	1 (3.0%)	0	1 (0.7%)
骨軟骨炎	0	0	1 (1.1%)	1 (0.7%)
骨壊死	0	0	1 (1.1%)	1 (0.7%)
足底筋膜炎	0	1 (3.0%)	0	1 (0.7%)
シェーグレン症候群	0	0	1 (1.1%)	1 (0.7%)
全身性エリテマトーデス	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	1 (3.7%)	10 (30.3%)	25 (28.7%)	36 (24.5%)
末梢性浮腫	0	3 (9.1%)	10 (11.5%)	13 (8.8%)
発熱	0	4 (12.1%)	5 (5.7%)	9 (6.1%)
末梢腫脹	1 (3.7%)	0	7 (8.0%)	8 (5.4%)
疲労	0	0	5 (5.7%)	5 (3.4%)
非心臓性胸痛	0	0	3 (3.4%)	3 (2.0%)
胸部不快感	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
胸痛	0	0	2 (2.3%)	2 (1.4%)
悪寒	0	0	2 (2.3%)	2 (1.4%)
浮腫	0	2 (6.1%)	0	2 (1.4%)
疼痛	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
無力症	0	0	1 (1.1%)	1 (0.7%)
顔面浮腫	0	1 (3.0%)	0	1 (0.7%)
ポリープ	0	0	1 (1.1%)	1 (0.7%)
顔面腫脹	0	0	1 (1.1%)	1 (0.7%)
口渇	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	7 (25.9%)	4 (12.1%)	23 (26.4%)	34 (23.1%)
ヘモグロビン減少	2 (7.4%)	0	12 (13.8%)	14 (9.5%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	1 (3.7%)	0	2 (2.3%)	3 (2.0%)
体重減少	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
体重増加	0	0	3 (3.4%)	3 (2.0%)
アラニンアミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
トランスアミナーゼ上昇	0	0	2 (2.3%)	2 (1.4%)
血中アルカリホスファターゼ増加	0	0	1 (1.1%)	1 (0.7%)
血中ビリルビン増加	0	0	1 (1.1%)	1 (0.7%)
血中ブドウ糖増加	1 (3.7%)	0	0	1 (0.7%)
血圧上昇	0	0	1 (1.1%)	1 (0.7%)
血中尿酸異常	0	0	1 (1.1%)	1 (0.7%)
血中尿酸増加	0	1 (3.0%)	0	1 (0.7%)
体温上昇	1 (3.7%)	0	0	1 (0.7%)
脳性ナトリウム利尿ペプチド増加	1 (3.7%)	0	0	1 (0.7%)
心拍数増加	1 (3.7%)	0	0	1 (0.7%)
Ｂ型肝炎抗体異常	0	1 (3.0%)	0	1 (0.7%)
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 (3.7%)	0	0	1 (0.7%)
好中球数減少	0	0	1 (1.1%)	1 (0.7%)
血小板数減少	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
神経系障害	5 (18.5%)	2 (6.1%)	27 (31.0%)	34 (23.1%)
頭痛	3 (11.1%)	2 (6.1%)	18 (20.7%)	23 (15.6%)
浮動性めまい	1 (3.7%)	0	4 (4.6%)	5 (3.4%)
失神	0	0	3 (3.4%)	3 (2.0%)
感覚鈍麻	0	0	2 (2.3%)	2 (1.4%)
労作性めまい	0	0	1 (1.1%)	1 (0.7%)
体位性めまい	0	0	1 (1.1%)	1 (0.7%)
労作性頭痛	0	0	1 (1.1%)	1 (0.7%)
不全片麻痺	0	0	1 (1.1%)	1 (0.7%)
ホルネル症候群	0	0	1 (1.1%)	1 (0.7%)
嗜眠	0	0	1 (1.1%)	1 (0.7%)
片頭痛	0	0	1 (1.1%)	1 (0.7%)
ヘルペス後神経痛	0	0	1 (1.1%)	1 (0.7%)
傾眠	1 (3.7%)	0	0	1 (0.7%)
心臓障害	0	7 (21.2%)	17 (19.5%)	24 (16.3%)
動悸	0	3 (9.1%)	7 (8.0%)	10 (6.8%)
狭心症	0	0	3 (3.4%)	3 (2.0%)
右室不全	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
頻脈	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
心房粗動	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
心不全	0	0	2 (2.3%)	2 (1.4%)
心房細動	0	0	1 (1.1%)	1 (0.7%)
心血管障害	0	0	1 (1.1%)	1 (0.7%)
肺性心	0	1 (3.0%)	0	1 (0.7%)
冠動脈疾患	0	0	1 (1.1%)	1 (0.7%)
心嚢液貯留	0	0	1 (1.1%)	1 (0.7%)
上室性頻脈	0	0	1 (1.1%)	1 (0.7%)
心室性不整脈	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
血液およびリンパ系障害	1 (3.7%)	6 (18.2%)	15 (17.2%)	22 (15.0%)
貧血	0	4 (12.1%)	7 (8.0%)	11 (7.5%)
鉄欠乏性貧血	0	2 (6.1%)	5 (5.7%)	7 (4.8%)
好中球減少症	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
血小板減少症	1 (3.7%)	1 (3.0%)	0	2 (1.4%)
慢性疾患の貧血	0	0	1 (1.1%)	1 (0.7%)
失血性貧血	0	0	1 (1.1%)	1 (0.7%)
骨髄浮腫	0	0	1 (1.1%)	1 (0.7%)
脾機能亢進	0	0	1 (1.1%)	1 (0.7%)
白血球増加症	0	1 (3.0%)	0	1 (0.7%)
白血球減少症	1 (3.7%)	0	0	1 (0.7%)
リンパ球減少症	1 (3.7%)	0	0	1 (0.7%)
正色素性貧血	0	0	1 (1.1%)	1 (0.7%)
汎血球減少症	0	0	1 (1.1%)	1 (0.7%)
代謝および栄養障害	1 (3.7%)	5 (15.2%)	13 (14.9%)	19 (12.9%)
低カリウム血症	1 (3.7%)	1 (3.0%)	2 (2.3%)	4 (2.7%)
鉄欠乏	0	0	4 (4.6%)	4 (2.7%)
食欲減退	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
高脂血症	0	0	2 (2.3%)	2 (1.4%)
高尿酸血症	0	0	2 (2.3%)	2 (1.4%)
ビタミンＢ１２欠乏	0	0	2 (2.3%)	2 (1.4%)
脱水	0	1 (3.0%)	0	1 (0.7%)
糖尿病	0	0	1 (1.1%)	1 (0.7%)
痛風	0	1 (3.0%)	0	1 (0.7%)
高血糖	0	0	1 (1.1%)	1 (0.7%)
低ナトリウム血症	0	1 (3.0%)	0	1 (0.7%)
空腹時血中ブドウ糖不良	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
眼障害	1 (3.7%)	5 (15.2%)	10 (11.5%)	16 (10.9%)
白内障	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
霧視	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
眼瞼浮腫	0	0	2 (2.3%)	2 (1.4%)
眼充血	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
眼窩周囲浮腫	0	0	2 (2.3%)	2 (1.4%)
眼刺激	0	1 (3.0%)	0	1 (0.7%)
眼痛	0	1 (3.0%)	0	1 (0.7%)
眼部腫脹	0	0	1 (1.1%)	1 (0.7%)
遠視	0	0	1 (1.1%)	1 (0.7%)
網膜出血	1 (3.7%)	0	0	1 (0.7%)
皮膚および皮下組織障害	0	3 (9.1%)	13 (14.9%)	16 (10.9%)
発疹	0	1 (3.0%)	4 (4.6%)	5 (3.4%)
血管浮腫	0	0	2 (2.3%)	2 (1.4%)
そう痒症	0	0	2 (2.3%)	2 (1.4%)
皮膚色素過剰	0	0	2 (2.3%)	2 (1.4%)
ざ瘡	0	0	1 (1.1%)	1 (0.7%)
脱毛症	0	0	1 (1.1%)	1 (0.7%)
冷汗	0	0	1 (1.1%)	1 (0.7%)
皮膚乾燥	0	0	1 (1.1%)	1 (0.7%)
斑状出血	0	0	1 (1.1%)	1 (0.7%)
紅斑	0	1 (3.0%)	0	1 (0.7%)
過剰肉芽組織	0	0	1 (1.1%)	1 (0.7%)
過角化	0	0	1 (1.1%)	1 (0.7%)
爪甲剥離症	0	0	1 (1.1%)	1 (0.7%)
丘疹	0	0	1 (1.1%)	1 (0.7%)
丘疹性皮疹	0	0	1 (1.1%)	1 (0.7%)
皮膚色素減少	0	0	1 (1.1%)	1 (0.7%)
皮膚病変	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
生殖系および乳房障害	1 (3.7%)	2 (6.1%)	9 (10.3%)	12 (8.2%)
重度月経出血	1 (3.7%)	0	3 (3.4%)	4 (2.7%)
子宮ポリープ	0	1 (3.0%)	3 (3.4%)	4 (2.7%)
腺筋症	0	0	2 (2.3%)	2 (1.4%)
月経中間期出血	0	0	2 (2.3%)	2 (1.4%)
卵巣嚢胞	0	0	2 (2.3%)	2 (1.4%)
腟出血	0	0	2 (2.3%)	2 (1.4%)
乳房腫瘤	0	0	1 (1.1%)	1 (0.7%)
子宮頚部嚢胞	0	0	1 (1.1%)	1 (0.7%)
子宮頚外反	0	0	1 (1.1%)	1 (0.7%)
子宮内膜増殖症	0	0	1 (1.1%)	1 (0.7%)
子宮内膜症	0	0	1 (1.1%)	1 (0.7%)
女性化乳房	0	0	1 (1.1%)	1 (0.7%)
卵巣嚢胞破裂	0	1 (3.0%)	0	1 (0.7%)
骨盤癒着症	0	0	1 (1.1%)	1 (0.7%)
頻発過多月経	0	0	1 (1.1%)	1 (0.7%)
血管障害	1 (3.7%)	2 (6.1%)	9 (10.3%)	12 (8.2%)
低血圧	0	1 (3.0%)	8 (9.2%)	9 (6.1%)
潮紅	0	0	1 (1.1%)	1 (0.7%)
血腫	1 (3.7%)	0	0	1 (0.7%)
ほてり	0	0	1 (1.1%)	1 (0.7%)
静脈瘤	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
傷害、中毒および処置合併症	1 (3.7%)	3 (9.1%)	7 (8.0%)	11 (7.5%)
処置による疼痛	0	0	2 (2.3%)	2 (1.4%)
上顆炎	0	1 (3.0%)	0	1 (0.7%)
足骨折	0	1 (3.0%)	0	1 (0.7%)
靭帯断裂	0	0	1 (1.1%)	1 (0.7%)
靭帯捻挫	0	0	1 (1.1%)	1 (0.7%)
過量投与	0	1 (3.0%)	0	1 (0.7%)
放射線肺線維症	1 (3.7%)	0	0	1 (0.7%)
肋骨骨折	0	0	1 (1.1%)	1 (0.7%)
熱傷	0	0	1 (1.1%)	1 (0.7%)
外傷性血腫	0	0	1 (1.1%)	1 (0.7%)
創傷	0	0	1 (1.1%)	1 (0.7%)
腎および尿路障害	1 (3.7%)	1 (3.0%)	7 (8.0%)	9 (6.1%)
腎機能障害	0	0	3 (3.4%)	3 (2.0%)
急性腎障害	0	0	2 (2.3%)	2 (1.4%)
慢性腎臓病	1 (3.7%)	0	0	1 (0.7%)
排尿困難	0	1 (3.0%)	0	1 (0.7%)
膜性糸球体腎炎	0	0	1 (1.1%)	1 (0.7%)
ループス腎炎	0	0	1 (1.1%)	1 (0.7%)
蛋白尿	0	0	1 (1.1%)	1 (0.7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (3.7%)	1 (3.0%)	3 (3.4%)	5 (3.4%)
乳癌	1 (3.7%)	0	0	1 (0.7%)
線維腫	0	0	1 (1.1%)	1 (0.7%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.1%)	1 (0.7%)
骨髄線維症	0	1 (3.0%)	0	1 (0.7%)
子宮平滑筋腫	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
肝胆道系障害	0	0	4 (4.6%)	4 (2.7%)
薬物性肝障害	0	0	1 (1.1%)	1 (0.7%)
肝硬変	0	0	1 (1.1%)	1 (0.7%)
脂肪肝	0	0	1 (1.1%)	1 (0.7%)
黄疸眼	0	0	1 (1.1%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.1%)	1 (0.7%)
精神障害	1 (3.7%)	1 (3.0%)	1 (1.1%)	3 (2.0%)
不眠症	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
不安	0	1 (3.0%)	0	1 (0.7%)
内分泌障害	1 (3.7%)	0	0	1 (0.7%)
甲状腺腫	1 (3.7%)	0	0	1 (0.7%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age at baseline: >=65 years	8	10	20	38
Subjects with 1 or more AEs	8 (100.0%)	9 (90.0%)	19 (95.0%)	36 (94.7%)
System organ class Preferred term				
感染症および寄生虫症	4 (50.0%)	3 (30.0%)	9 (45.0%)	16 (42.1%)
ＣＯＶＩＤ－１９	1 (12.5%)	2 (20.0%)	4 (20.0%)	7 (18.4%)
肺炎	0	1 (10.0%)	2 (10.0%)	3 (7.9%)
上咽頭炎	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
尿路感染	0	1 (10.0%)	1 (5.0%)	2 (5.3%)
真菌性肛門感染	0	0	1 (5.0%)	1 (2.6%)
蜂巣炎	1 (12.5%)	0	0	1 (2.6%)
サイトメガロウイルス性脈絡網膜炎	0	0	1 (5.0%)	1 (2.6%)
クロストリジウム菌性胃腸炎	0	0	1 (5.0%)	1 (2.6%)
陰部ヘルペス	0	0	1 (5.0%)	1 (2.6%)
限局性感染	1 (12.5%)	0	0	1 (2.6%)
口腔ヘルペス	0	0	1 (5.0%)	1 (2.6%)
パラインフルエンザウイルス感染	0	0	1 (5.0%)	1 (2.6%)
シュードモナス性肺炎	0	1 (10.0%)	0	1 (2.6%)
ブドウ球菌性肺炎	0	1 (10.0%)	0	1 (2.6%)
歯膿瘍	0	0	1 (5.0%)	1 (2.6%)
上気道感染	1 (12.5%)	0	0	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	3 (37.5%)	3 (30.0%)	8 (40.0%)	14 (36.8%)
胃炎	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
悪心	0	1 (10.0%)	2 (10.0%)	3 (7.9%)
便秘	0	1 (10.0%)	1 (5.0%)	2 (5.3%)
消化不良	0	0	2 (10.0%)	2 (5.3%)
嘔吐	0	0	2 (10.0%)	2 (5.3%)
腹部不快感	0	0	1 (5.0%)	1 (2.6%)
腹痛	0	0	1 (5.0%)	1 (2.6%)
虚血性大腸炎	0	1 (10.0%)	0	1 (2.6%)
下痢	0	0	1 (5.0%)	1 (2.6%)
口内乾燥	0	0	1 (5.0%)	1 (2.6%)
鼓腸	0	1 (10.0%)	0	1 (2.6%)
胃腸障害	0	0	1 (5.0%)	1 (2.6%)
胃食道逆流性疾患	1 (12.5%)	0	0	1 (2.6%)
裂孔ヘルニア	0	1 (10.0%)	0	1 (2.6%)
口腔内潰瘍形成	0	0	1 (5.0%)	1 (2.6%)
食道炎	0	0	1 (5.0%)	1 (2.6%)
亜イレウス	1 (12.5%)	0	0	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	4 (50.0%)	1 (10.0%)	9 (45.0%)	14 (36.8%)
関節痛	1 (12.5%)	1 (10.0%)	2 (10.0%)	4 (10.5%)
背部痛	1 (12.5%)	0	3 (15.0%)	4 (10.5%)
椎間板突出	2 (25.0%)	0	0	2 (5.3%)
筋骨格痛	0	0	2 (10.0%)	2 (5.3%)
四肢不快感	0	0	1 (5.0%)	1 (2.6%)
筋骨格系胸痛	0	0	1 (5.0%)	1 (2.6%)
筋肉痛	0	0	1 (5.0%)	1 (2.6%)
骨減少症	0	0	1 (5.0%)	1 (2.6%)
骨粗鬆症	1 (12.5%)	0	0	1 (2.6%)
四肢痛	0	0	1 (5.0%)	1 (2.6%)
顎痛	0	0	1 (5.0%)	1 (2.6%)
仙腸骨炎	0	0	1 (5.0%)	1 (2.6%)
呼吸器、胸郭および縦隔障害	3 (37.5%)	4 (40.0%)	5 (25.0%)	12 (31.6%)
呼吸困難	0	2 (20.0%)	1 (5.0%)	3 (7.9%)
低酸素症	2 (25.0%)	0	0	2 (5.3%)
肺動脈性肺高血圧症	1 (12.5%)	1 (10.0%)	0	2 (5.3%)
気管支分泌物貯留	0	1 (10.0%)	0	1 (2.6%)
咳嗽	0	0	1 (5.0%)	1 (2.6%)
鼻出血	1 (12.5%)	0	0	1 (2.6%)
口腔咽頭痛	0	0	1 (5.0%)	1 (2.6%)
起坐呼吸	0	0	1 (5.0%)	1 (2.6%)
気胸	0	1 (10.0%)	0	1 (2.6%)
肺静脈閉塞性疾患	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
血液およびリンパ系障害	3 (37.5%)	1 (10.0%)	7 (35.0%)	11 (28.9%)
貧血	2 (25.0%)	1 (10.0%)	5 (25.0%)	8 (21.1%)
白血球減少症	0	0	2 (10.0%)	2 (5.3%)
鉄欠乏性貧血	0	0	1 (5.0%)	1 (2.6%)
白血球増加症	1 (12.5%)	0	0	1 (2.6%)
リンパ球減少症	0	0	1 (5.0%)	1 (2.6%)
単球減少症	0	0	1 (5.0%)	1 (2.6%)
好中球減少症	0	0	1 (5.0%)	1 (2.6%)
一般・全身障害および投与部位の状態	1 (12.5%)	1 (10.0%)	9 (45.0%)	11 (28.9%)
末梢性浮腫	1 (12.5%)	0	6 (30.0%)	7 (18.4%)
胸部不快感	0	0	1 (5.0%)	1 (2.6%)
全身性浮腫	0	0	1 (5.0%)	1 (2.6%)
倦怠感	0	0	1 (5.0%)	1 (2.6%)
末梢腫脹	0	0	1 (5.0%)	1 (2.6%)
発熱	0	1 (10.0%)	0	1 (2.6%)
腫脹	0	0	1 (5.0%)	1 (2.6%)
顔面腫脹	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	3 (37.5%)	1 (10.0%)	6 (30.0%)	10 (26.3%)
ビタミンＢ１２欠乏	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
脂質異常症	0	1 (10.0%)	0	1 (2.6%)
痛風	0	0	1 (5.0%)	1 (2.6%)
高カリウム血症	0	0	1 (5.0%)	1 (2.6%)
高尿酸血症	0	0	1 (5.0%)	1 (2.6%)
血液量増加症	1 (12.5%)	0	0	1 (2.6%)
低カリウム血症	0	0	1 (5.0%)	1 (2.6%)
低ナトリウム血症	0	0	1 (5.0%)	1 (2.6%)
２型糖尿病	1 (12.5%)	0	0	1 (2.6%)
ビタミンＤ欠乏	1 (12.5%)	0	0	1 (2.6%)
心臓障害	2 (25.0%)	1 (10.0%)	5 (25.0%)	8 (21.1%)
右室不全	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
心不全	0	0	2 (10.0%)	2 (5.3%)
狭心症	0	0	1 (5.0%)	1 (2.6%)
心房粗動	1 (12.5%)	0	0	1 (2.6%)
徐脈	0	0	1 (5.0%)	1 (2.6%)
冠動脈疾患	0	0	1 (5.0%)	1 (2.6%)
左室不全	0	0	1 (5.0%)	1 (2.6%)
洞結節機能不全	0	1 (10.0%)	0	1 (2.6%)
心室性期外収縮	0	0	1 (5.0%)	1 (2.6%)
血管障害	1 (12.5%)	2 (20.0%)	5 (25.0%)	8 (21.1%)
低血圧	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
潮紅	0	0	2 (10.0%)	2 (5.3%)
ほてり	0	1 (10.0%)	0	1 (2.6%)
高血圧	0	1 (10.0%)	0	1 (2.6%)
末梢静脈疾患	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	2 (25.0%)	2 (20.0%)	3 (15.0%)	7 (18.4%)
ヘモグロビン減少	2 (25.0%)	1 (10.0%)	0	3 (7.9%)
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	0	1 (10.0%)	1 (5.0%)	2 (5.3%)
血中クレアチニン増加	0	0	1 (5.0%)	1 (2.6%)
血中ブドウ糖増加	1 (12.5%)	0	0	1 (2.6%)
心雑音	0	0	1 (5.0%)	1 (2.6%)
酸素飽和度低下	0	0	1 (5.0%)	1 (2.6%)
神経系障害	1 (12.5%)	0	6 (30.0%)	7 (18.4%)
頭痛	0	0	3 (15.0%)	3 (7.9%)
浮動性めまい	0	0	1 (5.0%)	1 (2.6%)
労作性めまい	1 (12.5%)	0	0	1 (2.6%)
体位性めまい	1 (12.5%)	0	0	1 (2.6%)
顔面麻痺	0	0	1 (5.0%)	1 (2.6%)
感覚鈍麻	0	0	1 (5.0%)	1 (2.6%)
失神寸前の状態	0	0	1 (5.0%)	1 (2.6%)
傷害、中毒および処置合併症	1 (12.5%)	0	3 (15.0%)	4 (10.5%)
挫傷	0	0	1 (5.0%)	1 (2.6%)
転倒	0	0	1 (5.0%)	1 (2.6%)
ワクチン接種後症候群	1 (12.5%)	0	0	1 (2.6%)
硬膜下血腫	0	0	1 (5.0%)	1 (2.6%)
歯牙破折	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
眼障害	1 (12.5%)	1 (10.0%)	1 (5.0%)	3 (7.9%)
白内障	1 (12.5%)	0	0	1 (2.6%)
網膜静脈閉塞	0	1 (10.0%)	0	1 (2.6%)
視力障害	0	0	1 (5.0%)	1 (2.6%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (12.5%)	1 (10.0%)	1 (5.0%)	3 (7.9%)
基底細胞癌	0	1 (10.0%)	0	1 (2.6%)
乳癌	1 (12.5%)	0	0	1 (2.6%)
前立腺癌	0	0	1 (5.0%)	1 (2.6%)
皮膚および皮下組織障害	0	1 (10.0%)	2 (10.0%)	3 (7.9%)
接触皮膚炎	0	0	1 (5.0%)	1 (2.6%)
紅斑	0	0	1 (5.0%)	1 (2.6%)
発疹	0	1 (10.0%)	0	1 (2.6%)
皮膚色素過剰	0	0	1 (5.0%)	1 (2.6%)
皮膚潰瘍	0	0	1 (5.0%)	1 (2.6%)
免疫系障害	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
節足動物刺傷アレルギー	1 (12.5%)	0	0	1 (2.6%)
過敏症	0	0	1 (5.0%)	1 (2.6%)
精神障害	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
不眠症	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
腎および尿路障害	1 (12.5%)	1 (10.0%)	0	2 (5.3%)
慢性腎臓病	0	1 (10.0%)	0	1 (2.6%)
血尿	1 (12.5%)	0	0	1 (2.6%)
尿閉	1 (12.5%)	0	0	1 (2.6%)

TSFAEOL02D: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
耳および迷路障害	1 (12.5%)	0	0	1 (2.6%)
聴覚過敏	1 (12.5%)	0	0	1 (2.6%)

[TSFAEOL02D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02D.SAS] 02MAR2023, 08:36

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more AEs	25 (86.2%)	30 (90.9%)	78 (95.1%)	133 (92.4%)
System organ class				
Preferred term				

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	16 (55.2%)	14 (42.4%)	34 (41.5%)	64 (44.4%)
ＣＯＶＩＤ－１９	6 (20.7%)	6 (18.2%)	16 (19.5%)	28 (19.4%)
上気道感染	3 (10.3%)	3 (9.1%)	2 (2.4%)	8 (5.6%)
尿路感染	1 (3.4%)	2 (6.1%)	5 (6.1%)	8 (5.6%)
上咽頭炎	0	2 (6.1%)	3 (3.7%)	5 (3.5%)
肺炎	0	2 (6.1%)	3 (3.7%)	5 (3.5%)
インフルエンザ	0	0	4 (4.9%)	4 (2.8%)
口腔ヘルペス	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
副鼻腔炎	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
ＣＯＶＩＤ－１９肺炎	0	0	2 (2.4%)	2 (1.4%)
蜂巣炎	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
結膜炎	1 (3.4%)	1 (3.0%)	0	2 (1.4%)
Ｂ型肝炎	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
限局性感染	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
パラインフルエンザウイルス感染	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
鼻炎	1 (3.4%)	1 (3.0%)	0	2 (1.4%)
急性副鼻腔炎	0	0	1 (1.2%)	1 (0.7%)
真菌性肛門感染	0	0	1 (1.2%)	1 (0.7%)
細菌感染	0	0	1 (1.2%)	1 (0.7%)
体部白癬	1 (3.4%)	0	0	1 (0.7%)
気管支炎	0	0	1 (1.2%)	1 (0.7%)
細菌性気管支炎	0	0	1 (1.2%)	1 (0.7%)
カンジダ感染	0	1 (3.0%)	0	1 (0.7%)
子宮頚管炎	0	0	1 (1.2%)	1 (0.7%)
慢性扁桃炎	0	0	1 (1.2%)	1 (0.7%)
サイトメガロウイルス性脈絡網膜炎	0	0	1 (1.2%)	1 (0.7%)
憩室炎	1 (3.4%)	0	0	1 (0.7%)
子宮内膜炎	0	0	1 (1.2%)	1 (0.7%)
消化管感染	0	0	1 (1.2%)	1 (0.7%)
陰部ヘルペス	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
歯肉炎	0	0	1 (1.2%)	1 (0.7%)
血液学的感染	0	0	1 (1.2%)	1 (0.7%)
Ｃ型肝炎	0	1 (3.0%)	0	1 (0.7%)
帯状疱疹	0	0	1 (1.2%)	1 (0.7%)
食道カンジダ症	0	0	1 (1.2%)	1 (0.7%)
中耳炎	0	1 (3.0%)	0	1 (0.7%)
耳管炎	0	0	1 (1.2%)	1 (0.7%)
歯冠周囲炎	0	0	1 (1.2%)	1 (0.7%)
咽頭炎	0	1 (3.0%)	0	1 (0.7%)
細菌性咽頭炎	1 (3.4%)	0	0	1 (0.7%)
咽頭扁桃炎	0	1 (3.0%)	0	1 (0.7%)
細菌性肺炎	0	0	1 (1.2%)	1 (0.7%)
シュードモナス性肺炎	0	1 (3.0%)	0	1 (0.7%)
ブドウ球菌性肺炎	0	1 (3.0%)	0	1 (0.7%)
急性ＣＯＶＩＤ－１９後症候群	0	0	1 (1.2%)	1 (0.7%)
気道感染	0	0	1 (1.2%)	1 (0.7%)
ウイルス性気道感染	1 (3.4%)	0	0	1 (0.7%)
卵管卵巣炎	0	0	1 (1.2%)	1 (0.7%)
ＣＯＶＩＤ－１９の疑い	1 (3.4%)	0	0	1 (0.7%)
歯膿瘍	0	0	1 (1.2%)	1 (0.7%)
腟感染	0	1 (3.0%)	0	1 (0.7%)
ウイルス感染	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	11 (37.9%)	6 (18.2%)	25 (30.5%)	42 (29.2%)
背部痛	2 (6.9%)	1 (3.0%)	7 (8.5%)	10 (6.9%)
筋肉痛	3 (10.3%)	1 (3.0%)	5 (6.1%)	9 (6.3%)
関節痛	2 (6.9%)	1 (3.0%)	4 (4.9%)	7 (4.9%)
四肢痛	1 (3.4%)	1 (3.0%)	5 (6.1%)	7 (4.9%)
椎間板突出	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
筋骨格系胸痛	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
筋骨格痛	0	0	2 (2.4%)	2 (1.4%)
変形性関節症	0	0	2 (2.4%)	2 (1.4%)
全身性強皮症	2 (6.9%)	0	0	2 (1.4%)
筋力低下	0	0	1 (1.2%)	1 (0.7%)
筋骨格不快感	0	1 (3.0%)	0	1 (0.7%)
骨軟骨炎	0	0	1 (1.2%)	1 (0.7%)
骨壊死	0	0	1 (1.2%)	1 (0.7%)
骨減少症	0	0	1 (1.2%)	1 (0.7%)
骨粗鬆症	1 (3.4%)	0	0	1 (0.7%)
顎痛	0	0	1 (1.2%)	1 (0.7%)
足底筋膜炎	0	1 (3.0%)	0	1 (0.7%)
仙腸骨炎	0	0	1 (1.2%)	1 (0.7%)
シェーグレン症候群	0	0	1 (1.2%)	1 (0.7%)
全身性エリテマトーデス	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	5 (17.2%)	7 (21.2%)	28 (34.1%)	40 (27.8%)
悪心	0	1 (3.0%)	6 (7.3%)	7 (4.9%)
嘔吐	0	2 (6.1%)	5 (6.1%)	7 (4.9%)
胃炎	3 (10.3%)	0	3 (3.7%)	6 (4.2%)
下痢	0	1 (3.0%)	4 (4.9%)	5 (3.5%)
腹痛	0	0	4 (4.9%)	4 (2.8%)
便秘	0	2 (6.1%)	1 (1.2%)	3 (2.1%)
消化不良	0	0	3 (3.7%)	3 (2.1%)
腹部不快感	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
上腹部痛	0	0	2 (2.4%)	2 (1.4%)
口内乾燥	0	0	2 (2.4%)	2 (1.4%)
痔出血	0	0	2 (2.4%)	2 (1.4%)
痔核	0	0	2 (2.4%)	2 (1.4%)
食道炎	0	0	2 (2.4%)	2 (1.4%)
食道静脈瘤	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
腹部膨満	0	0	1 (1.2%)	1 (0.7%)
肛門出血	0	1 (3.0%)	0	1 (0.7%)
慢性胃炎	1 (3.4%)	0	0	1 (0.7%)
大腸炎	0	0	1 (1.2%)	1 (0.7%)
虚血性大腸炎	0	1 (3.0%)	0	1 (0.7%)
小腸炎	0	0	1 (1.2%)	1 (0.7%)
鼓腸	0	0	1 (1.2%)	1 (0.7%)
胃障害	0	1 (3.0%)	0	1 (0.7%)
胃食道逆流性疾患	1 (3.4%)	0	0	1 (0.7%)
裂孔ヘルニア	0	1 (3.0%)	0	1 (0.7%)
腰ヘルニア	0	0	1 (1.2%)	1 (0.7%)
口腔内潰瘍形成	0	0	1 (1.2%)	1 (0.7%)
舌嚢胞	0	0	1 (1.2%)	1 (0.7%)
歯痛	0	0	1 (1.2%)	1 (0.7%)
上部消化管出血	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
呼吸器、胸郭および縦隔障害	4 (13.8%)	11 (33.3%)	24 (29.3%)	39 (27.1%)
咳嗽	0	3 (9.1%)	8 (9.8%)	11 (7.6%)
呼吸困難	0	4 (12.1%)	4 (4.9%)	8 (5.6%)
鼻閉	1 (3.4%)	2 (6.1%)	4 (4.9%)	7 (4.9%)
肺動脈性肺高血圧症	1 (3.4%)	1 (3.0%)	3 (3.7%)	5 (3.5%)
労作性呼吸困難	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
鼻出血	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
アレルギー性鼻炎	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
鼻漏	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
アレルギー性副鼻腔炎	0	1 (3.0%)	0	1 (0.7%)
喘息	0	0	1 (1.2%)	1 (0.7%)
気管支反応性亢進	0	0	1 (1.2%)	1 (0.7%)
気管支分泌物貯留	0	1 (3.0%)	0	1 (0.7%)
喀血	0	0	1 (1.2%)	1 (0.7%)
低酸素症	1 (3.4%)	0	0	1 (0.7%)
鼻中隔弯曲	0	0	1 (1.2%)	1 (0.7%)
口腔咽頭痛	0	1 (3.0%)	0	1 (0.7%)
起坐呼吸	0	0	1 (1.2%)	1 (0.7%)
咽頭腫脹	0	0	1 (1.2%)	1 (0.7%)
気胸	0	1 (3.0%)	0	1 (0.7%)
湿性咳嗽	1 (3.4%)	0	0	1 (0.7%)
肺塞栓症	1 (3.4%)	0	0	1 (0.7%)
睡眠時無呼吸症候群	0	0	1 (1.2%)	1 (0.7%)
咽喉刺激感	0	0	1 (1.2%)	1 (0.7%)
気管の炎症	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	2 (6.9%)	10 (30.3%)	26 (31.7%)	38 (26.4%)
末梢性浮腫	1 (3.4%)	2 (6.1%)	13 (15.9%)	16 (11.1%)
発熱	0	5 (15.2%)	2 (2.4%)	7 (4.9%)
末梢腫脹	1 (3.4%)	0	5 (6.1%)	6 (4.2%)
疲労	0	0	4 (4.9%)	4 (2.8%)
胸部不快感	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
胸痛	0	0	2 (2.4%)	2 (1.4%)
悪寒	0	0	2 (2.4%)	2 (1.4%)
非心臓性胸痛	0	0	2 (2.4%)	2 (1.4%)
浮腫	0	2 (6.1%)	0	2 (1.4%)
疼痛	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
顔面腫脹	0	0	2 (2.4%)	2 (1.4%)
無力症	0	0	1 (1.2%)	1 (0.7%)
顔面浮腫	0	1 (3.0%)	0	1 (0.7%)
全身性浮腫	0	0	1 (1.2%)	1 (0.7%)
倦怠感	0	0	1 (1.2%)	1 (0.7%)
腫脹	0	0	1 (1.2%)	1 (0.7%)
口渇	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	7 (24.1%)	5 (15.2%)	22 (26.8%)	34 (23.6%)
ヘモグロビン減少	4 (13.8%)	1 (3.0%)	10 (12.2%)	15 (10.4%)
アラニンアミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
血中ブドウ糖増加	2 (6.9%)	0	0	2 (1.4%)
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	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	0	0	2 (2.4%)	2 (1.4%)
トランスアミナーゼ上昇	0	0	2 (2.4%)	2 (1.4%)
体重減少	0	0	2 (2.4%)	2 (1.4%)
体重増加	0	0	2 (2.4%)	2 (1.4%)
血中アルカリホスファターゼ増加	0	0	1 (1.2%)	1 (0.7%)
血中ビリルビン増加	0	0	1 (1.2%)	1 (0.7%)
血中クレアチニン増加	0	0	1 (1.2%)	1 (0.7%)
血圧上昇	0	0	1 (1.2%)	1 (0.7%)
血中尿酸異常	0	0	1 (1.2%)	1 (0.7%)
血中尿酸増加	0	1 (3.0%)	0	1 (0.7%)
体温上昇	1 (3.4%)	0	0	1 (0.7%)
脳性ナトリウム利尿ペプチド増加	1 (3.4%)	0	0	1 (0.7%)
心雑音	0	0	1 (1.2%)	1 (0.7%)
心拍数増加	1 (3.4%)	0	0	1 (0.7%)
Ｂ型肝炎抗体異常	0	1 (3.0%)	0	1 (0.7%)
好中球数減少	0	0	1 (1.2%)	1 (0.7%)
酸素飽和度低下	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
神経系障害	6 (20.7%)	2 (6.1%)	25 (30.5%)	33 (22.9%)
頭痛	3 (10.3%)	2 (6.1%)	17 (20.7%)	22 (15.3%)
浮動性めまい	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
感覚鈍麻	0	0	3 (3.7%)	3 (2.1%)
失神	0	0	3 (3.7%)	3 (2.1%)
労作性めまい	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
体位性めまい	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
労作性頭痛	0	0	1 (1.2%)	1 (0.7%)
顔面麻痺	0	0	1 (1.2%)	1 (0.7%)
不全片麻痺	0	0	1 (1.2%)	1 (0.7%)
ホルネル症候群	0	0	1 (1.2%)	1 (0.7%)
嗜眠	0	0	1 (1.2%)	1 (0.7%)
片頭痛	0	0	1 (1.2%)	1 (0.7%)
ヘルペス後神経痛	0	0	1 (1.2%)	1 (0.7%)
傾眠	1 (3.4%)	0	0	1 (0.7%)
血液およびリンパ系障害	2 (6.9%)	6 (18.2%)	18 (22.0%)	26 (18.1%)
貧血	1 (3.4%)	4 (12.1%)	11 (13.4%)	16 (11.1%)
鉄欠乏性貧血	0	2 (6.1%)	5 (6.1%)	7 (4.9%)
白血球減少症	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
好中球減少症	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
リンパ球減少症	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
血小板減少症	1 (3.4%)	1 (3.0%)	0	2 (1.4%)
失血性貧血	0	0	1 (1.2%)	1 (0.7%)
骨髄浮腫	0	0	1 (1.2%)	1 (0.7%)
脾機能亢進	0	0	1 (1.2%)	1 (0.7%)
白血球増加症	0	1 (3.0%)	0	1 (0.7%)
単球減少症	0	0	1 (1.2%)	1 (0.7%)
汎血球減少症	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
心臓障害	1 (3.4%)	7 (21.2%)	14 (17.1%)	22 (15.3%)
動悸	0	3 (9.1%)	5 (6.1%)	8 (5.6%)
狭心症	0	0	3 (3.7%)	3 (2.1%)
心房粗動	1 (3.4%)	1 (3.0%)	1 (1.2%)	3 (2.1%)
右室不全	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
心不全	0	0	2 (2.4%)	2 (1.4%)
頻脈	0	0	2 (2.4%)	2 (1.4%)
心房細動	0	0	1 (1.2%)	1 (0.7%)
心血管障害	0	0	1 (1.2%)	1 (0.7%)
肺性心	0	1 (3.0%)	0	1 (0.7%)
左室不全	0	0	1 (1.2%)	1 (0.7%)
心嚢液貯留	0	0	1 (1.2%)	1 (0.7%)
洞結節機能不全	0	1 (3.0%)	0	1 (0.7%)
上室性頻脈	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	4 (13.8%)	5 (15.2%)	12 (14.6%)	21 (14.6%)
低カリウム血症	1 (3.4%)	1 (3.0%)	2 (2.4%)	4 (2.8%)
鉄欠乏	0	0	3 (3.7%)	3 (2.1%)
ビタミンＢ１２欠乏	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
痛風	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
低ナトリウム血症	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
食欲減退	0	0	1 (1.2%)	1 (0.7%)
脱水	0	1 (3.0%)	0	1 (0.7%)
糖尿病	0	0	1 (1.2%)	1 (0.7%)
脂質異常症	0	1 (3.0%)	0	1 (0.7%)
高脂血症	0	0	1 (1.2%)	1 (0.7%)
高尿酸血症	0	0	1 (1.2%)	1 (0.7%)
血液量増加症	1 (3.4%)	0	0	1 (0.7%)
空腹時血中ブドウ糖不良	0	1 (3.0%)	0	1 (0.7%)
２型糖尿病	1 (3.4%)	0	0	1 (0.7%)
ビタミンＤ欠乏	1 (3.4%)	0	0	1 (0.7%)
眼障害	2 (6.9%)	6 (18.2%)	9 (11.0%)	17 (11.8%)
白内障	1 (3.4%)	1 (3.0%)	1 (1.2%)	3 (2.1%)
霧視	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
眼瞼浮腫	0	0	2 (2.4%)	2 (1.4%)
眼充血	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
眼窩周囲浮腫	0	0	2 (2.4%)	2 (1.4%)
眼刺激	0	1 (3.0%)	0	1 (0.7%)
眼痛	0	1 (3.0%)	0	1 (0.7%)
眼部腫脹	0	0	1 (1.2%)	1 (0.7%)
遠視	0	0	1 (1.2%)	1 (0.7%)
網膜出血	1 (3.4%)	0	0	1 (0.7%)
網膜静脈閉塞	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
血管障害	2 (6.9%)	3 (9.1%)	11 (13.4%)	16 (11.1%)
低血圧	1 (3.4%)	1 (3.0%)	8 (9.8%)	10 (6.9%)
潮紅	0	0	2 (2.4%)	2 (1.4%)
血腫	1 (3.4%)	0	0	1 (0.7%)
ほてり	0	1 (3.0%)	0	1 (0.7%)
末梢静脈疾患	0	0	1 (1.2%)	1 (0.7%)
静脈瘤	0	1 (3.0%)	0	1 (0.7%)
傷害、中毒および処置合併症	1 (3.4%)	2 (6.1%)	9 (11.0%)	12 (8.3%)
処置による疼痛	0	0	2 (2.4%)	2 (1.4%)
挫傷	0	0	1 (1.2%)	1 (0.7%)
足骨折	0	1 (3.0%)	0	1 (0.7%)
靭帯断裂	0	0	1 (1.2%)	1 (0.7%)
靭帯捻挫	0	0	1 (1.2%)	1 (0.7%)
過量投与	0	1 (3.0%)	0	1 (0.7%)
放射線肺線維症	1 (3.4%)	0	0	1 (0.7%)
肋骨骨折	0	0	1 (1.2%)	1 (0.7%)
硬膜下血腫	0	0	1 (1.2%)	1 (0.7%)
熱傷	0	0	1 (1.2%)	1 (0.7%)
歯牙破折	0	0	1 (1.2%)	1 (0.7%)
外傷性血腫	0	0	1 (1.2%)	1 (0.7%)
創傷	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
皮膚および皮下組織障害	0	3 (9.1%)	9 (11.0%)	12 (8.3%)
発疹	0	1 (3.0%)	3 (3.7%)	4 (2.8%)
皮膚色素過剰	0	0	3 (3.7%)	3 (2.1%)
血管浮腫	0	0	2 (2.4%)	2 (1.4%)
紅斑	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
ざ瘡	0	0	1 (1.2%)	1 (0.7%)
脱毛症	0	0	1 (1.2%)	1 (0.7%)
冷汗	0	0	1 (1.2%)	1 (0.7%)
接触皮膚炎	0	0	1 (1.2%)	1 (0.7%)
斑状出血	0	0	1 (1.2%)	1 (0.7%)
爪甲剥離症	0	0	1 (1.2%)	1 (0.7%)
丘疹	0	0	1 (1.2%)	1 (0.7%)
そう痒症	0	0	1 (1.2%)	1 (0.7%)
丘疹性皮疹	0	0	1 (1.2%)	1 (0.7%)
皮膚色素減少	0	0	1 (1.2%)	1 (0.7%)
皮膚病変	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
生殖系および乳房障害	1 (3.4%)	2 (6.1%)	8 (9.8%)	11 (7.6%)
重度月経出血	1 (3.4%)	0	3 (3.7%)	4 (2.8%)
子宮ポリープ	0	1 (3.0%)	3 (3.7%)	4 (2.8%)
腺筋症	0	0	2 (2.4%)	2 (1.4%)
月経中間期出血	0	0	2 (2.4%)	2 (1.4%)
卵巣嚢胞	0	0	2 (2.4%)	2 (1.4%)
腟出血	0	0	2 (2.4%)	2 (1.4%)
乳房腫瘤	0	0	1 (1.2%)	1 (0.7%)
子宮頚部嚢胞	0	0	1 (1.2%)	1 (0.7%)
子宮頚外反	0	0	1 (1.2%)	1 (0.7%)
子宮内膜増殖症	0	0	1 (1.2%)	1 (0.7%)
子宮内膜症	0	0	1 (1.2%)	1 (0.7%)
卵巣嚢胞破裂	0	1 (3.0%)	0	1 (0.7%)
骨盤癒着症	0	0	1 (1.2%)	1 (0.7%)
頻発過多月経	0	0	1 (1.2%)	1 (0.7%)
腎および尿路障害	1 (3.4%)	2 (6.1%)	4 (4.9%)	7 (4.9%)
急性腎障害	0	0	2 (2.4%)	2 (1.4%)
慢性腎臓病	1 (3.4%)	1 (3.0%)	0	2 (1.4%)
排尿困難	0	1 (3.0%)	0	1 (0.7%)
膜性糸球体腎炎	0	0	1 (1.2%)	1 (0.7%)
蛋白尿	0	0	1 (1.2%)	1 (0.7%)
腎機能障害	0	0	1 (1.2%)	1 (0.7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (6.9%)	1 (3.0%)	3 (3.7%)	6 (4.2%)
乳癌	2 (6.9%)	0	0	2 (1.4%)
線維腫	0	0	1 (1.2%)	1 (0.7%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
骨髄線維症	0	1 (3.0%)	0	1 (0.7%)
子宮平滑筋腫	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
精神障害	1 (3.4%)	1 (3.0%)	2 (2.4%)	4 (2.8%)
不眠症	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
不安	0	1 (3.0%)	0	1 (0.7%)
肝胆道系障害	0	0	3 (3.7%)	3 (2.1%)
肝硬変	0	0	1 (1.2%)	1 (0.7%)
脂肪肝	0	0	1 (1.2%)	1 (0.7%)
黄疸眼	0	0	1 (1.2%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.2%)	1 (0.7%)
耳および迷路障害	1 (3.4%)	0	0	1 (0.7%)
聴覚過敏	1 (3.4%)	0	0	1 (0.7%)
内分泌障害	1 (3.4%)	0	0	1 (0.7%)
甲状腺腫	1 (3.4%)	0	0	1 (0.7%)
免疫系障害	0	0	1 (1.2%)	1 (0.7%)
過敏症	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more AEs	6 (100.0%)	8 (80.0%)	23 (92.0%)	37 (90.2%)
System organ class Preferred term				
感染症および寄生虫症	3 (50.0%)	6 (60.0%)	16 (64.0%)	25 (61.0%)
ＣＯＶＩＤ－１９	0	2 (20.0%)	9 (36.0%)	11 (26.8%)
上気道感染	0	1 (10.0%)	3 (12.0%)	4 (9.8%)
上咽頭炎	1 (16.7%)	0	1 (4.0%)	2 (4.9%)
気管支炎	0	1 (10.0%)	0	1 (2.4%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (4.0%)	1 (2.4%)
蜂巣炎	0	1 (10.0%)	0	1 (2.4%)
胃腸炎	0	0	1 (4.0%)	1 (2.4%)
クロストリジウム菌性胃腸炎	0	0	1 (4.0%)	1 (2.4%)
インフルエンザ	0	0	1 (4.0%)	1 (2.4%)
肺炎	0	0	1 (4.0%)	1 (2.4%)
ウイルス性肺炎	0	0	1 (4.0%)	1 (2.4%)
副鼻腔炎	1 (16.7%)	0	0	1 (2.4%)
ＣＯＶＩＤ－１９の疑い	1 (16.7%)	0	0	1 (2.4%)
尿路感染	0	1 (10.0%)	0	1 (2.4%)
ウイルス性上気道感染	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	3 (50.0%)	1 (10.0%)	9 (36.0%)	13 (31.7%)
胃食道逆流性疾患	2 (33.3%)	0	1 (4.0%)	3 (7.3%)
腹部不快感	0	0	2 (8.0%)	2 (4.9%)
下痢	0	0	2 (8.0%)	2 (4.9%)
痔出血	0	0	2 (8.0%)	2 (4.9%)
嘔吐	0	0	2 (8.0%)	2 (4.9%)
口内乾燥	0	0	1 (4.0%)	1 (2.4%)
消化不良	0	0	1 (4.0%)	1 (2.4%)
小腸炎	0	0	1 (4.0%)	1 (2.4%)
鼓腸	0	1 (10.0%)	0	1 (2.4%)
排便回数増加	1 (16.7%)	0	0	1 (2.4%)
胃炎	0	0	1 (4.0%)	1 (2.4%)
胃腸障害	0	0	1 (4.0%)	1 (2.4%)
痔核	0	0	1 (4.0%)	1 (2.4%)
悪心	0	0	1 (4.0%)	1 (2.4%)
亜イレウス	1 (16.7%)	0	0	1 (2.4%)
歯痛	0	0	1 (4.0%)	1 (2.4%)
呼吸器、胸郭および縦隔障害	2 (33.3%)	3 (30.0%)	7 (28.0%)	12 (29.3%)
咳嗽	0	1 (10.0%)	2 (8.0%)	3 (7.3%)
呼吸困難	0	1 (10.0%)	2 (8.0%)	3 (7.3%)
肺動脈性肺高血圧症	1 (16.7%)	1 (10.0%)	1 (4.0%)	3 (7.3%)
鼻閉	0	0	2 (8.0%)	2 (4.9%)
労作性呼吸困難	0	0	1 (4.0%)	1 (2.4%)
鼻出血	0	0	1 (4.0%)	1 (2.4%)
低酸素症	1 (16.7%)	0	0	1 (2.4%)
口腔咽頭痛	0	0	1 (4.0%)	1 (2.4%)
肺静脈閉塞性疾患	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
心臓障害	1 (16.7%)	1 (10.0%)	8 (32.0%)	10 (24.4%)
右室不全	1 (16.7%)	0	2 (8.0%)	3 (7.3%)
心不全	0	0	2 (8.0%)	2 (4.9%)
冠動脈疾患	0	0	2 (8.0%)	2 (4.9%)
動悸	0	0	2 (8.0%)	2 (4.9%)
狭心症	0	0	1 (4.0%)	1 (2.4%)
徐脈	0	0	1 (4.0%)	1 (2.4%)
頻脈	0	1 (10.0%)	0	1 (2.4%)
心室性不整脈	0	0	1 (4.0%)	1 (2.4%)
心室性期外収縮	0	0	1 (4.0%)	1 (2.4%)
一般・全身障害および投与部位の状態	0	1 (10.0%)	8 (32.0%)	9 (22.0%)
末梢性浮腫	0	1 (10.0%)	3 (12.0%)	4 (9.8%)
末梢腫脹	0	0	3 (12.0%)	3 (7.3%)
発熱	0	0	3 (12.0%)	3 (7.3%)
疲労	0	0	1 (4.0%)	1 (2.4%)
非心臓性胸痛	0	0	1 (4.0%)	1 (2.4%)
ポリープ	0	0	1 (4.0%)	1 (2.4%)
筋骨格系および結合組織障害	2 (33.3%)	1 (10.0%)	6 (24.0%)	9 (22.0%)
関節痛	1 (16.7%)	1 (10.0%)	2 (8.0%)	4 (9.8%)
筋肉痛	0	0	2 (8.0%)	2 (4.9%)
滑液包炎	0	1 (10.0%)	0	1 (2.4%)
椎間板突出	1 (16.7%)	0	0	1 (2.4%)
四肢不快感	0	0	1 (4.0%)	1 (2.4%)
変形性関節症	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	0	1 (10.0%)	7 (28.0%)	8 (19.5%)
高尿酸血症	0	0	2 (8.0%)	2 (4.9%)
食欲減退	0	1 (10.0%)	0	1 (2.4%)
高血糖	0	0	1 (4.0%)	1 (2.4%)
高カリウム血症	0	0	1 (4.0%)	1 (2.4%)
高脂血症	0	0	1 (4.0%)	1 (2.4%)
低カリウム血症	0	0	1 (4.0%)	1 (2.4%)
鉄欠乏	0	0	1 (4.0%)	1 (2.4%)
ビタミンＢ１２欠乏	0	0	1 (4.0%)	1 (2.4%)
神経系障害	0	0	8 (32.0%)	8 (19.5%)
頭痛	0	0	4 (16.0%)	4 (9.8%)
浮動性めまい	0	0	3 (12.0%)	3 (7.3%)
失神寸前の状態	0	0	1 (4.0%)	1 (2.4%)
血液およびリンパ系障害	2 (33.3%)	1 (10.0%)	4 (16.0%)	7 (17.1%)
貧血	1 (16.7%)	1 (10.0%)	1 (4.0%)	3 (7.3%)
慢性疾患の貧血	0	0	1 (4.0%)	1 (2.4%)
鉄欠乏性貧血	0	0	1 (4.0%)	1 (2.4%)
白血球増加症	1 (16.7%)	0	0	1 (2.4%)
正色素性貧血	0	0	1 (4.0%)	1 (2.4%)
臨床検査	2 (33.3%)	1 (10.0%)	4 (16.0%)	7 (17.1%)
ヘモグロビン減少	0	0	2 (8.0%)	2 (4.9%)
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 (16.7%)	0	0	1 (2.4%)
血小板数減少	0	0	1 (4.0%)	1 (2.4%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	1 (16.7%)	0	0	1 (2.4%)
体重減少	0	1 (10.0%)	0	1 (2.4%)
体重増加	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
皮膚および皮下組織障害	0	1 (10.0%)	6 (24.0%)	7 (17.1%)
発疹	0	1 (10.0%)	1 (4.0%)	2 (4.9%)
皮膚乾燥	0	0	1 (4.0%)	1 (2.4%)
過剰肉芽組織	0	0	1 (4.0%)	1 (2.4%)
過角化	0	0	1 (4.0%)	1 (2.4%)
そう痒症	0	0	1 (4.0%)	1 (2.4%)
皮膚潰瘍	0	0	1 (4.0%)	1 (2.4%)
腎および尿路障害	1 (16.7%)	0	3 (12.0%)	4 (9.8%)
腎機能障害	0	0	2 (8.0%)	2 (4.9%)
血尿	1 (16.7%)	0	0	1 (2.4%)
ループス腎炎	0	0	1 (4.0%)	1 (2.4%)
尿閉	1 (16.7%)	0	0	1 (2.4%)
血管障害	0	1 (10.0%)	3 (12.0%)	4 (9.8%)
低血圧	0	0	2 (8.0%)	2 (4.9%)
潮紅	0	0	1 (4.0%)	1 (2.4%)
ほてり	0	0	1 (4.0%)	1 (2.4%)
高血圧	0	1 (10.0%)	0	1 (2.4%)
傷害、中毒および処置合併症	1 (16.7%)	1 (10.0%)	1 (4.0%)	3 (7.3%)
上顎炎	0	1 (10.0%)	0	1 (2.4%)
転倒	0	0	1 (4.0%)	1 (2.4%)
ワクチン接種後症候群	1 (16.7%)	0	0	1 (2.4%)
眼障害	0	0	2 (8.0%)	2 (4.9%)
白内障	0	0	1 (4.0%)	1 (2.4%)
視力障害	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL02E: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
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）	0	1 (10.0%)	1 (4.0%)	2 (4.9%)
基底細胞癌	0	1 (10.0%)	0	1 (2.4%)
前立腺癌	0	0	1 (4.0%)	1 (2.4%)
肝胆道系障害	0	0	1 (4.0%)	1 (2.4%)
薬物性肝障害	0	0	1 (4.0%)	1 (2.4%)
免疫系障害	1 (16.7%)	0	0	1 (2.4%)
節足動物刺傷アレルギー	1 (16.7%)	0	0	1 (2.4%)
精神障害	1 (16.7%)	0	0	1 (2.4%)
不眠症	1 (16.7%)	0	0	1 (2.4%)
生殖系および乳房障害	0	0	1 (4.0%)	1 (2.4%)
女性化乳房	0	0	1 (4.0%)	1 (2.4%)

[TSFAEOL02E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02E.SAS] 02MAR2023, 08:36

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more AEs	18 (90.0%)	26 (89.7%)	61 (92.4%)	105 (91.3%)
System organ class				
Preferred term				

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander
Note: If race is not reported, the subjects are excluded.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	10 (50.0%)	14 (48.3%)	25 (37.9%)	49 (42.6%)
ＣＯＶＩＤ－１９	3 (15.0%)	5 (17.2%)	9 (13.6%)	17 (14.8%)
尿路感染	1 (5.0%)	3 (10.3%)	3 (4.5%)	7 (6.1%)
上気道感染	1 (5.0%)	3 (10.3%)	2 (3.0%)	6 (5.2%)
インフルエンザ	0	0	4 (6.1%)	4 (3.5%)
副鼻腔炎	1 (5.0%)	1 (3.4%)	2 (3.0%)	4 (3.5%)
上咽頭炎	0	1 (3.4%)	2 (3.0%)	3 (2.6%)
気管支炎	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
ＣＯＶＩＤ－１９肺炎	0	0	2 (3.0%)	2 (1.7%)
蜂巣炎	1 (5.0%)	1 (3.4%)	0	2 (1.7%)
口腔ヘルペス	0	0	2 (3.0%)	2 (1.7%)
肺炎	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
急性副鼻腔炎	0	0	1 (1.5%)	1 (0.9%)
体部白癬	1 (5.0%)	0	0	1 (0.9%)
細菌性気管支炎	0	0	1 (1.5%)	1 (0.9%)
カンジダ感染	0	1 (3.4%)	0	1 (0.9%)
子宮頚管炎	0	0	1 (1.5%)	1 (0.9%)
慢性扁桃炎	0	0	1 (1.5%)	1 (0.9%)
結膜炎	1 (5.0%)	0	0	1 (0.9%)
憩室炎	1 (5.0%)	0	0	1 (0.9%)
子宮内膜炎	0	0	1 (1.5%)	1 (0.9%)
クロストリジウム菌性胃腸炎	0	0	1 (1.5%)	1 (0.9%)
消化管感染	0	0	1 (1.5%)	1 (0.9%)
陰部ヘルペス	0	0	1 (1.5%)	1 (0.9%)
歯肉炎	0	0	1 (1.5%)	1 (0.9%)
血液学的感染	0	0	1 (1.5%)	1 (0.9%)
Ｂ型肝炎	0	0	1 (1.5%)	1 (0.9%)
帯状疱疹	0	0	1 (1.5%)	1 (0.9%)
限局性感染	1 (5.0%)	0	0	1 (0.9%)
食道カンジダ症	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
中耳炎	0	1 (3.4%)	0	1 (0.9%)
耳管炎	0	0	1 (1.5%)	1 (0.9%)
パラインフルエンザウイルス感染	0	0	1 (1.5%)	1 (0.9%)
咽頭炎	0	1 (3.4%)	0	1 (0.9%)
細菌性咽頭炎	1 (5.0%)	0	0	1 (0.9%)
咽頭扁桃炎	0	1 (3.4%)	0	1 (0.9%)
細菌性肺炎	0	0	1 (1.5%)	1 (0.9%)
シュードモナス性肺炎	0	1 (3.4%)	0	1 (0.9%)
ブドウ球菌性肺炎	0	1 (3.4%)	0	1 (0.9%)
ウイルス性肺炎	0	0	1 (1.5%)	1 (0.9%)
気道感染	0	0	1 (1.5%)	1 (0.9%)
ウイルス性気道感染	1 (5.0%)	0	0	1 (0.9%)
鼻炎	1 (5.0%)	0	0	1 (0.9%)
卵管卵巣炎	0	0	1 (1.5%)	1 (0.9%)
歯膿瘍	0	0	1 (1.5%)	1 (0.9%)
腟感染	0	1 (3.4%)	0	1 (0.9%)
ウイルス感染	0	0	1 (1.5%)	1 (0.9%)
ウイルス性上気道感染	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	5 (25.0%)	6 (20.7%)	24 (36.4%)	35 (30.4%)
嘔吐	0	2 (6.9%)	5 (7.6%)	7 (6.1%)
下痢	0	1 (3.4%)	5 (7.6%)	6 (5.2%)
悪心	0	0	6 (9.1%)	6 (5.2%)
胃炎	3 (15.0%)	0	2 (3.0%)	5 (4.3%)
口内乾燥	0	0	3 (4.5%)	3 (2.6%)
消化不良	0	0	3 (4.5%)	3 (2.6%)
腹痛	0	0	2 (3.0%)	2 (1.7%)
便秘	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
鼓腸	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
胃食道逆流性疾患	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
痔出血	0	0	2 (3.0%)	2 (1.7%)
痔核	0	0	2 (3.0%)	2 (1.7%)
食道炎	0	0	2 (3.0%)	2 (1.7%)
歯痛	0	0	2 (3.0%)	2 (1.7%)
腹部不快感	0	0	1 (1.5%)	1 (0.9%)
腹部膨満	0	0	1 (1.5%)	1 (0.9%)
大腸炎	0	0	1 (1.5%)	1 (0.9%)
虚血性大腸炎	0	1 (3.4%)	0	1 (0.9%)
小腸炎	0	0	1 (1.5%)	1 (0.9%)
排便回数増加	1 (5.0%)	0	0	1 (0.9%)
胃障害	0	1 (3.4%)	0	1 (0.9%)
胃腸障害	0	0	1 (1.5%)	1 (0.9%)
裂孔ヘルニア	0	1 (3.4%)	0	1 (0.9%)
腰ヘルニア	0	0	1 (1.5%)	1 (0.9%)
亜イレウス	1 (5.0%)	0	0	1 (0.9%)
舌嚢胞	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
呼吸器、胸郭および縦隔障害	4 (20.0%)	10 (34.5%)	20 (30.3%)	34 (29.6%)
咳嗽	0	1 (3.4%)	8 (12.1%)	9 (7.8%)
呼吸困難	0	4 (13.8%)	3 (4.5%)	7 (6.1%)
肺動脈性肺高血圧症	1 (5.0%)	2 (6.9%)	3 (4.5%)	6 (5.2%)
鼻閉	0	0	5 (7.6%)	5 (4.3%)
鼻出血	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
低酸素症	2 (10.0%)	0	0	2 (1.7%)
アレルギー性鼻炎	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
鼻漏	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
アレルギー性副鼻腔炎	0	1 (3.4%)	0	1 (0.9%)
気管支反応性亢進	0	0	1 (1.5%)	1 (0.9%)
気管支分泌物貯留	0	1 (3.4%)	0	1 (0.9%)
鼻中隔弯曲	0	0	1 (1.5%)	1 (0.9%)
口腔咽頭痛	0	1 (3.4%)	0	1 (0.9%)
起坐呼吸	0	0	1 (1.5%)	1 (0.9%)
咽頭腫脹	0	0	1 (1.5%)	1 (0.9%)
気胸	0	1 (3.4%)	0	1 (0.9%)
湿性咳嗽	1 (5.0%)	0	0	1 (0.9%)
肺塞栓症	1 (5.0%)	0	0	1 (0.9%)
睡眠時無呼吸症候群	0	0	1 (1.5%)	1 (0.9%)
咽喉刺激感	0	0	1 (1.5%)	1 (0.9%)
気管の炎症	0	1 (3.4%)	0	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	8 (40.0%)	4 (13.8%)	17 (25.8%)	29 (25.2%)
関節痛	2 (10.0%)	2 (6.9%)	4 (6.1%)	8 (7.0%)
背部痛	2 (10.0%)	1 (3.4%)	4 (6.1%)	7 (6.1%)
変形性関節症	0	0	3 (4.5%)	3 (2.6%)
四肢痛	1 (5.0%)	0	2 (3.0%)	3 (2.6%)
全身性強皮症	2 (10.0%)	0	0	2 (1.7%)
滑液包炎	0	1 (3.4%)	0	1 (0.9%)
椎間板突出	1 (5.0%)	0	0	1 (0.9%)
四肢不快感	0	0	1 (1.5%)	1 (0.9%)
筋骨格系胸痛	0	0	1 (1.5%)	1 (0.9%)
筋骨格痛	0	0	1 (1.5%)	1 (0.9%)
筋肉痛	1 (5.0%)	0	0	1 (0.9%)
骨軟骨炎	0	0	1 (1.5%)	1 (0.9%)
骨壊死	0	0	1 (1.5%)	1 (0.9%)
骨減少症	0	0	1 (1.5%)	1 (0.9%)
顎痛	0	0	1 (1.5%)	1 (0.9%)
足底筋膜炎	0	1 (3.4%)	0	1 (0.9%)
仙腸骨炎	0	0	1 (1.5%)	1 (0.9%)
シェーグレン症候群	0	0	1 (1.5%)	1 (0.9%)
全身性エリテマトーデス	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	1 (5.0%)	4 (13.8%)	22 (33.3%)	27 (23.5%)
末梢性浮腫	1 (5.0%)	1 (3.4%)	11 (16.7%)	13 (11.3%)
末梢腫脹	0	0	5 (7.6%)	5 (4.3%)
発熱	0	3 (10.3%)	2 (3.0%)	5 (4.3%)
疲労	0	0	4 (6.1%)	4 (3.5%)
非心臓性胸痛	0	0	3 (4.5%)	3 (2.6%)
顔面腫脹	0	0	2 (3.0%)	2 (1.7%)
無力症	0	0	1 (1.5%)	1 (0.9%)
胸部不快感	0	0	1 (1.5%)	1 (0.9%)
悪寒	0	0	1 (1.5%)	1 (0.9%)
全身性浮腫	0	0	1 (1.5%)	1 (0.9%)
疼痛	0	0	1 (1.5%)	1 (0.9%)
ポリープ	0	0	1 (1.5%)	1 (0.9%)
腫脹	0	0	1 (1.5%)	1 (0.9%)
口渇	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	6 (30.0%)	4 (13.8%)	17 (25.8%)	27 (23.5%)
ヘモグロビン減少	3 (15.0%)	1 (3.4%)	7 (10.6%)	11 (9.6%)
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 (5.0%)	1 (3.4%)	1 (1.5%)	3 (2.6%)
血中ブドウ糖増加	2 (10.0%)	0	0	2 (1.7%)
トランスアミナーゼ上昇	0	0	2 (3.0%)	2 (1.7%)
体重減少	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
体重増加	0	0	2 (3.0%)	2 (1.7%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
血中アルカリホスファターゼ増加	0	0	1 (1.5%)	1 (0.9%)
血中ビリルビン増加	0	0	1 (1.5%)	1 (0.9%)
血中クレアチニン増加	0	0	1 (1.5%)	1 (0.9%)
血中尿酸異常	0	0	1 (1.5%)	1 (0.9%)
血中尿酸増加	0	1 (3.4%)	0	1 (0.9%)
体温上昇	1 (5.0%)	0	0	1 (0.9%)
脳性ナトリウム利尿ペプチド増加	1 (5.0%)	0	0	1 (0.9%)
心雑音	0	0	1 (1.5%)	1 (0.9%)
好中球数減少	0	0	1 (1.5%)	1 (0.9%)
酸素飽和度低下	0	0	1 (1.5%)	1 (0.9%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
神経系障害	4 (20.0%)	1 (3.4%)	22 (33.3%)	27 (23.5%)
頭痛	2 (10.0%)	1 (3.4%)	16 (24.2%)	19 (16.5%)
労作性めまい	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
体位性めまい	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
感覚鈍麻	0	0	2 (3.0%)	2 (1.7%)
失神	0	0	2 (3.0%)	2 (1.7%)
労作性頭痛	0	0	1 (1.5%)	1 (0.9%)
顔面麻痺	0	0	1 (1.5%)	1 (0.9%)
ホルネル症候群	0	0	1 (1.5%)	1 (0.9%)
片頭痛	0	0	1 (1.5%)	1 (0.9%)
ヘルペス後神経痛	0	0	1 (1.5%)	1 (0.9%)
失神寸前の状態	0	0	1 (1.5%)	1 (0.9%)
傾眠	1 (5.0%)	0	0	1 (0.9%)
血液およびリンパ系障害	3 (15.0%)	6 (20.7%)	13 (19.7%)	22 (19.1%)
貧血	1 (5.0%)	4 (13.8%)	6 (9.1%)	11 (9.6%)
鉄欠乏性貧血	0	2 (6.9%)	5 (7.6%)	7 (6.1%)
白血球減少症	1 (5.0%)	0	2 (3.0%)	3 (2.6%)
好中球減少症	1 (5.0%)	0	2 (3.0%)	3 (2.6%)
白血球増加症	1 (5.0%)	1 (3.4%)	0	2 (1.7%)
リンパ球減少症	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
血小板減少症	1 (5.0%)	1 (3.4%)	0	2 (1.7%)
失血性貧血	0	0	1 (1.5%)	1 (0.9%)
骨髄浮腫	0	0	1 (1.5%)	1 (0.9%)
脾機能亢進	0	0	1 (1.5%)	1 (0.9%)
単球減少症	0	0	1 (1.5%)	1 (0.9%)
汎血球減少症	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
心臓障害	1 (5.0%)	6 (20.7%)	13 (19.7%)	20 (17.4%)
動悸	0	1 (3.4%)	3 (4.5%)	4 (3.5%)
右室不全	1 (5.0%)	1 (3.4%)	2 (3.0%)	4 (3.5%)
狭心症	0	0	3 (4.5%)	3 (2.6%)
頻脈	0	1 (3.4%)	2 (3.0%)	3 (2.6%)
心不全	0	0	2 (3.0%)	2 (1.7%)
冠動脈疾患	0	0	2 (3.0%)	2 (1.7%)
心房細動	0	0	1 (1.5%)	1 (0.9%)
心房粗動	0	1 (3.4%)	0	1 (0.9%)
徐脈	0	0	1 (1.5%)	1 (0.9%)
心血管障害	0	0	1 (1.5%)	1 (0.9%)
肺性心	0	1 (3.4%)	0	1 (0.9%)
左室不全	0	0	1 (1.5%)	1 (0.9%)
洞結節機能不全	0	1 (3.4%)	0	1 (0.9%)
上室性頻脈	0	0	1 (1.5%)	1 (0.9%)
心室性期外収縮	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	2 (10.0%)	4 (13.8%)	12 (18.2%)	18 (15.7%)
ビタミンＢ１２欠乏	1 (5.0%)	0	3 (4.5%)	4 (3.5%)
鉄欠乏	0	0	3 (4.5%)	3 (2.6%)
食欲減退	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
痛風	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
高脂血症	0	0	2 (3.0%)	2 (1.7%)
脱水	0	1 (3.4%)	0	1 (0.9%)
糖尿病	0	0	1 (1.5%)	1 (0.9%)
高血糖	0	0	1 (1.5%)	1 (0.9%)
高カリウム血症	0	0	1 (1.5%)	1 (0.9%)
高尿酸血症	0	0	1 (1.5%)	1 (0.9%)
血液量増加症	1 (5.0%)	0	0	1 (0.9%)
低カリウム血症	0	1 (3.4%)	0	1 (0.9%)
低ナトリウム血症	0	1 (3.4%)	0	1 (0.9%)
ビタミンＤ欠乏	1 (5.0%)	0	0	1 (0.9%)
血管障害	2 (10.0%)	3 (10.3%)	13 (19.7%)	18 (15.7%)
低血圧	1 (5.0%)	1 (3.4%)	9 (13.6%)	11 (9.6%)
潮紅	0	0	3 (4.5%)	3 (2.6%)
血腫	1 (5.0%)	0	0	1 (0.9%)
ほてり	0	0	1 (1.5%)	1 (0.9%)
高血圧	0	1 (3.4%)	0	1 (0.9%)
末梢静脈疾患	0	0	1 (1.5%)	1 (0.9%)
静脈瘤	0	1 (3.4%)	0	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
眼障害	2 (10.0%)	4 (13.8%)	8 (12.1%)	14 (12.2%)
白内障	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
眼充血	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
眼窩周囲浮腫	0	0	2 (3.0%)	2 (1.7%)
眼刺激	0	1 (3.4%)	0	1 (0.9%)
眼痛	0	1 (3.4%)	0	1 (0.9%)
眼部腫脹	0	0	1 (1.5%)	1 (0.9%)
眼瞼浮腫	0	0	1 (1.5%)	1 (0.9%)
遠視	0	0	1 (1.5%)	1 (0.9%)
網膜出血	1 (5.0%)	0	0	1 (0.9%)
網膜静脈閉塞	0	1 (3.4%)	0	1 (0.9%)
霧視	0	0	1 (1.5%)	1 (0.9%)
視力障害	0	0	1 (1.5%)	1 (0.9%)
皮膚および皮下組織障害	0	4 (13.8%)	9 (13.6%)	13 (11.3%)
発疹	0	2 (6.9%)	3 (4.5%)	5 (4.3%)
紅斑	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
ざ瘡	0	0	1 (1.5%)	1 (0.9%)
血管浮腫	0	0	1 (1.5%)	1 (0.9%)
冷汗	0	0	1 (1.5%)	1 (0.9%)
接触皮膚炎	0	0	1 (1.5%)	1 (0.9%)
斑状出血	0	0	1 (1.5%)	1 (0.9%)
過剰肉芽組織	0	0	1 (1.5%)	1 (0.9%)
皮膚色素過剰	0	0	1 (1.5%)	1 (0.9%)
皮膚病変	0	1 (3.4%)	0	1 (0.9%)
皮膚潰瘍	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
生殖系および乳房障害	1 (5.0%)	2 (6.9%)	8 (12.1%)	11 (9.6%)
子宮ポリープ	0	1 (3.4%)	3 (4.5%)	4 (3.5%)
重度月経出血	1 (5.0%)	0	2 (3.0%)	3 (2.6%)
腺筋症	0	0	2 (3.0%)	2 (1.7%)
月経中間期出血	0	0	2 (3.0%)	2 (1.7%)
卵巣嚢胞	0	0	2 (3.0%)	2 (1.7%)
腟出血	0	0	2 (3.0%)	2 (1.7%)
乳房腫瘤	0	0	1 (1.5%)	1 (0.9%)
子宮頚部嚢胞	0	0	1 (1.5%)	1 (0.9%)
子宮頚外反	0	0	1 (1.5%)	1 (0.9%)
子宮内膜増殖症	0	0	1 (1.5%)	1 (0.9%)
子宮内膜症	0	0	1 (1.5%)	1 (0.9%)
女性化乳房	0	0	1 (1.5%)	1 (0.9%)
卵巣嚢胞破裂	0	1 (3.4%)	0	1 (0.9%)
骨盤癒着症	0	0	1 (1.5%)	1 (0.9%)
頻発過多月経	0	0	1 (1.5%)	1 (0.9%)
傷害、中毒および処置合併症	1 (5.0%)	3 (10.3%)	5 (7.6%)	9 (7.8%)
処置による疼痛	0	0	2 (3.0%)	2 (1.7%)
上顆炎	0	1 (3.4%)	0	1 (0.9%)
転倒	0	0	1 (1.5%)	1 (0.9%)
足骨折	0	1 (3.4%)	0	1 (0.9%)
靭帯断裂	0	0	1 (1.5%)	1 (0.9%)
過量投与	0	1 (3.4%)	0	1 (0.9%)
放射線肺線維症	1 (5.0%)	0	0	1 (0.9%)
歯牙破折	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (5.0%)	2 (6.9%)	3 (4.5%)	6 (5.2%)
基底細胞癌	0	1 (3.4%)	0	1 (0.9%)
乳癌	1 (5.0%)	0	0	1 (0.9%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.5%)	1 (0.9%)
骨髄線維症	0	1 (3.4%)	0	1 (0.9%)
前立腺癌	0	0	1 (1.5%)	1 (0.9%)
子宮平滑筋腫	0	0	1 (1.5%)	1 (0.9%)
腎および尿路障害	1 (5.0%)	2 (6.9%)	3 (4.5%)	6 (5.2%)
慢性腎臓病	1 (5.0%)	1 (3.4%)	0	2 (1.7%)
急性腎障害	0	0	1 (1.5%)	1 (0.9%)
排尿困難	0	1 (3.4%)	0	1 (0.9%)
膜性糸球体腎炎	0	0	1 (1.5%)	1 (0.9%)
蛋白尿	0	0	1 (1.5%)	1 (0.9%)
腎機能障害	0	0	1 (1.5%)	1 (0.9%)
肝胆道系障害	0	0	3 (4.5%)	3 (2.6%)
薬物性肝障害	0	0	1 (1.5%)	1 (0.9%)
脂肪肝	0	0	1 (1.5%)	1 (0.9%)
黄疸眼	0	0	1 (1.5%)	1 (0.9%)
耳および迷路障害	1 (5.0%)	0	0	1 (0.9%)
聴覚過敏	1 (5.0%)	0	0	1 (0.9%)
内分泌障害	1 (5.0%)	0	0	1 (0.9%)
甲状腺腫	1 (5.0%)	0	0	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
免疫系障害	0	0	1 (1.5%)	1 (0.9%)
過敏症	0	0	1 (1.5%)	1 (0.9%)
精神障害	0	1 (3.4%)	0	1 (0.9%)
不安	0	1 (3.4%)	0	1 (0.9%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African American	1	2	2	5
Subjects with 1 or more AEs	1 (100.0%)	2 (100.0%)	2 (100.0%)	5 (100.0%)
System organ class Preferred term				
筋骨格系および結合組織障害	1 (100.0%)	1 (50.0%)	1 (50.0%)	3 (60.0%)
関節痛	1 (100.0%)	0	0	1 (20.0%)
筋骨格不快感	0	1 (50.0%)	0	1 (20.0%)
筋肉痛	0	0	1 (50.0%)	1 (20.0%)
骨粗鬆症	1 (100.0%)	0	0	1 (20.0%)
一般・全身障害および投与部位の状態	0	2 (100.0%)	0	2 (40.0%)
胸部不快感	0	1 (50.0%)	0	1 (20.0%)
顔面浮腫	0	1 (50.0%)	0	1 (20.0%)
浮腫	0	1 (50.0%)	0	1 (20.0%)
疼痛	0	1 (50.0%)	0	1 (20.0%)
臨床検査	0	1 (50.0%)	1 (50.0%)	2 (40.0%)
ヘモグロビン減少	0	0	1 (50.0%)	1 (20.0%)
Ｂ型肝炎抗体異常	0	1 (50.0%)	0	1 (20.0%)
心臓障害	0	1 (50.0%)	0	1 (20.0%)
動悸	0	1 (50.0%)	0	1 (20.0%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
眼障害	0	1 (50.0%)	0	1 (20.0%)
霧視	0	1 (50.0%)	0	1 (20.0%)
傷害、中毒および処置合併症	0	0	1 (50.0%)	1 (20.0%)
外傷性血腫	0	0	1 (50.0%)	1 (20.0%)
神経系障害	0	1 (50.0%)	0	1 (20.0%)
頭痛	0	1 (50.0%)	0	1 (20.0%)
呼吸器、胸郭および縦隔障害	0	1 (50.0%)	0	1 (20.0%)
咳嗽	0	1 (50.0%)	0	1 (20.0%)
呼吸困難	0	1 (50.0%)	0	1 (20.0%)
鼻閉	0	1 (50.0%)	0	1 (20.0%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more AEs	11 (91.7%)	9 (90.0%)	35 (97.2%)	55 (94.8%)
System organ class Preferred term				
感染症および寄生虫症	8 (66.7%)	5 (50.0%)	24 (66.7%)	37 (63.8%)
ＣＯＶＩＤ－１９	3 (25.0%)	3 (30.0%)	16 (44.4%)	22 (37.9%)
上気道感染	2 (16.7%)	1 (10.0%)	3 (8.3%)	6 (10.3%)
上咽頭炎	1 (8.3%)	1 (10.0%)	2 (5.6%)	4 (6.9%)
肺炎	0	1 (10.0%)	3 (8.3%)	4 (6.9%)
ＣＯＶＩＤ－１９の疑い	2 (16.7%)	0	0	2 (3.4%)
尿路感染	0	0	2 (5.6%)	2 (3.4%)
真菌性肛門感染	0	0	1 (2.8%)	1 (1.7%)
細菌感染	0	0	1 (2.8%)	1 (1.7%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (2.8%)	1 (1.7%)
蜂巣炎	0	0	1 (2.8%)	1 (1.7%)
結膜炎	0	1 (10.0%)	0	1 (1.7%)
サイトメガロウイルス性脈絡網膜炎	0	0	1 (2.8%)	1 (1.7%)
胃腸炎	0	0	1 (2.8%)	1 (1.7%)
Ｂ型肝炎	1 (8.3%)	0	0	1 (1.7%)
Ｃ型肝炎	0	1 (10.0%)	0	1 (1.7%)
限局性感染	0	0	1 (2.8%)	1 (1.7%)
口腔ヘルペス	1 (8.3%)	0	0	1 (1.7%)
歯冠周囲炎	0	0	1 (2.8%)	1 (1.7%)
急性ＣＯＶＩＤ－１９後症候群	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	1 (8.3%)	5 (50.0%)	12 (33.3%)	18 (31.0%)
末梢性浮腫	0	2 (20.0%)	5 (13.9%)	7 (12.1%)
発熱	0	2 (20.0%)	3 (8.3%)	5 (8.6%)
末梢腫脹	1 (8.3%)	0	3 (8.3%)	4 (6.9%)
胸痛	0	0	2 (5.6%)	2 (3.4%)
胸部不快感	0	0	1 (2.8%)	1 (1.7%)
悪寒	0	0	1 (2.8%)	1 (1.7%)
疲労	0	0	1 (2.8%)	1 (1.7%)
倦怠感	0	0	1 (2.8%)	1 (1.7%)
浮腫	0	1 (10.0%)	0	1 (1.7%)
筋骨格系および結合組織障害	4 (33.3%)	2 (20.0%)	11 (30.6%)	17 (29.3%)
筋肉痛	2 (16.7%)	1 (10.0%)	5 (13.9%)	8 (13.8%)
四肢痛	0	1 (10.0%)	3 (8.3%)	4 (6.9%)
関節痛	0	0	2 (5.6%)	2 (3.4%)
椎間板突出	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
背部痛	0	0	1 (2.8%)	1 (1.7%)
筋力低下	0	0	1 (2.8%)	1 (1.7%)
筋骨格系胸痛	1 (8.3%)	0	0	1 (1.7%)
筋骨格痛	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	3 (25.0%)	1 (10.0%)	11 (30.6%)	15 (25.9%)
腹部不快感	1 (8.3%)	0	2 (5.6%)	3 (5.2%)
腹痛	0	0	2 (5.6%)	2 (3.4%)
上腹部痛	0	0	2 (5.6%)	2 (3.4%)
胃炎	0	0	2 (5.6%)	2 (3.4%)
胃食道逆流性疾患	2 (16.7%)	0	0	2 (3.4%)
痔出血	0	0	2 (5.6%)	2 (3.4%)
悪心	0	1 (10.0%)	1 (2.8%)	2 (3.4%)
食道静脈瘤	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
慢性胃炎	1 (8.3%)	0	0	1 (1.7%)
便秘	0	1 (10.0%)	0	1 (1.7%)
下痢	0	0	1 (2.8%)	1 (1.7%)
消化不良	0	0	1 (2.8%)	1 (1.7%)
小腸炎	0	0	1 (2.8%)	1 (1.7%)
口腔内潰瘍形成	0	0	1 (2.8%)	1 (1.7%)
上部消化管出血	0	0	1 (2.8%)	1 (1.7%)
嘔吐	0	0	1 (2.8%)	1 (1.7%)
呼吸器、胸郭および縦隔障害	1 (8.3%)	3 (30.0%)	11 (30.6%)	15 (25.9%)
咳嗽	0	2 (20.0%)	2 (5.6%)	4 (6.9%)
労作性呼吸困難	0	1 (10.0%)	3 (8.3%)	4 (6.9%)
呼吸困難	0	0	3 (8.3%)	3 (5.2%)
鼻出血	0	0	2 (5.6%)	2 (3.4%)
鼻閉	0	1 (10.0%)	1 (2.8%)	2 (3.4%)
肺動脈性肺高血圧症	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
喘息	0	0	1 (2.8%)	1 (1.7%)
喀血	0	0	1 (2.8%)	1 (1.7%)
口腔咽頭痛	0	0	1 (2.8%)	1 (1.7%)
肺静脈閉塞性疾患	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
臨床検査	3 (25.0%)	1 (10.0%)	8 (22.2%)	12 (20.7%)
ヘモグロビン減少	1 (8.3%)	0	4 (11.1%)	5 (8.6%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
アラニンアミノトランスフェラーゼ増加	0	1 (10.0%)	0	1 (1.7%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (10.0%)	0	1 (1.7%)
血圧上昇	0	0	1 (2.8%)	1 (1.7%)
心拍数増加	1 (8.3%)	0	0	1 (1.7%)
血小板数減少	0	0	1 (2.8%)	1 (1.7%)
体重減少	0	0	1 (2.8%)	1 (1.7%)
体重増加	0	0	1 (2.8%)	1 (1.7%)
血液およびリンパ系障害	1 (8.3%)	1 (10.0%)	9 (25.0%)	11 (19.0%)
貧血	1 (8.3%)	1 (10.0%)	6 (16.7%)	8 (13.8%)
慢性疾患の貧血	0	0	1 (2.8%)	1 (1.7%)
鉄欠乏性貧血	0	0	1 (2.8%)	1 (1.7%)
正色素性貧血	0	0	1 (2.8%)	1 (1.7%)
心臓障害	1 (8.3%)	1 (10.0%)	9 (25.0%)	11 (19.0%)
動悸	0	1 (10.0%)	4 (11.1%)	5 (8.6%)
心房粗動	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
心不全	0	0	2 (5.6%)	2 (3.4%)
右室不全	0	0	2 (5.6%)	2 (3.4%)
狭心症	0	0	1 (2.8%)	1 (1.7%)
心嚢液貯留	0	0	1 (2.8%)	1 (1.7%)
心室性不整脈	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
代謝および栄養障害	2 (16.7%)	2 (20.0%)	7 (19.4%)	11 (19.0%)
低カリウム血症	1 (8.3%)	0	3 (8.3%)	4 (6.9%)
高尿酸血症	0	0	2 (5.6%)	2 (3.4%)
脂質異常症	0	1 (10.0%)	0	1 (1.7%)
低ナトリウム血症	0	0	1 (2.8%)	1 (1.7%)
空腹時血中ブドウ糖不良	0	1 (10.0%)	0	1 (1.7%)
鉄欠乏	0	0	1 (2.8%)	1 (1.7%)
２型糖尿病	1 (8.3%)	0	0	1 (1.7%)
神経系障害	1 (8.3%)	0	10 (27.8%)	11 (19.0%)
浮動性めまい	1 (8.3%)	0	5 (13.9%)	6 (10.3%)
頭痛	0	0	4 (11.1%)	4 (6.9%)
不全片麻痺	0	0	1 (2.8%)	1 (1.7%)
感覚鈍麻	0	0	1 (2.8%)	1 (1.7%)
嗜眠	0	0	1 (2.8%)	1 (1.7%)
失神	0	0	1 (2.8%)	1 (1.7%)
皮膚および皮下組織障害	0	0	6 (16.7%)	6 (10.3%)
そう痒症	0	0	2 (5.6%)	2 (3.4%)
皮膚色素過剰	0	0	2 (5.6%)	2 (3.4%)
脱毛症	0	0	1 (2.8%)	1 (1.7%)
血管浮腫	0	0	1 (2.8%)	1 (1.7%)
皮膚乾燥	0	0	1 (2.8%)	1 (1.7%)
過角化	0	0	1 (2.8%)	1 (1.7%)
爪甲剥離症	0	0	1 (2.8%)	1 (1.7%)
丘疹	0	0	1 (2.8%)	1 (1.7%)
発疹	0	0	1 (2.8%)	1 (1.7%)
丘疹性皮疹	0	0	1 (2.8%)	1 (1.7%)
皮膚色素減少	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
傷害、中毒および処置合併症	1 (8.3%)	0	4 (11.1%)	5 (8.6%)
挫傷	0	0	1 (2.8%)	1 (1.7%)
靭帯捻挫	0	0	1 (2.8%)	1 (1.7%)
ワクチン接種後症候群	1 (8.3%)	0	0	1 (1.7%)
肋骨骨折	0	0	1 (2.8%)	1 (1.7%)
硬膜下血腫	0	0	1 (2.8%)	1 (1.7%)
熱傷	0	0	1 (2.8%)	1 (1.7%)
創傷	0	0	1 (2.8%)	1 (1.7%)
腎および尿路障害	1 (8.3%)	0	4 (11.1%)	5 (8.6%)
腎機能障害	0	0	2 (5.6%)	2 (3.4%)
急性腎障害	0	0	1 (2.8%)	1 (1.7%)
血尿	1 (8.3%)	0	0	1 (1.7%)
ループス腎炎	0	0	1 (2.8%)	1 (1.7%)
尿閉	1 (8.3%)	0	0	1 (1.7%)
精神障害	2 (16.7%)	0	2 (5.6%)	4 (6.9%)
不眠症	2 (16.7%)	0	2 (5.6%)	4 (6.9%)
眼障害	0	1 (10.0%)	2 (5.6%)	3 (5.2%)
白内障	0	1 (10.0%)	1 (2.8%)	2 (3.4%)
霧視	0	0	1 (2.8%)	1 (1.7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
乳癌	1 (8.3%)	0	0	1 (1.7%)
線維腫	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
血管障害	0	1 (10.0%)	1 (2.8%)	2 (3.4%)
ほてり	0	1 (10.0%)	0	1 (1.7%)
低血圧	0	0	1 (2.8%)	1 (1.7%)
肝胆道系障害	0	0	1 (2.8%)	1 (1.7%)
肝硬変	0	0	1 (2.8%)	1 (1.7%)
門脈圧亢進症	0	0	1 (2.8%)	1 (1.7%)
免疫系障害	1 (8.3%)	0	0	1 (1.7%)
節足動物刺傷アレルギー	1 (8.3%)	0	0	1 (1.7%)
生殖系および乳房障害	0	0	1 (2.8%)	1 (1.7%)
重度月経出血	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL02F: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	0	0	1	1
Subjects with 1 or more AEs	0	0	1 (100.0%)	1 (100.0%)
System organ class Preferred term				
筋骨格系および結合組織障害	0	0	1 (100.0%)	1 (100.0%)
背部痛	0	0	1 (100.0%)	1 (100.0%)

[TSFAEOL02F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02F.SAS] 02MAR2023, 08:36

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AEs	70 (90.9%)	74 (91.4%)	25 (96.2%)	170 (91.9%)
System organ class Preferred term				

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Note: One subject with missing baseline eGFR is only included in the Total column.
Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
感染症および寄生虫症	41 (53.2%)	38 (46.9%)	9 (34.6%)	89 (48.1%)
ＣＯＶＩＤ－１９	20 (26.0%)	16 (19.8%)	3 (11.5%)	39 (21.1%)
上気道感染	5 (6.5%)	7 (8.6%)	0	12 (6.5%)
尿路感染	4 (5.2%)	5 (6.2%)	0	9 (4.9%)
上咽頭炎	3 (3.9%)	4 (4.9%)	0	7 (3.8%)
肺炎	3 (3.9%)	3 (3.7%)	0	6 (3.2%)
インフルエンザ	3 (3.9%)	2 (2.5%)	0	5 (2.7%)
副鼻腔炎	1 (1.3%)	2 (2.5%)	1 (3.8%)	4 (2.2%)
ＣＯＶＩＤ－１９肺炎	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
蜂巣炎	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
口腔ヘルペス	0	3 (3.7%)	0	3 (1.6%)
気管支炎	0	2 (2.5%)	0	2 (1.1%)
結膜炎	2 (2.6%)	0	0	2 (1.1%)
Ｂ型肝炎	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
限局性感染	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
パラインフルエンザウイルス感染	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
鼻炎	2 (2.6%)	0	0	2 (1.1%)
ＣＯＶＩＤ－１９の疑い	2 (2.6%)	0	0	2 (1.1%)
急性副鼻腔炎	1 (1.3%)	0	0	1 (0.5%)
真菌性肛門感染	0	1 (1.2%)	0	1 (0.5%)
細菌感染	0	1 (1.2%)	0	1 (0.5%)
体部白癬	0	0	1 (3.8%)	1 (0.5%)
細菌性気管支炎	0	1 (1.2%)	0	1 (0.5%)
カンジダ感染	0	0	1 (3.8%)	1 (0.5%)
子宮頚管炎	1 (1.3%)	0	0	1 (0.5%)
慢性扁桃炎	1 (1.3%)	0	0	1 (0.5%)
サイトメガロウイルス性脈絡網膜炎	0	1 (1.2%)	0	1 (0.5%)
憩室炎	0	0	1 (3.8%)	1 (0.5%)
子宮内膜炎	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
胃腸炎	1 (1.3%)	0	0	1 (0.5%)
クロストリジウム菌性胃腸炎	0	0	1 (3.8%)	1 (0.5%)
消化管感染	0	1 (1.2%)	0	1 (0.5%)
陰部ヘルペス	0	1 (1.2%)	0	1 (0.5%)
歯肉炎	0	1 (1.2%)	0	1 (0.5%)
血液学的感染	1 (1.3%)	0	0	1 (0.5%)
Ｃ型肝炎	1 (1.3%)	0	0	1 (0.5%)
帯状疱疹	1 (1.3%)	0	0	1 (0.5%)
食道カンジダ症	0	1 (1.2%)	0	1 (0.5%)
中耳炎	0	1 (1.2%)	0	1 (0.5%)
耳管炎	1 (1.3%)	0	0	1 (0.5%)
歯冠周囲炎	1 (1.3%)	0	0	1 (0.5%)
咽頭炎	0	1 (1.2%)	0	1 (0.5%)
細菌性咽頭炎	1 (1.3%)	0	0	1 (0.5%)
咽頭扁桃炎	1 (1.3%)	0	0	1 (0.5%)
細菌性肺炎	0	0	0	1 (0.5%)
シュードモナス性肺炎	0	1 (1.2%)	0	1 (0.5%)
ブドウ球菌性肺炎	0	1 (1.2%)	0	1 (0.5%)
ウイルス性肺炎	1 (1.3%)	0	0	1 (0.5%)
急性ＣＯＶＩＤ－１９後症候群	1 (1.3%)	0	0	1 (0.5%)
気道感染	1 (1.3%)	0	0	1 (0.5%)
ウイルス性気道感染	0	1 (1.2%)	0	1 (0.5%)
卵管卵巣炎	1 (1.3%)	0	0	1 (0.5%)
歯膿瘍	0	1 (1.2%)	0	1 (0.5%)
腟感染	0	1 (1.2%)	0	1 (0.5%)
ウイルス感染	0	0	1 (3.8%)	1 (0.5%)
ウイルス性上気道感染	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
胃腸障害	21 (27.3%)	22 (27.2%)	9 (34.6%)	53 (28.6%)
嘔吐	2 (2.6%)	6 (7.4%)	1 (3.8%)	9 (4.9%)
悪心	2 (2.6%)	3 (3.7%)	3 (11.5%)	8 (4.3%)
下痢	2 (2.6%)	4 (4.9%)	1 (3.8%)	7 (3.8%)
胃炎	3 (3.9%)	3 (3.7%)	1 (3.8%)	7 (3.8%)
腹部不快感	2 (2.6%)	1 (1.2%)	1 (3.8%)	4 (2.2%)
腹痛	1 (1.3%)	1 (1.2%)	2 (7.7%)	4 (2.2%)
消化不良	2 (2.6%)	1 (1.2%)	1 (3.8%)	4 (2.2%)
胃食道逆流性疾患	2 (2.6%)	0	2 (7.7%)	4 (2.2%)
痔出血	3 (3.9%)	1 (1.2%)	0	4 (2.2%)
便秘	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
口内乾燥	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
痔核	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
上腹部痛	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
小腸炎	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
鼓腸	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
食道炎	0	2 (2.5%)	0	2 (1.1%)
歯痛	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
食道静脈瘤	2 (2.6%)	0	0	2 (1.1%)
腹部膨満	0	0	0	1 (0.5%)
肛門出血	1 (1.3%)	0	0	1 (0.5%)
慢性胃炎	1 (1.3%)	0	0	1 (0.5%)
大腸炎	0	1 (1.2%)	0	1 (0.5%)
虚血性大腸炎	0	1 (1.2%)	0	1 (0.5%)
排便回数増加	0	0	1 (3.8%)	1 (0.5%)
胃障害	1 (1.3%)	0	0	1 (0.5%)
胃腸障害	0	1 (1.2%)	0	1 (0.5%)
裂孔ヘルニア	0	1 (1.2%)	0	1 (0.5%)
腰ヘルニア	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
口腔内潰瘍形成	0	1 (1.2%)	0	1 (0.5%)
亜イレウス	0	1 (1.2%)	0	1 (0.5%)
舌嚢胞	1 (1.3%)	0	0	1 (0.5%)
上部消化管出血	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
筋骨格系および結合組織障害	17 (22.1%)	27 (33.3%)	7 (26.9%)	51 (27.6%)
関節痛	2 (2.6%)	7 (8.6%)	2 (7.7%)	11 (5.9%)
筋肉痛	6 (7.8%)	4 (4.9%)	1 (3.8%)	11 (5.9%)
背部痛	3 (3.9%)	7 (8.6%)	0	10 (5.4%)
四肢痛	0	5 (6.2%)	2 (7.7%)	7 (3.8%)
椎間板突出	2 (2.6%)	0	1 (3.8%)	3 (1.6%)
変形性関節症	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
筋骨格系胸痛	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
筋骨格痛	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
全身性強皮症	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
滑液包炎	0	1 (1.2%)	0	1 (0.5%)
四肢不快感	0	1 (1.2%)	0	1 (0.5%)
筋力低下	0	1 (1.2%)	0	1 (0.5%)
筋骨格不快感	0	0	1 (3.8%)	1 (0.5%)
骨軟骨炎	0	1 (1.2%)	0	1 (0.5%)
骨壊死	1 (1.3%)	0	0	1 (0.5%)
骨減少症	0	1 (1.2%)	0	1 (0.5%)
骨粗鬆症	0	1 (1.2%)	0	1 (0.5%)
顎痛	0	1 (1.2%)	0	1 (0.5%)
足底筋膜炎	0	1 (1.2%)	0	1 (0.5%)
仙腸骨炎	1 (1.3%)	0	0	1 (0.5%)
シェーグレン症候群	1 (1.3%)	0	0	1 (0.5%)
全身性エリテマトーデス	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
呼吸器、胸郭および縦隔障害	16 (20.8%)	28 (34.6%)	6 (23.1%)	51 (27.6%)
咳嗽	4 (5.2%)	7 (8.6%)	2 (7.7%)	14 (7.6%)
呼吸困難	3 (3.9%)	5 (6.2%)	3 (11.5%)	11 (5.9%)
鼻閉	3 (3.9%)	5 (6.2%)	1 (3.8%)	9 (4.9%)
肺動脈性肺高血圧症	3 (3.9%)	4 (4.9%)	1 (3.8%)	8 (4.3%)
労作性呼吸困難	1 (1.3%)	3 (3.7%)	0	4 (2.2%)
鼻出血	1 (1.3%)	3 (3.7%)	0	4 (2.2%)
低酸素症	0	2 (2.5%)	0	2 (1.1%)
口腔咽頭痛	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
アレルギー性鼻炎	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
鼻漏	0	2 (2.5%)	0	2 (1.1%)
アレルギー性副鼻腔炎	0	1 (1.2%)	0	1 (0.5%)
喘息	0	1 (1.2%)	0	1 (0.5%)
気管支反応性亢進	0	1 (1.2%)	0	1 (0.5%)
気管支分泌物貯留	0	1 (1.2%)	0	1 (0.5%)
喀血	1 (1.3%)	0	0	1 (0.5%)
鼻中隔弯曲	1 (1.3%)	0	0	1 (0.5%)
起坐呼吸	0	1 (1.2%)	0	1 (0.5%)
咽頭腫脹	0	1 (1.2%)	0	1 (0.5%)
気胸	0	1 (1.2%)	0	1 (0.5%)
湿性咳嗽	0	1 (1.2%)	0	1 (0.5%)
肺塞栓症	0	1 (1.2%)	0	1 (0.5%)
肺静脈閉塞性疾患	0	1 (1.2%)	0	1 (0.5%)
睡眠時無呼吸症候群	0	1 (1.2%)	0	1 (0.5%)
咽喉刺激感	1 (1.3%)	0	0	1 (0.5%)
気管の炎症	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
一般・全身障害および投与部位の状態	21 (27.3%)	20 (24.7%)	6 (23.1%)	47 (25.4%)
末梢性浮腫	8 (10.4%)	10 (12.3%)	2 (7.7%)	20 (10.8%)
発熱	5 (6.5%)	3 (3.7%)	2 (7.7%)	10 (5.4%)
末梢腫脹	6 (7.8%)	2 (2.5%)	1 (3.8%)	9 (4.9%)
疲労	2 (2.6%)	3 (3.7%)	0	5 (2.7%)
胸部不快感	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
非心臓性胸痛	0	3 (3.7%)	0	3 (1.6%)
胸痛	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
悪寒	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
浮腫	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
疼痛	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
顔面腫脹	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
無力症	0	1 (1.2%)	0	1 (0.5%)
顔面浮腫	1 (1.3%)	0	0	1 (0.5%)
全身性浮腫	0	1 (1.2%)	0	1 (0.5%)
倦怠感	0	1 (1.2%)	0	1 (0.5%)
ポリープ	0	1 (1.2%)	0	1 (0.5%)
腫脹	0	0	1 (3.8%)	1 (0.5%)
口渇	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
臨床検査	20 (26.0%)	15 (18.5%)	5 (19.2%)	41 (22.2%)
ヘモグロビン減少	10 (13.0%)	5 (6.2%)	2 (7.7%)	17 (9.2%)
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 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	2 (2.6%)	1 (1.2%)	0	3 (1.6%)
体重減少	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
体重増加	1 (1.3%)	1 (1.2%)	0	3 (1.6%)
アラニンアミノトランスフェラーゼ増加	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
アスパラギン酸アミノトランスフェラーゼ増加	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
血中ブドウ糖増加	0	2 (2.5%)	0	2 (1.1%)
トランスアミナーゼ上昇	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
血中アルカリホスファターゼ増加	0	1 (1.2%)	0	1 (0.5%)
血中ビリルビン増加	0	1 (1.2%)	0	1 (0.5%)
血中クレアチニン増加	0	1 (1.2%)	0	1 (0.5%)
血圧上昇	1 (1.3%)	0	0	1 (0.5%)
血中尿酸異常	0	0	1 (3.8%)	1 (0.5%)
血中尿酸増加	0	1 (1.2%)	0	1 (0.5%)
体温上昇	0	1 (1.2%)	0	1 (0.5%)
脳性ナトリウム利尿ペプチド増加	1 (1.3%)	0	0	1 (0.5%)
心雑音	0	1 (1.2%)	0	1 (0.5%)
心拍数増加	1 (1.3%)	0	0	1 (0.5%)
Ｂ型肝炎抗体異常	0	0	1 (3.8%)	1 (0.5%)
好中球数減少	1 (1.3%)	0	0	1 (0.5%)
酸素飽和度低下	0	0	1 (3.8%)	1 (0.5%)
血小板数減少	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
神経系障害	16 (20.8%)	20 (24.7%)	4 (15.4%)	41 (22.2%)
頭痛	11 (14.3%)	10 (12.3%)	4 (15.4%)	26 (14.1%)
浮動性めまい	2 (2.6%)	3 (3.7%)	1 (3.8%)	6 (3.2%)
感覚鈍麻	0	2 (2.5%)	1 (3.8%)	3 (1.6%)
失神	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
労作性めまい	0	2 (2.5%)	0	2 (1.1%)
体位性めまい	0	2 (2.5%)	0	2 (1.1%)
労作性頭痛	0	1 (1.2%)	0	1 (0.5%)
顔面麻痺	0	1 (1.2%)	0	1 (0.5%)
不全片麻痺	1 (1.3%)	0	0	1 (0.5%)
ホルネル症候群	0	1 (1.2%)	0	1 (0.5%)
嗜眠	0	1 (1.2%)	0	1 (0.5%)
片頭痛	1 (1.3%)	0	0	1 (0.5%)
ヘルペス後神経痛	0	1 (1.2%)	0	1 (0.5%)
失神寸前の状態	0	1 (1.2%)	0	1 (0.5%)
傾眠	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
血液およびリンパ系障害	10 (13.0%)	19 (23.5%)	4 (15.4%)	33 (17.8%)
貧血	4 (5.2%)	12 (14.8%)	3 (11.5%)	19 (10.3%)
鉄欠乏性貧血	4 (5.2%)	4 (4.9%)	0	8 (4.3%)
白血球減少症	0	2 (2.5%)	1 (3.8%)	3 (1.6%)
好中球減少症	0	2 (2.5%)	1 (3.8%)	3 (1.6%)
白血球増加症	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
リンパ球減少症	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
血小板減少症	0	2 (2.5%)	0	2 (1.1%)
慢性疾患の貧血	1 (1.3%)	0	0	1 (0.5%)
失血性貧血	1 (1.3%)	0	0	1 (0.5%)
骨髄浮腫	0	1 (1.2%)	0	1 (0.5%)
脾機能亢進	0	1 (1.2%)	0	1 (0.5%)
単球減少症	0	0	1 (3.8%)	1 (0.5%)
正色素性貧血	1 (1.3%)	0	0	1 (0.5%)
汎血球減少症	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
心臓障害	10 (13.0%)	18 (22.2%)	4 (15.4%)	32 (17.3%)
動悸	4 (5.2%)	5 (6.2%)	1 (3.8%)	10 (5.4%)
右室不全	1 (1.3%)	5 (6.2%)	0	6 (3.2%)
狭心症	3 (3.9%)	1 (1.2%)	0	4 (2.2%)
心不全	1 (1.3%)	2 (2.5%)	1 (3.8%)	4 (2.2%)
心房粗動	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
頻脈	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
冠動脈疾患	0	2 (2.5%)	0	2 (1.1%)
心房細動	0	1 (1.2%)	0	1 (0.5%)
徐脈	0	1 (1.2%)	0	1 (0.5%)
心血管障害	1 (1.3%)	0	0	1 (0.5%)
肺性心	0	1 (1.2%)	0	1 (0.5%)
左室不全	0	0	1 (3.8%)	1 (0.5%)
心嚢液貯留	1 (1.3%)	0	0	1 (0.5%)
洞結節機能不全	0	1 (1.2%)	0	1 (0.5%)
上室性頻脈	0	1 (1.2%)	0	1 (0.5%)
心室性不整脈	0	1 (1.2%)	0	1 (0.5%)
心室性期外収縮	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
代謝および栄養障害	10 (13.0%)	13 (16.0%)	6 (23.1%)	29 (15.7%)
低カリウム血症	3 (3.9%)	1 (1.2%)	1 (3.8%)	5 (2.7%)
鉄欠乏	3 (3.9%)	1 (1.2%)	0	4 (2.2%)
ビタミンＢ１２欠乏	2 (2.6%)	1 (1.2%)	1 (3.8%)	4 (2.2%)
高尿酸血症	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
食欲減退	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
痛風	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
高脂血症	0	2 (2.5%)	0	2 (1.1%)
低ナトリウム血症	0	2 (2.5%)	0	2 (1.1%)
脱水	0	1 (1.2%)	0	1 (0.5%)
糖尿病	0	1 (1.2%)	0	1 (0.5%)
脂質異常症	0	0	1 (3.8%)	1 (0.5%)
高血糖	0	1 (1.2%)	0	1 (0.5%)
高カリウム血症	0	0	1 (3.8%)	1 (0.5%)
血液量増加症	0	0	1 (3.8%)	1 (0.5%)
空腹時血中ブドウ糖不良	1 (1.3%)	0	0	1 (0.5%)
２型糖尿病	0	0	1 (3.8%)	1 (0.5%)
ビタミンＤ欠乏	0	1 (1.2%)	0	1 (0.5%)
血管障害	1 (1.3%)	11 (13.6%)	8 (30.8%)	20 (10.8%)
低血圧	1 (1.3%)	7 (8.6%)	4 (15.4%)	12 (6.5%)
潮紅	0	2 (2.5%)	1 (3.8%)	3 (1.6%)
ほてり	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
血腫	0	1 (1.2%)	0	1 (0.5%)
高血圧	0	1 (1.2%)	0	1 (0.5%)
末梢静脈疾患	0	0	1 (3.8%)	1 (0.5%)
静脈瘤	0	0	1 (3.8%)	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
眼障害	7 (9.1%)	11 (13.6%)	1 (3.8%)	19 (10.3%)
白内障	1 (1.3%)	2 (2.5%)	1 (3.8%)	4 (2.2%)
霧視	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
眼瞼浮腫	2 (2.6%)	0	0	2 (1.1%)
眼充血	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
眼窩周囲浮腫	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
眼刺激	0	1 (1.2%)	0	1 (0.5%)
眼痛	0	1 (1.2%)	0	1 (0.5%)
眼部腫脹	0	1 (1.2%)	0	1 (0.5%)
遠視	1 (1.3%)	0	0	1 (0.5%)
網膜出血	1 (1.3%)	0	0	1 (0.5%)
網膜静脈閉塞	0	1 (1.2%)	0	1 (0.5%)
視力障害	0	1 (1.2%)	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
皮膚および皮下組織障害	8 (10.4%)	7 (8.6%)	4 (15.4%)	19 (10.3%)
発疹	1 (1.3%)	3 (3.7%)	2 (7.7%)	6 (3.2%)
皮膚色素過剰	1 (1.3%)	1 (1.2%)	1 (3.8%)	3 (1.6%)
血管浮腫	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
紅斑	0	2 (2.5%)	0	2 (1.1%)
そう痒症	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
ざ瘡	1 (1.3%)	0	0	1 (0.5%)
脱毛症	0	0	1 (3.8%)	1 (0.5%)
冷汗	0	1 (1.2%)	0	1 (0.5%)
接触皮膚炎	0	1 (1.2%)	0	1 (0.5%)
皮膚乾燥	1 (1.3%)	0	0	1 (0.5%)
斑状出血	0	1 (1.2%)	0	1 (0.5%)
過剰肉芽組織	0	1 (1.2%)	0	1 (0.5%)
過角化	1 (1.3%)	0	0	1 (0.5%)
爪甲剥離症	1 (1.3%)	0	0	1 (0.5%)
丘疹	1 (1.3%)	0	0	1 (0.5%)
丘疹性皮疹	0	0	1 (3.8%)	1 (0.5%)
皮膚色素減少	0	0	1 (3.8%)	1 (0.5%)
皮膚病変	1 (1.3%)	0	0	1 (0.5%)
皮膚潰瘍	0	0	1 (3.8%)	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
傷害、中毒および処置合併症	3 (3.9%)	10 (12.3%)	2 (7.7%)	15 (8.1%)
処置による疼痛	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
挫傷	0	1 (1.2%)	0	1 (0.5%)
上顆炎	0	1 (1.2%)	0	1 (0.5%)
転倒	0	1 (1.2%)	0	1 (0.5%)
足骨折	1 (1.3%)	0	0	1 (0.5%)
靭帯断裂	0	1 (1.2%)	0	1 (0.5%)
靭帯捻挫	0	0	1 (3.8%)	1 (0.5%)
過量投与	0	1 (1.2%)	0	1 (0.5%)
ワクチン接種後症候群	1 (1.3%)	0	0	1 (0.5%)
放射線肺線維症	0	1 (1.2%)	0	1 (0.5%)
肋骨骨折	0	1 (1.2%)	0	1 (0.5%)
硬膜下血腫	0	1 (1.2%)	0	1 (0.5%)
熱傷	1 (1.3%)	0	0	1 (0.5%)
歯牙破折	0	1 (1.2%)	0	1 (0.5%)
外傷性血腫	0	1 (1.2%)	0	1 (0.5%)
創傷	0	0	1 (3.8%)	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
生殖系および乳房障害	6 (7.8%)	6 (7.4%)	0	12 (6.5%)
重度月経出血	3 (3.9%)	1 (1.2%)	0	4 (2.2%)
子宮ポリープ	2 (2.6%)	2 (2.5%)	0	4 (2.2%)
腺筋症	2 (2.6%)	0	0	2 (1.1%)
月経中間期出血	2 (2.6%)	0	0	2 (1.1%)
卵巣嚢胞	2 (2.6%)	0	0	2 (1.1%)
腟出血	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
乳房腫瘤	0	1 (1.2%)	0	1 (0.5%)
子宮頚部嚢胞	1 (1.3%)	0	0	1 (0.5%)
子宮頚外反	1 (1.3%)	0	0	1 (0.5%)
子宮内膜増殖症	1 (1.3%)	0	0	1 (0.5%)
子宮内膜症	1 (1.3%)	0	0	1 (0.5%)
女性化乳房	0	1 (1.2%)	0	1 (0.5%)
卵巣嚢胞破裂	0	1 (1.2%)	0	1 (0.5%)
骨盤癒着症	1 (1.3%)	0	0	1 (0.5%)
頻発過多月経	1 (1.3%)	0	0	1 (0.5%)
腎および尿路障害	4 (5.2%)	4 (4.9%)	2 (7.7%)	11 (5.9%)
腎機能障害	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
急性腎障害	1 (1.3%)	0	0	2 (1.1%)
慢性腎臓病	0	0	2 (7.7%)	2 (1.1%)
排尿困難	0	1 (1.2%)	0	1 (0.5%)
膜性糸球体腎炎	0	1 (1.2%)	0	1 (0.5%)
血尿	1 (1.3%)	0	0	1 (0.5%)
ループス腎炎	1 (1.3%)	0	0	1 (0.5%)
蛋白尿	0	1 (1.2%)	0	1 (0.5%)
尿閉	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	3 (3.9%)	4 (4.9%)	1 (3.8%)	8 (4.3%)
乳癌	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
基底細胞癌	0	1 (1.2%)	0	1 (0.5%)
線維腫	1 (1.3%)	0	0	1 (0.5%)
卵巣粘液性嚢胞腺癌	1 (1.3%)	0	0	1 (0.5%)
骨髄線維症	0	1 (1.2%)	0	1 (0.5%)
前立腺癌	0	1 (1.2%)	0	1 (0.5%)
子宮平滑筋腫	1 (1.3%)	0	0	1 (0.5%)
精神障害	4 (5.2%)	1 (1.2%)	0	5 (2.7%)
不眠症	3 (3.9%)	1 (1.2%)	0	4 (2.2%)
不安	1 (1.3%)	0	0	1 (0.5%)
肝胆道系障害	1 (1.3%)	3 (3.7%)	0	4 (2.2%)
薬物性肝障害	0	1 (1.2%)	0	1 (0.5%)
肝硬変	1 (1.3%)	0	0	1 (0.5%)
脂肪肝	0	1 (1.2%)	0	1 (0.5%)
黄疸眼	0	1 (1.2%)	0	1 (0.5%)
門脈圧亢進症	1 (1.3%)	0	0	1 (0.5%)
免疫系障害	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
節足動物刺傷アレルギー	1 (1.3%)	0	0	1 (0.5%)
過敏症	0	0	1 (3.8%)	1 (0.5%)
耳および迷路障害	0	0	1 (3.8%)	1 (0.5%)
聴覚過敏	0	0	1 (3.8%)	1 (0.5%)

TSFAEOL02R: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
内分泌障害	0	1 (1.2%)	0	1 (0.5%)
甲状腺腫	0	1 (1.2%)	0	1 (0.5%)

[TSFAEOL02R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02R.SAS] 20APR2023, 11:09

TSFAEOL02T: Number of Subjects With Treatment-emergent Adverse Events during the Tadalafil 20 mg Titration Phase (M/T FDC Week 1) by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan[a]	DB-M/T FDC[a]	DB-Tadalafil[b]	DB-M/T FDC[b]	DB-Macitentan[a]	DB-Tadalafil[b]	DB-M/T FDC[a]
Analysis set: Combination Safety Set	11	21	19	37	24	24	48
Subjects with 1 or more AEs	6 (54.5%)	13 (61.9%)	2 (10.5%)	10 (27.0%)	6 (25.0%)	7 (29.2%)	27 (56.3%)
System organ class Preferred term							
一般・全身障害および投与部位の状態	0	1 (4.8%)	0	1 (2.7%)	1 (4.2%)	3 (12.5%)	10 (20.8%)
末梢性浮腫	0	0	0	1 (2.7%)	1 (4.2%)	1 (4.2%)	4 (8.3%)
末梢腫脹	0	0	0	0	0	0	2 (4.2%)
無力症	0	0	0	0	0	0	1 (2.1%)
疼痛	0	0	0	0	0	1 (4.2%)	1 (2.1%)
発熱	0	0	0	0	0	1 (4.2%)	1 (2.1%)
腫脹	0	0	0	0	0	0	1 (2.1%)
顔面腫脹	0	0	0	0	0	0	1 (2.1%)
胸部不快感	0	0	0	0	0	1 (4.2%)	0
疲労	0	1 (4.8%)	0	0	0	0	0
浮腫	0	0	0	0	0	1 (4.2%)	0
口渇	0	0	0	1 (2.7%)	0	0	0

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] Subjects from this arms are to start on Macitentan 10mg/Tadalafil 20 mg during the first week of combination treatment. M/T FDC treatment-emergent period is defined from first intake of macitentan and tadalafil in DB or OL treatment period up to:
first day (excluded) of treatment with Tadalafil 40mg for participants who uptitrate, and up to EOT + 30 days for patients who do not uptitrate.
One subject is excluded from the analysis as she mistakenly took M/T FDC tablets from FDC Day 1 and did not undergo Tadalafil titration part.

[b] Subjects from this arms are to start on Macitentan 10mg/Tadalafil 40 mg during the first week of combination treatment. M/T FDC treatment-emergent period is defined from first intake of macitentan and tadalafil in DB or OL treatment period up to M/T FDC day 7 (included).

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

TSFAEOL02T: Number of Subjects With Treatment-emergent Adverse Events during the Tadalafil 20 mg Titration Phase (M/T FDC Week 1) by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan[a]	DB-M/T FDC[a]	DB-Tadalafil[b]	DB-M/T FDC[b]	DB-Macitentan[a]	DB-Tadalafil[b]	DB-M/T FDC[a]
神経系障害	2 (18.2%)	4 (19.0%)	0	4 (10.8%)	0	1 (4.2%)	8 (16.7%)
頭痛	2 (18.2%)	4 (19.0%)	0	4 (10.8%)	0	1 (4.2%)	6 (12.5%)
浮動性めまい	0	0	0	0	0	0	1 (2.1%)
労作性めまい	0	0	0	0	0	0	1 (2.1%)
労作性頭痛	0	0	0	0	0	0	1 (2.1%)
胃腸障害	0	4 (19.0%)	2 (10.5%)	3 (8.1%)	1 (4.2%)	0	7 (14.6%)
消化不良	0	0	0	0	0	0	3 (6.3%)
便秘	0	0	0	0	0	0	1 (2.1%)
下痢	0	0	0	0	0	0	1 (2.1%)
鼓腸	0	0	0	0	0	0	1 (2.1%)
胃腸障害	0	0	0	0	0	0	1 (2.1%)
嘔吐	0	0	1 (5.3%)	1 (2.7%)	0	0	1 (2.1%)
腹部不快感	0	0	0	0	1 (4.2%)	0	0
口内乾燥	0	0	0	1 (2.7%)	0	0	0
胃炎	0	0	0	1 (2.7%)	0	0	0
痔核	0	1 (4.8%)	0	0	0	0	0
腰ヘルニア	0	1 (4.8%)	0	0	0	0	0
悪心	0	2 (9.5%)	1 (5.3%)	1 (2.7%)	0	0	0
食道炎	0	0	0	1 (2.7%)	0	0	0
筋骨格系および結合組織障害	3 (27.3%)	5 (23.8%)	0	0	1 (4.2%)	2 (8.3%)	4 (8.3%)
筋肉痛	0	2 (9.5%)	0	0	1 (4.2%)	0	3 (6.3%)
顎痛	0	0	0	0	0	0	1 (2.1%)
関節痛	1 (9.1%)	0	0	0	0	1 (4.2%)	0
背部痛	1 (9.1%)	2 (9.5%)	0	0	0	1 (4.2%)	0
筋力低下	0	1 (4.8%)	0	0	0	0	0
筋骨格痛	0	1 (4.8%)	0	0	0	0	0
四肢痛	1 (9.1%)	1 (4.8%)	0	0	0	0	0

TSFAEOL02T: Number of Subjects With Treatment-emergent Adverse Events during the Tadalafil 20 mg Titration Phase (M/T FDC Week 1) by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan[a]	DB-M/T FDC[a]	DB-Tadalafil[b]	DB-M/T FDC[b]	DB-Macitentan[a]	DB-Tadalafil[b]	DB-M/T FDC[a]
心臓障害	0	1 (4.8%)	0	0	0	0	2 (4.2%)
心不全	0	1 (4.8%)	0	0	0	0	1 (2.1%)
頻脈	0	0	0	0	0	0	1 (2.1%)
呼吸器、胸郭および縦隔障害	1 (9.1%)	2 (9.5%)	0	2 (5.4%)	0	1 (4.2%)	2 (4.2%)
呼吸困難	0	0	0	0	0	1 (4.2%)	1 (2.1%)
鼻閉	0	1 (4.8%)	0	1 (2.7%)	0	1 (4.2%)	1 (2.1%)
咳嗽	0	0	0	0	0	1 (4.2%)	0
労作性呼吸困難	0	0	0	1 (2.7%)	0	0	0
肺塞栓症	1 (9.1%)	0	0	0	0	0	0
アレルギー性鼻炎	0	1 (4.8%)	0	0	0	0	0
血管障害	1 (9.1%)	2 (9.5%)	0	1 (2.7%)	1 (4.2%)	0	2 (4.2%)
潮紅	0	0	0	0	0	0	2 (4.2%)
血腫	1 (9.1%)	0	0	0	0	0	0
低血圧	0	2 (9.5%)	0	1 (2.7%)	1 (4.2%)	0	0
眼障害	0	0	0	1 (2.7%)	0	0	1 (2.1%)
眼瞼浮腫	0	0	0	1 (2.7%)	0	0	1 (2.1%)
眼窩周囲浮腫	0	0	0	1 (2.7%)	0	0	0
免疫系障害	0	0	0	0	0	0	1 (2.1%)
過敏症	0	0	0	0	0	0	1 (2.1%)

TSFAEOL02T: Number of Subjects With Treatment-emergent Adverse Events during the Tadalafil 20 mg Titration Phase (M/T FDC Week 1) by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	Prior ERA strata		Prior PDE-5i strata		Treatment-naive		
	DB-Macitentan[a]	DB-M/T FDC[a]	DB-Tadalafil[b]	DB-M/T FDC[b]	DB-Macitentan[a]	DB-Tadalafil[b]	DB-M/T FDC[a]
感染症および寄生虫症	0	0	0	1 (2.7%)	3 (12.5%)	0	1 (2.1%)
歯膿瘍	0	0	0	0	0	0	1 (2.1%)
ＣＯＶＩＤ－１９	0	0	0	0	1 (4.2%)	0	0
上咽頭炎	0	0	0	1 (2.7%)	0	0	0
口腔ヘルペス	0	0	0	0	1 (4.2%)	0	0
上気道感染	0	0	0	0	1 (4.2%)	0	0
傷害、中毒および処置合併症	0	0	0	0	0	0	1 (2.1%)
歯牙破折	0	0	0	0	0	0	1 (2.1%)
臨床検査	2 (18.2%)	1 (4.8%)	0	0	1 (4.2%)	0	1 (2.1%)
心雑音	0	0	0	0	0	0	1 (2.1%)
血中ブドウ糖増加	0	0	0	0	1 (4.2%)	0	0
血中尿酸異常	0	1 (4.8%)	0	0	0	0	0
心拍数増加	1 (9.1%)	0	0	0	0	0	0
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 (9.1%)	0	0	0	0	0	0
皮膚および皮下組織障害	0	1 (4.8%)	0	0	0	0	1 (2.1%)
血管浮腫	0	0	0	0	0	0	1 (2.1%)
発疹	0	1 (4.8%)	0	0	0	0	0
血液およびリンパ系障害	0	0	0	0	0	2 (8.3%)	0
貧血	0	0	0	0	0	1 (4.2%)	0
白血球増加症	0	0	0	0	0	1 (4.2%)	0

[TSFAEOL02T.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL02T.SAS] 02MAR2023, 08:36

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TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age group: 18-64 years	27	33	87	147
Subjects with 1 or more SAEs	4 (14.8%)	5 (15.2%)	18 (20.7%)	27 (18.4%)
System organ class Preferred term				
感染症および寄生虫症	2 (7.4%)	1 (3.0%)	9 (10.3%)	12 (8.2%)
ＣＯＶＩＤ－１９	0	0	3 (3.4%)	3 (2.0%)
肺炎	0	1 (3.0%)	2 (2.3%)	3 (2.0%)
ＣＯＶＩＤ－１９肺炎	0	0	2 (2.3%)	2 (1.4%)
憩室炎	1 (3.7%)	0	0	1 (0.7%)
胃腸炎	0	0	1 (1.1%)	1 (0.7%)
インフルエンザ	0	0	1 (1.1%)	1 (0.7%)
パラインフルエンザウイルス感染	1 (3.7%)	0	0	1 (0.7%)
ウイルス性肺炎	0	0	1 (1.1%)	1 (0.7%)
ウイルス性上気道感染	0	0	1 (1.1%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
心臓障害	0	3 (9.1%)	5 (5.7%)	8 (5.4%)
心房粗動	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
右室不全	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
心房細動	0	0	1 (1.1%)	1 (0.7%)
心不全	0	0	1 (1.1%)	1 (0.7%)
肺性心	0	1 (3.0%)	0	1 (0.7%)
動悸	0	0	1 (1.1%)	1 (0.7%)
上室性頻脈	0	0	1 (1.1%)	1 (0.7%)
生殖系および乳房障害	0	2 (6.1%)	3 (3.4%)	5 (3.4%)
子宮ポリープ	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
子宮内膜症	0	0	1 (1.1%)	1 (0.7%)
月経中間期出血	0	0	1 (1.1%)	1 (0.7%)
卵巣嚢胞破裂	0	1 (3.0%)	0	1 (0.7%)
胃腸障害	0	0	3 (3.4%)	3 (2.0%)
痔出血	0	0	1 (1.1%)	1 (0.7%)
舌嚢胞	0	0	1 (1.1%)	1 (0.7%)
上部消化管出血	0	0	1 (1.1%)	1 (0.7%)
食道静脈瘤	0	0	1 (1.1%)	1 (0.7%)
呼吸器、胸郭および縦隔障害	1 (3.7%)	0	2 (2.3%)	3 (2.0%)
肺動脈性肺高血圧症	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
呼吸困難	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
骨壊死	0	0	1 (1.1%)	1 (0.7%)
全身性強皮症	1 (3.7%)	0	0	1 (0.7%)
神経系障害	0	0	2 (2.3%)	2 (1.4%)
不全片麻痺	0	0	1 (1.1%)	1 (0.7%)
ホルネル症候群	0	0	1 (1.1%)	1 (0.7%)
腎および尿路障害	0	0	2 (2.3%)	2 (1.4%)
急性腎障害	0	0	1 (1.1%)	1 (0.7%)
膜性糸球体腎炎	0	0	1 (1.1%)	1 (0.7%)
血液およびリンパ系障害	0	0	1 (1.1%)	1 (0.7%)
正色素性貧血	0	0	1 (1.1%)	1 (0.7%)
一般・全身障害および投与部位の状態	0	0	1 (1.1%)	1 (0.7%)
胸痛	0	0	1 (1.1%)	1 (0.7%)
肝胆道系障害	0	0	1 (1.1%)	1 (0.7%)
肝硬変	0	0	1 (1.1%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.1%)	1 (0.7%)
傷害、中毒および処置合併症	0	1 (3.0%)	0	1 (0.7%)
過量投与	0	1 (3.0%)	0	1 (0.7%)

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
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）	0	0	1 (1.1%)	1 (0.7%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.1%)	1 (0.7%)
血管障害	0	0	1 (1.1%)	1 (0.7%)
低血圧	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age group: >=65 years	8	10	20	38
Subjects with 1 or more SAEs	3 (37.5%)	4 (40.0%)	11 (55.0%)	18 (47.4%)
System organ class Preferred term				
心臓障害	1 (12.5%)	1 (10.0%)	4 (20.0%)	6 (15.8%)
右室不全	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
心不全	0	0	1 (5.0%)	1 (2.6%)
冠動脈疾患	0	0	1 (5.0%)	1 (2.6%)
左室不全	0	0	1 (5.0%)	1 (2.6%)
洞結節機能不全	0	1 (10.0%)	0	1 (2.6%)
感染症および寄生虫症	0	0	4 (20.0%)	4 (10.5%)
ＣＯＶＩＤ－１９	0	0	2 (10.0%)	2 (5.3%)
クロストリジウム菌性胃腸炎	0	0	1 (5.0%)	1 (2.6%)
パラインフルエンザウイルス感染	0	0	1 (5.0%)	1 (2.6%)
呼吸器、胸郭および縦隔障害	1 (12.5%)	1 (10.0%)	2 (10.0%)	4 (10.5%)
呼吸困難	0	0	1 (5.0%)	1 (2.6%)
低酸素症	1 (12.5%)	0	0	1 (2.6%)
気胸	0	1 (10.0%)	0	1 (2.6%)
肺静脈閉塞性疾患	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	1 (12.5%)	1 (10.0%)	1 (5.0%)	3 (7.9%)
虚血性大腸炎	0	1 (10.0%)	0	1 (2.6%)
胃炎	0	0	1 (5.0%)	1 (2.6%)
裂孔ヘルニア	0	1 (10.0%)	0	1 (2.6%)
亜イレウス	1 (12.5%)	0	0	1 (2.6%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (12.5%)	1 (10.0%)	1 (5.0%)	3 (7.9%)
基底細胞癌	0	1 (10.0%)	0	1 (2.6%)
乳癌	1 (12.5%)	0	0	1 (2.6%)
前立腺癌	0	0	1 (5.0%)	1 (2.6%)
血液およびリンパ系障害	0	0	1 (5.0%)	1 (2.6%)
貧血	0	0	1 (5.0%)	1 (2.6%)
眼障害	0	1 (10.0%)	0	1 (2.6%)
網膜静脈閉塞	0	1 (10.0%)	0	1 (2.6%)
一般・全身障害および投与部位の状態	0	0	1 (5.0%)	1 (2.6%)
末梢腫脹	0	0	1 (5.0%)	1 (2.6%)
顔面腫脹	0	0	1 (5.0%)	1 (2.6%)
傷害、中毒および処置合併症	0	0	1 (5.0%)	1 (2.6%)
硬膜下血腫	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL03D: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
筋骨格系および結合組織障害	1 (12.5%)	0	0	1 (2.6%)
椎間板突出	1 (12.5%)	0	0	1 (2.6%)

[TSFAEOL03D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL03D.SAS] 02MAR2023, 08:36

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more SAEs	5 (17.2%)	8 (24.2%)	21 (25.6%)	34 (23.6%)
System organ class Preferred term				
心臓障害	0	4 (12.1%)	7 (8.5%)	11 (7.6%)
心房粗動	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
心不全	0	0	2 (2.4%)	2 (1.4%)
右室不全	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
心房細動	0	0	1 (1.2%)	1 (0.7%)
肺性心	0	1 (3.0%)	0	1 (0.7%)
左室不全	0	0	1 (1.2%)	1 (0.7%)
動悸	0	0	1 (1.2%)	1 (0.7%)
洞結節機能不全	0	1 (3.0%)	0	1 (0.7%)
上室性頻脈	0	0	1 (1.2%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	2 (6.9%)	1 (3.0%)	7 (8.5%)	10 (6.9%)
ＣＯＶＩＤ－１９	0	0	3 (3.7%)	3 (2.1%)
肺炎	0	1 (3.0%)	2 (2.4%)	3 (2.1%)
パラインフルエンザウイルス感染	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (1.2%)	1 (0.7%)
憩室炎	1 (3.4%)	0	0	1 (0.7%)
インフルエンザ	0	0	1 (1.2%)	1 (0.7%)
生殖系および乳房障害	0	2 (6.1%)	3 (3.7%)	5 (3.5%)
子宮ポリープ	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
子宮内膜症	0	0	1 (1.2%)	1 (0.7%)
月経中間期出血	0	0	1 (1.2%)	1 (0.7%)
卵巣嚢胞破裂	0	1 (3.0%)	0	1 (0.7%)
呼吸器、胸郭および縦隔障害	1 (3.4%)	1 (3.0%)	3 (3.7%)	5 (3.5%)
呼吸困難	0	0	2 (2.4%)	2 (1.4%)
肺動脈性肺高血圧症	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
気胸	0	1 (3.0%)	0	1 (0.7%)
胃腸障害	0	1 (3.0%)	3 (3.7%)	4 (2.8%)
虚血性大腸炎	0	1 (3.0%)	0	1 (0.7%)
胃炎	0	0	1 (1.2%)	1 (0.7%)
裂孔ヘルニア	0	1 (3.0%)	0	1 (0.7%)
舌嚢胞	0	0	1 (1.2%)	1 (0.7%)
上部消化管出血	0	0	1 (1.2%)	1 (0.7%)
食道静脈瘤	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
一般・全身障害および投与部位の状態	0	0	2 (2.4%)	2 (1.4%)
胸痛	0	0	1 (1.2%)	1 (0.7%)
末梢腫脹	0	0	1 (1.2%)	1 (0.7%)
顔面腫脹	0	0	1 (1.2%)	1 (0.7%)
傷害、中毒および処置合併症	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
過量投与	0	1 (3.0%)	0	1 (0.7%)
硬膜下血腫	0	0	1 (1.2%)	1 (0.7%)
筋骨格系および結合組織障害	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
骨壊死	0	0	1 (1.2%)	1 (0.7%)
全身性強皮症	1 (3.4%)	0	0	1 (0.7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
乳癌	1 (3.4%)	0	0	1 (0.7%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.2%)	1 (0.7%)
神経系障害	0	0	2 (2.4%)	2 (1.4%)
不全片麻痺	0	0	1 (1.2%)	1 (0.7%)
ホルネル症候群	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
腎および尿路障害	0	0	2 (2.4%)	2 (1.4%)
急性腎障害	0	0	1 (1.2%)	1 (0.7%)
膜性糸球体腎炎	0	0	1 (1.2%)	1 (0.7%)
血液およびリンパ系障害	0	0	1 (1.2%)	1 (0.7%)
貧血	0	0	1 (1.2%)	1 (0.7%)
眼障害	0	1 (3.0%)	0	1 (0.7%)
網膜静脈閉塞	0	1 (3.0%)	0	1 (0.7%)
肝胆道系障害	0	0	1 (1.2%)	1 (0.7%)
肝硬変	0	0	1 (1.2%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more SAEs	2 (33.3%)	1 (10.0%)	8 (32.0%)	11 (26.8%)
System organ class Preferred term				
感染症および寄生虫症	0	0	6 (24.0%)	6 (14.6%)
ＣＯＶＩＤ－１９	0	0	2 (8.0%)	2 (4.9%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (4.0%)	1 (2.4%)
胃腸炎	0	0	1 (4.0%)	1 (2.4%)
クロストリジウム菌性胃腸炎	0	0	1 (4.0%)	1 (2.4%)
ウイルス性肺炎	0	0	1 (4.0%)	1 (2.4%)
ウイルス性上気道感染	0	0	1 (4.0%)	1 (2.4%)
心臓障害	1 (16.7%)	0	2 (8.0%)	3 (7.3%)
右室不全	1 (16.7%)	0	2 (8.0%)	3 (7.3%)
冠動脈疾患	0	0	1 (4.0%)	1 (2.4%)
胃腸障害	1 (16.7%)	0	1 (4.0%)	2 (4.9%)
痔出血	0	0	1 (4.0%)	1 (2.4%)
亜イレウス	1 (16.7%)	0	0	1 (2.4%)
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）	0	1 (10.0%)	1 (4.0%)	2 (4.9%)
基底細胞癌	0	1 (10.0%)	0	1 (2.4%)
前立腺癌	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL03E: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
呼吸器、胸郭および縦隔障害	1 (16.7%)	0	1 (4.0%)	2 (4.9%)
低酸素症	1 (16.7%)	0	0	1 (2.4%)
肺静脈閉塞性疾患	0	0	1 (4.0%)	1 (2.4%)
血液およびリンパ系障害	0	0	1 (4.0%)	1 (2.4%)
正色素性貧血	0	0	1 (4.0%)	1 (2.4%)
筋骨格系および結合組織障害	1 (16.7%)	0	0	1 (2.4%)
椎間板突出	1 (16.7%)	0	0	1 (2.4%)
血管障害	0	0	1 (4.0%)	1 (2.4%)
低血圧	0	0	1 (4.0%)	1 (2.4%)

[TSFAEOL03E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL03E.SAS] 02MAR2023, 08:36

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more SAEs	4 (20.0%)	8 (27.6%)	20 (30.3%)	32 (27.8%)
System organ class Preferred term				
心臓障害	1 (5.0%)	4 (13.8%)	5 (7.6%)	10 (8.7%)
右室不全	1 (5.0%)	1 (3.4%)	1 (1.5%)	3 (2.6%)
心房細動	0	0	1 (1.5%)	1 (0.9%)
心房粗動	0	1 (3.4%)	0	1 (0.9%)
心不全	0	0	1 (1.5%)	1 (0.9%)
肺性心	0	1 (3.4%)	0	1 (0.9%)
冠動脈疾患	0	0	1 (1.5%)	1 (0.9%)
左室不全	0	0	1 (1.5%)	1 (0.9%)
洞結節機能不全	0	1 (3.4%)	0	1 (0.9%)
上室性頻脈	0	0	1 (1.5%)	1 (0.9%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander
Note: If race is not reported, the subjects are excluded.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
感染症および寄生虫症	1 (5.0%)	0	8 (12.1%)	9 (7.8%)
ＣＯＶＩＤ－１９	0	0	2 (3.0%)	2 (1.7%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (1.5%)	1 (0.9%)
憩室炎	1 (5.0%)	0	0	1 (0.9%)
クロストリジウム菌性胃腸炎	0	0	1 (1.5%)	1 (0.9%)
パラインフルエンザウイルス感染	0	0	1 (1.5%)	1 (0.9%)
肺炎	0	0	1 (1.5%)	1 (0.9%)
ウイルス性肺炎	0	0	1 (1.5%)	1 (0.9%)
ウイルス性上気道感染	0	0	1 (1.5%)	1 (0.9%)
胃腸障害	1 (5.0%)	1 (3.4%)	3 (4.5%)	5 (4.3%)
虚血性大腸炎	0	1 (3.4%)	0	1 (0.9%)
胃炎	0	0	1 (1.5%)	1 (0.9%)
痔出血	0	0	1 (1.5%)	1 (0.9%)
裂孔ヘルニア	0	1 (3.4%)	0	1 (0.9%)
亜イレウス	1 (5.0%)	0	0	1 (0.9%)
舌嚢胞	0	0	1 (1.5%)	1 (0.9%)
生殖系および乳房障害	0	2 (6.9%)	3 (4.5%)	5 (4.3%)
子宮ポリープ	0	1 (3.4%)	1 (1.5%)	2 (1.7%)
子宮内膜症	0	0	1 (1.5%)	1 (0.9%)
月経中間期出血	0	0	1 (1.5%)	1 (0.9%)
卵巣嚢胞破裂	0	1 (3.4%)	0	1 (0.9%)
呼吸器、胸郭および縦隔障害	2 (10.0%)	1 (3.4%)	2 (3.0%)	5 (4.3%)
肺動脈性肺高血圧症	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
呼吸困難	0	0	1 (1.5%)	1 (0.9%)
低酸素症	1 (5.0%)	0	0	1 (0.9%)
気胸	0	1 (3.4%)	0	1 (0.9%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
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）	0	1 (3.4%)	2 (3.0%)	3 (2.6%)
基底細胞癌	0	1 (3.4%)	0	1 (0.9%)
卵巣粘液性嚢胞腺癌	0	0	1 (1.5%)	1 (0.9%)
前立腺癌	0	0	1 (1.5%)	1 (0.9%)
筋骨格系および結合組織障害	1 (5.0%)	0	1 (1.5%)	2 (1.7%)
骨壊死	0	0	1 (1.5%)	1 (0.9%)
全身性強皮症	1 (5.0%)	0	0	1 (0.9%)
眼障害	0	1 (3.4%)	0	1 (0.9%)
網膜静脈閉塞	0	1 (3.4%)	0	1 (0.9%)
一般・全身障害および投与部位の状態	0	0	1 (1.5%)	1 (0.9%)
末梢腫脹	0	0	1 (1.5%)	1 (0.9%)
顔面腫脹	0	0	1 (1.5%)	1 (0.9%)
傷害、中毒および処置合併症	0	1 (3.4%)	0	1 (0.9%)
過量投与	0	1 (3.4%)	0	1 (0.9%)
神経系障害	0	0	1 (1.5%)	1 (0.9%)
ホルネル症候群	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
腎および尿路障害	0	0	1 (1.5%)	1 (0.9%)
膜性糸球体腎炎	0	0	1 (1.5%)	1 (0.9%)
血管障害	0	0	1 (1.5%)	1 (0.9%)
低血圧	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African Americ	1	2	2	5
Subjects with 1 or more SAEs	0	0	0	0
System organ class Preferred term				

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more SAEs	2 (16.7%)	1 (10.0%)	8 (22.2%)	11 (19.0%)
System organ class Preferred term				
感染症および寄生虫症	0	1 (10.0%)	4 (11.1%)	5 (8.6%)
ＣＯＶＩＤ－１９	0	0	3 (8.3%)	3 (5.2%)
肺炎	0	1 (10.0%)	1 (2.8%)	2 (3.4%)
ＣＯＶＩＤ－１９肺炎	0	0	1 (2.8%)	1 (1.7%)
胃腸炎	0	0	1 (2.8%)	1 (1.7%)
心臓障害	0	0	4 (11.1%)	4 (6.9%)
右室不全	0	0	2 (5.6%)	2 (3.4%)
心房粗動	0	0	1 (2.8%)	1 (1.7%)
心不全	0	0	1 (2.8%)	1 (1.7%)
動悸	0	0	1 (2.8%)	1 (1.7%)
血液およびリンパ系障害	0	0	2 (5.6%)	2 (3.4%)
貧血	0	0	1 (2.8%)	1 (1.7%)
正色素性貧血	0	0	1 (2.8%)	1 (1.7%)
呼吸器、胸郭および縦隔障害	0	0	2 (5.6%)	2 (3.4%)
呼吸困難	0	0	1 (2.8%)	1 (1.7%)
肺静脈閉塞性疾患	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	0	0	1 (2.8%)	1 (1.7%)
上部消化管出血	0	0	1 (2.8%)	1 (1.7%)
食道静脈瘤	0	0	1 (2.8%)	1 (1.7%)
一般・全身障害および投与部位の状態	0	0	1 (2.8%)	1 (1.7%)
胸痛	0	0	1 (2.8%)	1 (1.7%)
肝胆道系障害	0	0	1 (2.8%)	1 (1.7%)
肝硬変	0	0	1 (2.8%)	1 (1.7%)
門脈圧亢進症	0	0	1 (2.8%)	1 (1.7%)
傷害、中毒および処置合併症	0	0	1 (2.8%)	1 (1.7%)
硬膜下血腫	0	0	1 (2.8%)	1 (1.7%)
筋骨格系および結合組織障害	1 (8.3%)	0	0	1 (1.7%)
椎間板突出	1 (8.3%)	0	0	1 (1.7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (8.3%)	0	0	1 (1.7%)
乳癌	1 (8.3%)	0	0	1 (1.7%)
神経系障害	0	0	1 (2.8%)	1 (1.7%)
不全片麻痺	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
腎および尿路障害	0	0	1 (2.8%)	1 (1.7%)
急性腎障害	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL03F: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	0	0	1	1
Subjects with 1 or more SAEs	0	0	0	0
System organ class Preferred term				

[TSFAEOL03F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL03F.SAS] 02MAR2023, 08:36

TSFAEOL04: Number of Subjects With Treatment-emergent Adverse Events Leading to Premature Discontinuation of Study Treatment in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with 1 or more AEs leading to discontinuation of M/T FDC study treatment	4 (11.4%)	1 (2.3%)	12 (11.2%)	17 (9.2%)
System organ class Preferred term				
臨床検査	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
ヘモグロビン減少	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (0.9%)	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (0.9%)	1 (0.5%)
トランスアミナーゼ上昇	0	0	1 (0.9%)	1 (0.5%)
感染症および寄生虫症	2 (5.7%)	0	1 (0.9%)	3 (1.6%)
ＣＯＶＩＤ－１９	0	0	1 (0.9%)	1 (0.5%)
結膜炎	1 (2.9%)	0	0	1 (0.5%)
Ｂ型肝炎	1 (2.9%)	0	0	1 (0.5%)
呼吸器、胸郭および縦隔障害	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
呼吸困難	0	0	1 (0.9%)	1 (0.5%)
肺動脈性肺高血圧症	1 (2.9%)	0	0	1 (0.5%)
肺静脈閉塞性疾患	0	0	1 (0.9%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

TSFAEOL04: Number of Subjects With Treatment-emergent Adverse Events Leading to Premature Discontinuation of Study Treatment in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
胃腸障害	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
胃障害	0	1 (2.3%)	0	1 (0.5%)
悪心	0	0	1 (0.9%)	1 (0.5%)
一般・全身障害および投与部位の状態	0	0	2 (1.9%)	2 (1.1%)
末梢性浮腫	0	0	1 (0.9%)	1 (0.5%)
末梢腫脹	0	0	1 (0.9%)	1 (0.5%)
顔面腫脹	0	0	1 (0.9%)	1 (0.5%)
血液およびリンパ系障害	0	0	1 (0.9%)	1 (0.5%)
貧血	0	0	1 (0.9%)	1 (0.5%)
心臓障害	0	1 (2.3%)	0	1 (0.5%)
動悸	0	1 (2.3%)	0	1 (0.5%)
肝胆道系障害	0	0	1 (0.9%)	1 (0.5%)
薬物性肝障害	0	0	1 (0.9%)	1 (0.5%)
免疫系障害	0	0	1 (0.9%)	1 (0.5%)
過敏症	0	0	1 (0.9%)	1 (0.5%)
筋骨格系および結合組織障害	0	0	1 (0.9%)	1 (0.5%)
筋肉痛	0	0	1 (0.9%)	1 (0.5%)
皮膚および皮下組織障害	0	0	1 (0.9%)	1 (0.5%)
血管浮腫	0	0	1 (0.9%)	1 (0.5%)
血管障害	0	0	1 (0.9%)	1 (0.5%)
低血圧	0	0	1 (0.9%)	1 (0.5%)

[TSFAEOL04.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL04.SAS] 02MAR2023, 08:36

TSFAEOL07R: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by Preferred Term , by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more SAEs	11 (14.3%)	26 (32.1%)	8 (30.8%)	45 (24.3%)
Preferred term				
ＣＯＶＩＤ－１９	2 (2.6%)	3 (3.7%)	0	5 (2.7%)
右室不全	1 (1.3%)	4 (4.9%)	0	5 (2.7%)
肺炎	3 (3.9%)	0	0	3 (1.6%)
心房粗動	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
ＣＯＶＩＤ－１９肺炎	0	2 (2.5%)	0	2 (1.1%)
心不全	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
呼吸困難	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
パラインフルエンザウイルス感染	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
肺動脈性肺高血圧症	0	1 (1.2%)	1 (3.8%)	2 (1.1%)
子宮ポリープ	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
急性腎障害	1 (1.3%)	0	0	1 (0.5%)
貧血	0	1 (1.2%)	0	1 (0.5%)
心房細動	0	1 (1.2%)	0	1 (0.5%)
基底細胞癌	0	1 (1.2%)	0	1 (0.5%)
乳癌	0	0	1 (3.8%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; SAE = Serious adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Note: One subject with missing baseline eGFR is only included in the Total column.
Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL07R: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by Preferred Term , by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
胸痛	1 (1.3%)	0	0	1 (0.5%)
虚血性大腸炎	0	1 (1.2%)	0	1 (0.5%)
肺性心	0	1 (1.2%)	0	1 (0.5%)
冠動脈疾患	0	1 (1.2%)	0	1 (0.5%)
憩室炎	0	0	1 (3.8%)	1 (0.5%)
子宮内膜症	1 (1.3%)	0	0	1 (0.5%)
胃炎	0	1 (1.2%)	0	1 (0.5%)
胃腸炎	1 (1.3%)	0	0	1 (0.5%)
クロストリジウム菌性胃腸炎	0	0	1 (3.8%)	1 (0.5%)
膜性糸球体腎炎	0	1 (1.2%)	0	1 (0.5%)
痔出血	0	1 (1.2%)	0	1 (0.5%)
不全片麻痺	1 (1.3%)	0	0	1 (0.5%)
肝硬変	1 (1.3%)	0	0	1 (0.5%)
裂孔ヘルニア	0	1 (1.2%)	0	1 (0.5%)
ホルネル症候群	0	1 (1.2%)	0	1 (0.5%)
低血圧	0	1 (1.2%)	0	1 (0.5%)
低酸素症	0	1 (1.2%)	0	1 (0.5%)
インフルエンザ	0	1 (1.2%)	0	1 (0.5%)
月経中間期出血	1 (1.3%)	0	0	1 (0.5%)
椎間板突出	1 (1.3%)	0	0	1 (0.5%)
左室不全	0	0	1 (3.8%)	1 (0.5%)
卵巣粘液性嚢胞腺癌	1 (1.3%)	0	0	1 (0.5%)
正色素性貧血	1 (1.3%)	0	0	1 (0.5%)
骨壊死	1 (1.3%)	0	0	1 (0.5%)
卵巣嚢胞破裂	0	1 (1.2%)	0	1 (0.5%)
過量投与	0	1 (1.2%)	0	1 (0.5%)
動悸	1 (1.3%)	0	0	1 (0.5%)
末梢腫脹	0	0	1 (3.8%)	1 (0.5%)
ウイルス性肺炎	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL07R: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by Preferred Term , by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
気胸	0	1 (1.2%)	0	1 (0.5%)
門脈圧亢進症	1 (1.3%)	0	0	1 (0.5%)

TSFAEOL07R: Number of Subjects With Treatment-emergent Serious Adverse Events in the Combined Double-blind and Open-label Period by Preferred Term , by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
前立腺癌	0	1 (1.2%)	0	1 (0.5%)
肺静脈閉塞性疾患	0	1 (1.2%)	0	1 (0.5%)
網膜静脈閉塞	0	1 (1.2%)	0	1 (0.5%)
洞結節機能不全	0	1 (1.2%)	0	1 (0.5%)
硬膜下血腫	0	1 (1.2%)	0	1 (0.5%)
亜イレウス	0	1 (1.2%)	0	1 (0.5%)
上室性頻脈	0	1 (1.2%)	0	1 (0.5%)
顔面腫脹	0	0	1 (3.8%)	1 (0.5%)
全身性強皮症	0	1 (1.2%)	0	1 (0.5%)
舌嚢胞	1 (1.3%)	0	0	1 (0.5%)
上部消化管出血	1 (1.3%)	0	0	1 (0.5%)
食道静脈瘤	1 (1.3%)	0	0	1 (0.5%)
ウイルス性上気道感染	0	1 (1.2%)	0	1 (0.5%)

[TSFAEOL07R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL07R.SAS] 20APR2023, 11:09

TSFAEOL09R: Number of Subjects With Treatment-emergent Adverse Events Leading to Premature Discontinuation of Study Treatment in the Combined Double-blind and Open-label Period by Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AEs leading to discontinuation of M/T FDC	8 (10.4%)	7 (8.6%)	2 (7.7%)	17 (9.2%)
Preferred term				
ヘモグロビン減少	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
アラニンアミノトランスフェラーゼ増加	0	1 (1.2%)	0	1 (0.5%)
貧血	0	1 (1.2%)	0	1 (0.5%)
血管浮腫	1 (1.3%)	0	0	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (1.2%)	0	1 (0.5%)
ＣＯＶＩＤ－１９	0	1 (1.2%)	0	1 (0.5%)
結膜炎	1 (1.3%)	0	0	1 (0.5%)
薬物性肝障害	0	1 (1.2%)	0	1 (0.5%)
呼吸困難	0	0	1 (3.8%)	1 (0.5%)
胃障害	1 (1.3%)	0	0	1 (0.5%)
Ｂ型肝炎	1 (1.3%)	0	0	1 (0.5%)
過敏症	0	0	1 (3.8%)	1 (0.5%)
低血圧	0	0	1 (3.8%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Note: One subject with missing baseline eGFR is only included in the Total column.
Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL09R: Number of Subjects With Treatment-emergent Adverse Events Leading to Premature Discontinuation of Study Treatment in the Combined Double-blind and Open-label Period by Preferred Term, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
筋肉痛	1 (1.3%)	0	0	1 (0.5%)
悪心	0	1 (1.2%)	0	1 (0.5%)
末梢性浮腫	1 (1.3%)	0	0	1 (0.5%)
動悸	1 (1.3%)	0	0	1 (0.5%)
末梢腫脹	0	0	1 (3.8%)	1 (0.5%)
肺動脈性肺高血圧症	0	1 (1.2%)	0	1 (0.5%)
肺静脈閉塞性疾患	0	1 (1.2%)	0	1 (0.5%)
顔面腫脹	0	0	1 (3.8%)	1 (0.5%)
トランスアミナーゼ上昇	1 (1.3%)	0	0	1 (0.5%)

[TSFAEOL09R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL09R.SAS] 20APR2023, 11:09

TSFAEOL13D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age group: 18-64 years	27	33	87	147
Subjects with 1 or more AESIs	0	1 (3.0%)	8 (9.2%)	9 (6.1%)
Severity[a]				
Mild	0	1 (3.0%)	5 (5.7%)	6 (4.1%)
Moderate	0	0	3 (3.4%)	3 (2.0%)
Severe	0	0	0	0
Preferred term				
低血圧	0	1 (3.0%)	8 (9.2%)	9 (6.1%)
Total number of recurrent AESIs	0	1	8	9
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	1 (12.5%)	1 (11.1%)
Recovered or Resolved	0	1 (100.0%)	7 (87.5%)	8 (88.9%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (1.1%)	1 (0.7%)
低血圧	0	0	1 (1.1%)	1 (0.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (1.1%)	1 (0.7%)
低血圧	0	0	1 (1.1%)	1 (0.7%)

TSFAEOL13D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (1.1%)	1 (0.7%)
低血圧	0	0	1 (1.1%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL13D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age group: >=65 years	8	10	20	38
Subjects with 1 or more AESIs	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
Severity[a]				
Mild	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
Moderate	0	0	1 (5.0%)	1 (2.6%)
Severe	0	0	0	0
Preferred term				
低血圧	1 (12.5%)	0	2 (10.0%)	3 (7.9%)
Total number of recurrent AESIs	1	0	3	4
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	1 (100.0%)	0	2 (66.7%)	3 (75.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (33.3%)	1 (25.0%)
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (5.0%)	1 (2.6%)
低血圧	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL13D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL13D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL13D.SAS] 02MAR2023, 10:29

TSFAEOL13E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more AESIs	1 (3.4%)	1 (3.0%)	8 (9.8%)	10 (6.9%)
Severity[a]				
Mild	1 (3.4%)	1 (3.0%)	6 (7.3%)	8 (5.6%)
Moderate	0	0	2 (2.4%)	2 (1.4%)
Severe	0	0	0	0
Preferred term				
低血圧	1 (3.4%)	1 (3.0%)	8 (9.8%)	10 (6.9%)
Total number of recurrent AESIs	1	1	9	11
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	1 (11.1%)	1 (9.1%)
Recovered or Resolved	1 (100.0%)	1 (100.0%)	7 (77.8%)	9 (81.8%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (11.1%)	1 (9.1%)
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (1.2%)	1 (0.7%)
低血圧	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL13E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (1.2%)	1 (0.7%)
低血圧	0	0	1 (1.2%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL13E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more AESIs	0	0	2 (8.0%)	2 (4.9%)
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	2 (8.0%)	2 (4.9%)
Severe	0	0	0	0
Preferred term				
低血圧	0	0	2 (8.0%)	2 (4.9%)
Total number of recurrent AESIs	0	0	2	2
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	2 (100.0%)	2 (100.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (4.0%)	1 (2.4%)
低血圧	0	0	1 (4.0%)	1 (2.4%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (4.0%)	1 (2.4%)
低血圧	0	0	1 (4.0%)	1 (2.4%)

TSFAEOL13E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL13E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL13E.SAS] 02MAR2023, 10:29

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more AESIs	1 (5.0%)	1 (3.4%)	9 (13.6%)	11 (9.6%)
Severity[a]				
Mild	1 (5.0%)	1 (3.4%)	6 (9.1%)	8 (7.0%)
Moderate	0	0	3 (4.5%)	3 (2.6%)
Severe	0	0	0	0
Preferred term				
低血圧	1 (5.0%)	1 (3.4%)	9 (13.6%)	11 (9.6%)
Total number of recurrent AESIs	1	1	10	12
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	1 (10.0%)	1 (8.3%)
Recovered or Resolved	1 (100.0%)	1 (100.0%)	9 (90.0%)	11 (91.7%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (1.5%)	1 (0.9%)
低血圧	0	0	1 (1.5%)	1 (0.9%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (1.5%)	1 (0.9%)
低血圧	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	2 (3.0%)	2 (1.7%)
低血圧	0	0	2 (3.0%)	2 (1.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander

Note: If race is not reported, the subjects are excluded.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African American	1	2	2	5
Subjects with 1 or more AESIs	0	0	0	0
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	0	0	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more AESIs	0	0	1 (2.8%)	1 (1.7%)
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	1 (2.8%)	1 (1.7%)
Severe	0	0	0	0
Preferred term				
低血圧	0	0	1 (2.8%)	1 (1.7%)
Total number of recurrent AESIs	0	0	1	1
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (100.0%)	1 (100.0%)
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	-	-	1	1
Subjects with 1 or more AESIs	-	-	0	0
Severity[a]				
Mild	-	-	0	0
Moderate	-	-	0	0
Severe	-	-	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	-	-	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	-	-	0	0
No data to report	-	-	-	-

TSFAEOL13F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL13F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL13F.SAS] 02MAR2023, 10:29

TSFAEOL13R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hypotension in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AESIs	1 (1.3%)	7 (8.6%)	4 (15.4%)	12 (6.5%)
Severity[a]				
Mild	1 (1.3%)	4 (4.9%)	3 (11.5%)	8 (4.3%)
Moderate	0	3 (3.7%)	1 (3.8%)	4 (2.2%)
Severe	0	0	0	0
Preferred term				
低血圧	1 (1.3%)	7 (8.6%)	4 (15.4%)	12 (6.5%)
Total number of recurrent AESIs	1	8	4	13

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.

Note: Adverse events are coded using MedDRA Version 25.1.

Note: One subject with missing baseline eGFR is only included in the Total column.

Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL13R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: 低血圧 in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	1 (25.0%)	1 (7.7%)
Recovered or Resolved	1 (100.0%)	7 (87.5%)	3 (75.0%)	11 (84.6%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	1 (12.5%)	0	1 (7.7%)
Subjects with 1 or more serious AESIs	0	1 (1.2%)	0	1 (0.5%)
低血圧	0	1 (1.2%)	0	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (3.8%)	1 (0.5%)
低血圧	0	0	1 (3.8%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	2 (2.5%)	0	2 (1.1%)
低血圧	0	2 (2.5%)	0	2 (1.1%)

[TSFAEOL13R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL13R.SAS] 20APR2023, 11:09

TSFAEOL14D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age group: 18-64 years	27	33	87	147
Subjects with 1 or more AESIs	2 (7.4%)	5 (15.2%)	23 (26.4%)	30 (20.4%)
Severity[a]				
Mild	1 (3.7%)	3 (9.1%)	13 (14.9%)	17 (11.6%)
Moderate	1 (3.7%)	2 (6.1%)	9 (10.3%)	12 (8.2%)
Severe	0	0	1 (1.1%)	1 (0.7%)
Preferred term				
ヘモグロビン減少	2 (7.4%)	0	12 (13.8%)	14 (9.5%)
貧血	0	4 (12.1%)	7 (8.0%)	11 (7.5%)
鉄欠乏性貧血	0	2 (6.1%)	5 (5.7%)	7 (4.8%)
慢性疾患の貧血	0	0	1 (1.1%)	1 (0.7%)
失血性貧血	0	0	1 (1.1%)	1 (0.7%)
骨髄線維症	0	1 (3.0%)	0	1 (0.7%)
正色素性貧血	0	0	1 (1.1%)	1 (0.7%)
汎血球減少症	0	0	1 (1.1%)	1 (0.7%)
Total number of recurrent AESIs	2	7	33	42
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	6 (85.7%)	10 (30.3%)	16 (38.1%)
Recovered or Resolved	2 (100.0%)	1 (14.3%)	22 (66.7%)	25 (59.5%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (3.0%)	1 (2.4%)
Unknown	0	0	0	0

TSFAEOL14D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more serious AESIs	0	0	1 (1.1%)	1 (0.7%)
正色素性貧血	0	0	1 (1.1%)	1 (0.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
ヘモグロビン減少	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
Subjects with 1 or more AESIs leading to treatment interruption	1 (3.7%)	0	3 (3.4%)	4 (2.7%)
ヘモグロビン減少	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
貧血	0	0	1 (1.1%)	1 (0.7%)
正色素性貧血	0	0	1 (1.1%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL14D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age group: >=65 years	8	10	20	38
Subjects with 1 or more AESIs	3 (37.5%)	2 (20.0%)	6 (30.0%)	11 (28.9%)
Severity[a]				
Mild	2 (25.0%)	2 (20.0%)	5 (25.0%)	9 (23.7%)
Moderate	1 (12.5%)	0	1 (5.0%)	2 (5.3%)
Severe	0	0	0	0
Preferred term				
貧血	2 (25.0%)	1 (10.0%)	5 (25.0%)	8 (21.1%)
ヘモグロビン減少	2 (25.0%)	1 (10.0%)	0	3 (7.9%)
鉄欠乏性貧血	0	0	1 (5.0%)	1 (2.6%)
Total number of recurrent AESIs	4	2	6	12
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	2 (50.0%)	0	3 (50.0%)	5 (41.7%)
Recovered or Resolved	1 (25.0%)	2 (100.0%)	3 (50.0%)	6 (50.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	1 (25.0%)	0	0	1 (8.3%)
Subjects with 1 or more serious AESIs	0	0	1 (5.0%)	1 (2.6%)
貧血	0	0	1 (5.0%)	1 (2.6%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (5.0%)	1 (2.6%)
貧血	0	0	1 (5.0%)	1 (2.6%)

TSFAEOL14D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

[TSFAEOL14D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL14D.SAS] 02MAR2023, 10:29

TSFAEOL14E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more AESIs	4 (13.8%)	6 (18.2%)	23 (28.0%)	33 (22.9%)
Severity[a]				
Mild	2 (6.9%)	4 (12.1%)	15 (18.3%)	21 (14.6%)
Moderate	2 (6.9%)	2 (6.1%)	8 (9.8%)	12 (8.3%)
Severe	0	0	0	0
Preferred term				
貧血	1 (3.4%)	4 (12.1%)	11 (13.4%)	16 (11.1%)
ヘモグロビン減少	4 (13.8%)	1 (3.0%)	10 (12.2%)	15 (10.4%)
鉄欠乏性貧血	0	2 (6.1%)	5 (6.1%)	7 (4.9%)
失血性貧血	0	0	1 (1.2%)	1 (0.7%)
骨髄線維症	0	1 (3.0%)	0	1 (0.7%)
汎血球減少症	0	0	1 (1.2%)	1 (0.7%)
Total number of recurrent AESIs	5	8	31	44
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	1 (20.0%)	5 (62.5%)	12 (38.7%)	18 (40.9%)
Recovered or Resolved	3 (60.0%)	3 (37.5%)	18 (58.1%)	24 (54.5%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (3.2%)	1 (2.3%)
Unknown	1 (20.0%)	0	0	1 (2.3%)
Subjects with 1 or more serious AESIs	0	0	1 (1.2%)	1 (0.7%)
貧血	0	0	1 (1.2%)	1 (0.7%)

TSFAEOL14E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
ヘモグロビン減少	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
貧血	0	0	1 (1.2%)	1 (0.7%)
Subjects with 1 or more AESIs leading to treatment interruption	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
ヘモグロビン減少	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
貧血	0	0	1 (1.2%)	1 (0.7%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL14E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more AESIs	1 (16.7%)	1 (10.0%)	6 (24.0%)	8 (19.5%)
Severity[a]				
Mild	1 (16.7%)	1 (10.0%)	3 (12.0%)	5 (12.2%)
Moderate	0	0	2 (8.0%)	2 (4.9%)
Severe	0	0	1 (4.0%)	1 (2.4%)
Preferred term				
貧血	1 (16.7%)	1 (10.0%)	1 (4.0%)	3 (7.3%)
ヘモグロビン減少	0	0	2 (8.0%)	2 (4.9%)
慢性疾患の貧血	0	0	1 (4.0%)	1 (2.4%)
鉄欠乏性貧血	0	0	1 (4.0%)	1 (2.4%)
正色素性貧血	0	0	1 (4.0%)	1 (2.4%)
Total number of recurrent AESIs	1	1	8	10
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	1 (100.0%)	1 (100.0%)	1 (12.5%)	3 (30.0%)
Recovered or Resolved	0	0	7 (87.5%)	7 (70.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (4.0%)	1 (2.4%)
正色素性貧血	0	0	1 (4.0%)	1 (2.4%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-

TSFAEOL14E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (4.0%)	1 (2.4%)
正色素性貧血	0	0	1 (4.0%)	1 (2.4%)

[TSFAEOL14E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL14E.SAS] 02MAR2023, 10:29

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more AESIs	3 (15.0%)	6 (20.7%)	16 (24.2%)	25 (21.7%)
Severity[a]				
Mild	2 (10.0%)	4 (13.8%)	11 (16.7%)	17 (14.8%)
Moderate	1 (5.0%)	2 (6.9%)	5 (7.6%)	8 (7.0%)
Severe	0	0	0	0
Preferred term				
貧血	1 (5.0%)	4 (13.8%)	6 (9.1%)	11 (9.6%)
ヘモグロビン減少	3 (15.0%)	1 (3.4%)	7 (10.6%)	11 (9.6%)
鉄欠乏性貧血	0	2 (6.9%)	5 (7.6%)	7 (6.1%)
失血性貧血	0	0	1 (1.5%)	1 (0.9%)
骨髄線維症	0	1 (3.4%)	0	1 (0.9%)
汎血球減少症	0	0	1 (1.5%)	1 (0.9%)
Total number of recurrent AESIs	4	8	21	33
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	1 (25.0%)	5 (62.5%)	4 (19.0%)	10 (30.3%)
Recovered or Resolved	2 (50.0%)	3 (37.5%)	17 (81.0%)	22 (66.7%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	1 (25.0%)	0	0	1 (3.0%)
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	1 (5.0%)	0	0	1 (0.9%)
ヘモグロビン減少	1 (5.0%)	0	0	1 (0.9%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander

Note: If race is not reported, the subjects are excluded.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African American	1	2	2	5
Subjects with 1 or more AESIs	0	0	1 (50.0%)	1 (20.0%)
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	1 (50.0%)	1 (20.0%)
Severe	0	0	0	0
Preferred term				
ヘモグロビン減少	0	0	1 (50.0%)	1 (20.0%)
Total number of recurrent AESIs	0	0	2	2
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	2 (100.0%)	2 (100.0%)
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (50.0%)	1 (20.0%)
ヘモグロビン減少	0	0	1 (50.0%)	1 (20.0%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	1 (50.0%)	1 (20.0%)
ヘモグロビン減少	0	0	1 (50.0%)	1 (20.0%)

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more AESIs	2 (16.7%)	1 (10.0%)	12 (33.3%)	15 (25.9%)
Severity[a]				
Mild	1 (8.3%)	1 (10.0%)	7 (19.4%)	9 (15.5%)
Moderate	1 (8.3%)	0	4 (11.1%)	5 (8.6%)
Severe	0	0	1 (2.8%)	1 (1.7%)
Preferred term				
貧血	1 (8.3%)	1 (10.0%)	6 (16.7%)	8 (13.8%)
ヘモグロビン減少	1 (8.3%)	0	4 (11.1%)	5 (8.6%)
慢性疾患の貧血	0	0	1 (2.8%)	1 (1.7%)
鉄欠乏性貧血	0	0	1 (2.8%)	1 (1.7%)
正色素性貧血	0	0	1 (2.8%)	1 (1.7%)
Total number of recurrent AESIs	2	1	16	19
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	1 (50.0%)	1 (100.0%)	7 (43.8%)	9 (47.4%)
Recovered or Resolved	1 (50.0%)	0	8 (50.0%)	9 (47.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (6.3%)	1 (5.3%)
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	2 (5.6%)	2 (3.4%)
貧血	0	0	1 (2.8%)	1 (1.7%)
正色素性貧血	0	0	1 (2.8%)	1 (1.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
貧血	0	0	1 (2.8%)	1 (1.7%)
ヘモグロビン減少	1 (8.3%)	0	0	1 (1.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	2 (5.6%)	2 (3.4%)
貧血	0	0	1 (2.8%)	1 (1.7%)
正色素性貧血	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	-	-	1	1
Subjects with 1 or more AESIs	-	-	0	0
Severity[a]				
Mild	-	-	0	0
Moderate	-	-	0	0
Severe	-	-	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	-	-	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	-	-	0	0
No data to report	-	-	-	-

TSFAEOL14F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL14F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL14F.SAS] 02MAR2023, 10:29

TSFAEOL14R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AESIs	17 (22.1%)	19 (23.5%)	5 (19.2%)	41 (22.2%)
Severity[a]				
Mild	12 (15.6%)	10 (12.3%)	4 (15.4%)	26 (14.1%)
Moderate	4 (5.2%)	9 (11.1%)	1 (3.8%)	14 (7.6%)
Severe	1 (1.3%)	0	0	1 (0.5%)
Preferred term				
貧血	4 (5.2%)	12 (14.8%)	3 (11.5%)	19 (10.3%)
ヘモグロビン減少	10 (13.0%)	5 (6.2%)	2 (7.7%)	17 (9.2%)
鉄欠乏性貧血	4 (5.2%)	4 (4.9%)	0	8 (4.3%)
慢性疾患の貧血	1 (1.3%)	0	0	1 (0.5%)
失血性貧血	1 (1.3%)	0	0	1 (0.5%)
骨髄線維症	0	1 (1.2%)	0	1 (0.5%)
正色素性貧血	1 (1.3%)	0	0	1 (0.5%)
汎血球減少症	0	1 (1.2%)	0	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.

Note: Adverse events are coded using MedDRA Version 25.1.

Note: One subject with missing baseline eGFR is only included in the Total column.

Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL14R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Anemia in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Total number of recurrent AESIs	24	25	5	54
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	7 (29.2%)	13 (52.0%)	1 (20.0%)	21 (38.9%)
Recovered or Resolved	17 (70.8%)	11 (44.0%)	3 (60.0%)	31 (57.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	1 (4.0%)	0	1 (1.9%)
Unknown	0	0	1 (20.0%)	1 (1.9%)
Subjects with 1 or more serious AESIs	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
貧血	0	1 (1.2%)	0	1 (0.5%)
正色素性貧血	1 (1.3%)	0	0	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
ヘモグロビン減少	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
貧血	0	1 (1.2%)	0	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	2 (2.6%)	2 (2.5%)	0	4 (2.2%)
ヘモグロビン減少	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
貧血	0	1 (1.2%)	0	1 (0.5%)
正色素性貧血	1 (1.3%)	0	0	1 (0.5%)

[TSFAEOL14R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL14R.SAS] 20APR2023, 11:09

TSFAEOL15D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age group: 18-64 years	27	33	87	147
Subjects with 1 or more AESIs	1 (3.7%)	5 (15.2%)	17 (19.5%)	23 (15.6%)
Severity[a]				
Mild	1 (3.7%)	4 (12.1%)	11 (12.6%)	16 (10.9%)
Moderate	0	1 (3.0%)	6 (6.9%)	7 (4.8%)
Severe	0	0	0	0
Preferred term				
末梢性浮腫	0	3 (9.1%)	10 (11.5%)	13 (8.8%)
末梢腫脹	1 (3.7%)	0	7 (8.0%)	8 (5.4%)
浮腫	0	2 (6.1%)	0	2 (1.4%)
骨髄浮腫	0	0	1 (1.1%)	1 (0.7%)
心嚢液貯留	0	0	1 (1.1%)	1 (0.7%)
Total number of recurrent AESIs	1	8	22	31
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (12.5%)	6 (27.3%)	7 (22.6%)
Recovered or Resolved	1 (100.0%)	7 (87.5%)	15 (68.2%)	23 (74.2%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (4.5%)	1 (3.2%)
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0

TSFAEOL15D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (1.1%)	1 (0.7%)
末梢性浮腫	0	0	1 (1.1%)	1 (0.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL15D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age group: >=65 years	8	10	20	38
Subjects with 1 or more AESIs	2 (25.0%)	0	7 (35.0%)	9 (23.7%)
Severity[a]				
Mild	2 (25.0%)	0	5 (25.0%)	7 (18.4%)
Moderate	0	0	1 (5.0%)	1 (2.6%)
Severe	0	0	1 (5.0%)	1 (2.6%)
Preferred term				
末梢性浮腫	1 (12.5%)	0	6 (30.0%)	7 (18.4%)
全身性浮腫	0	0	1 (5.0%)	1 (2.6%)
血液量増加症	1 (12.5%)	0	0	1 (2.6%)
末梢腫脹	0	0	1 (5.0%)	1 (2.6%)
腫脹	0	0	1 (5.0%)	1 (2.6%)
Total number of recurrent AESIs	2	0	10	12
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	3 (30.0%)	3 (25.0%)
Recovered or Resolved	2 (100.0%)	0	7 (70.0%)	9 (75.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (5.0%)	1 (2.6%)
末梢腫脹	0	0	1 (5.0%)	1 (2.6%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-

TSFAEOL15D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (5.0%)	1 (2.6%)
末梢腫脹	0	0	1 (5.0%)	1 (2.6%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

[TSFAEOL15D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL15D.SAS] 02MAR2023, 10:29

TSFAEOL15E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more AESIs	3 (10.3%)	4 (12.1%)	19 (23.2%)	26 (18.1%)
Severity[a]				
Mild	3 (10.3%)	3 (9.1%)	12 (14.6%)	18 (12.5%)
Moderate	0	1 (3.0%)	6 (7.3%)	7 (4.9%)
Severe	0	0	1 (1.2%)	1 (0.7%)
Preferred term				
末梢性浮腫	1 (3.4%)	2 (6.1%)	13 (15.9%)	16 (11.1%)
末梢腫脹	1 (3.4%)	0	5 (6.1%)	6 (4.2%)
浮腫	0	2 (6.1%)	0	2 (1.4%)
骨髄浮腫	0	0	1 (1.2%)	1 (0.7%)
全身性浮腫	0	0	1 (1.2%)	1 (0.7%)
血液量増加症	1 (3.4%)	0	0	1 (0.7%)
心嚢液貯留	0	0	1 (1.2%)	1 (0.7%)
腫脹	0	0	1 (1.2%)	1 (0.7%)
Total number of recurrent AESIs	3	7	25	35
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (14.3%)	7 (28.0%)	8 (22.9%)
Recovered or Resolved	3 (100.0%)	6 (85.7%)	17 (68.0%)	26 (74.3%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (4.0%)	1 (2.9%)

TSFAEOL15E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more serious AESIs	0	0	1 (1.2%)	1 (0.7%)
末梢腫脹	0	0	1 (1.2%)	1 (0.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	2 (2.4%)	2 (1.4%)
末梢性浮腫	0	0	1 (1.2%)	1 (0.7%)
末梢腫脹	0	0	1 (1.2%)	1 (0.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL15E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more AESIs	0	1 (10.0%)	5 (20.0%)	6 (14.6%)
Severity[a]				
Mild	0	1 (10.0%)	4 (16.0%)	5 (12.2%)
Moderate	0	0	1 (4.0%)	1 (2.4%)
Severe	0	0	0	0
Preferred term				
末梢性浮腫	0	1 (10.0%)	3 (12.0%)	4 (9.8%)
末梢腫脹	0	0	3 (12.0%)	3 (7.3%)
Total number of recurrent AESIs	0	1	7	8
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	2 (28.6%)	2 (25.0%)
Recovered or Resolved	0	1 (100.0%)	5 (71.4%)	6 (75.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-

TSFAEOL15E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

[TSFAEOL15E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL15E.SAS] 02MAR2023, 10:29

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more AESIs	2 (10.0%)	1 (3.4%)	17 (25.8%)	20 (17.4%)
Severity[a]				
Mild	2 (10.0%)	0	12 (18.2%)	14 (12.2%)
Moderate	0	1 (3.4%)	4 (6.1%)	5 (4.3%)
Severe	0	0	1 (1.5%)	1 (0.9%)
Preferred term				
末梢性浮腫	1 (5.0%)	1 (3.4%)	11 (16.7%)	13 (11.3%)
末梢腫脹	0	0	5 (7.6%)	5 (4.3%)
骨髄浮腫	0	0	1 (1.5%)	1 (0.9%)
全身性浮腫	0	0	1 (1.5%)	1 (0.9%)
血液量増加症	1 (5.0%)	0	0	1 (0.9%)
腫脹	0	0	1 (1.5%)	1 (0.9%)
Total number of recurrent AESIs	2	3	22	27
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (33.3%)	6 (27.3%)	7 (25.9%)
Recovered or Resolved	2 (100.0%)	2 (66.7%)	15 (68.2%)	19 (70.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	1 (4.5%)	1 (3.7%)
Subjects with 1 or more serious AESIs	0	0	1 (1.5%)	1 (0.9%)
末梢腫脹	0	0	1 (1.5%)	1 (0.9%)

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	2 (3.0%)	2 (1.7%)
末梢性浮腫	0	0	1 (1.5%)	1 (0.9%)
末梢腫脹	0	0	1 (1.5%)	1 (0.9%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander

Note: If race is not reported, the subjects are excluded.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African American	1	2	2	5
Subjects with 1 or more AESIs	0	1 (50.0%)	0	1 (20.0%)
Severity[a]				
Mild	0	1 (50.0%)	0	1 (20.0%)
Moderate	0	0	0	0
Severe	0	0	0	0
Preferred term				
浮腫	0	1 (50.0%)	0	1 (20.0%)
Total number of recurrent AESIs	0	1	0	1
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	1 (100.0%)	0	1 (100.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more AESIs	1 (8.3%)	3 (30.0%)	7 (19.4%)	11 (19.0%)
Severity[a]				
Mild	1 (8.3%)	3 (30.0%)	4 (11.1%)	8 (13.8%)
Moderate	0	0	3 (8.3%)	3 (5.2%)
Severe	0	0	0	0
Preferred term				
末梢性浮腫	0	2 (20.0%)	5 (13.9%)	7 (12.1%)
末梢腫脹	1 (8.3%)	0	3 (8.3%)	4 (6.9%)
浮腫	0	1 (10.0%)	0	1 (1.7%)
心嚢液貯留	0	0	1 (2.8%)	1 (1.7%)
Total number of recurrent AESIs	1	4	10	15
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	3 (30.0%)	3 (20.0%)
Recovered or Resolved	1 (100.0%)	4 (100.0%)	7 (70.0%)	12 (80.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	-	-	1	1
Subjects with 1 or more AESIs	-	-	0	0
Severity[a]				
Mild	-	-	0	0
Moderate	-	-	0	0
Severe	-	-	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	-	-	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	-	-	0	0
No data to report	-	-	-	-

TSFAEOL15F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL15F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL15F.SAS] 02MAR2023, 10:29

TSFAEOL15R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AESIs	14 (18.2%)	13 (16.0%)	5 (19.2%)	32 (17.3%)
Severity[a]				
Mild	11 (14.3%)	8 (9.9%)	4 (15.4%)	23 (12.4%)
Moderate	3 (3.9%)	5 (6.2%)	0	8 (4.3%)
Severe	0	0	1 (3.8%)	1 (0.5%)
Preferred term				
末梢性浮腫	8 (10.4%)	10 (12.3%)	2 (7.7%)	20 (10.8%)
末梢腫脹	6 (7.8%)	2 (2.5%)	1 (3.8%)	9 (4.9%)
浮腫	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
骨髄浮腫	0	1 (1.2%)	0	1 (0.5%)
全身性浮腫	0	1 (1.2%)	0	1 (0.5%)
血液量増加症	0	0	1 (3.8%)	1 (0.5%)
心嚢液貯留	1 (1.3%)	0	0	1 (0.5%)
腫脹	0	0	1 (3.8%)	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.

Note: Adverse events are coded using MedDRA Version 25.1.

Note: One subject with missing baseline eGFR is only included in the Total column.

Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL15R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Edema and Fluid Retention in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Total number of recurrent AESIs	21	16	6	43
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	3 (14.3%)	5 (31.3%)	2 (33.3%)	10 (23.3%)
Recovered or Resolved	18 (85.7%)	10 (62.5%)	4 (66.7%)	32 (74.4%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	1 (6.3%)	0	1 (2.3%)
Subjects with 1 or more serious AESIs	0	0	1 (3.8%)	1 (0.5%)
末梢腫脹	0	0	1 (3.8%)	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (1.3%)	0	1 (3.8%)	2 (1.1%)
末梢性浮腫	1 (1.3%)	0	0	1 (0.5%)
末梢腫脹	0	0	1 (3.8%)	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

[TSFAEOL15R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL15R.SAS] 20APR2023, 11:09

TSFAEOL16D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age group: 18-64 years	27	33	87	147
Subjects with 1 or more AESIs	1 (3.7%)	2 (6.1%)	6 (6.9%)	9 (6.1%)
Severity[a]				
Mild	1 (3.7%)	2 (6.1%)	2 (2.3%)	5 (3.4%)
Moderate	0	0	3 (3.4%)	3 (2.0%)
Severe	0	0	1 (1.1%)	1 (0.7%)
Preferred term				
アラニンアミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.1%)	2 (1.4%)
Ｂ型肝炎	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
トランスアミナーゼ上昇	0	0	2 (2.3%)	2 (1.4%)
食道静脈瘤	1 (3.7%)	0	1 (1.1%)	2 (1.4%)
血中アルカリホスファターゼ増加	0	0	1 (1.1%)	1 (0.7%)
血中ビリルビン増加	0	0	1 (1.1%)	1 (0.7%)
薬物性肝障害	0	0	1 (1.1%)	1 (0.7%)
肝硬変	0	0	1 (1.1%)	1 (0.7%)
脂肪肝	0	0	1 (1.1%)	1 (0.7%)
Ｂ型肝炎抗体異常	0	1 (3.0%)	0	1 (0.7%)
Ｃ型肝炎	0	1 (3.0%)	0	1 (0.7%)
黄疸眼	0	0	1 (1.1%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.1%)	1 (0.7%)
Total number of recurrent AESIs	2	4	15	21
AESI outcome[b]				

TSFAEOL16D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (25.0%)	10 (66.7%)	11 (52.4%)
Recovered or Resolved	2 (100.0%)	3 (75.0%)	4 (26.7%)	9 (42.9%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (6.7%)	1 (4.8%)
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (1.1%)	1 (0.7%)
肝硬変	0	0	1 (1.1%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.1%)	1 (0.7%)
食道静脈瘤	0	0	1 (1.1%)	1 (0.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (3.7%)	0	3 (3.4%)	4 (2.7%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (1.1%)	1 (0.7%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (1.1%)	1 (0.7%)
薬物性肝障害	0	0	1 (1.1%)	1 (0.7%)
Ｂ型肝炎	1 (3.7%)	0	0	1 (0.7%)
トランスアミナーゼ上昇	0	0	1 (1.1%)	1 (0.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0

TSFAEOL16D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL16D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Age group: >=65 years	8	10	20	38
Subjects with 1 or more AESIs	0	0	0	0
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	0	0	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL16D: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Age group; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL16D.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL16D.SAS] 02MAR2023, 10:29

TSFAEOL16E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Sex: Female	29	33	82	144
Subjects with 1 or more AESIs	1 (3.4%)	2 (6.1%)	5 (6.1%)	8 (5.6%)
Severity[a]				
Mild	1 (3.4%)	2 (6.1%)	2 (2.4%)	5 (3.5%)
Moderate	0	0	2 (2.4%)	2 (1.4%)
Severe	0	0	1 (1.2%)	1 (0.7%)
Preferred term				
アラニンアミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (3.0%)	1 (1.2%)	2 (1.4%)
Ｂ型肝炎	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
トランスアミナーゼ上昇	0	0	2 (2.4%)	2 (1.4%)
食道静脈瘤	1 (3.4%)	0	1 (1.2%)	2 (1.4%)
血中アルカリホスファターゼ増加	0	0	1 (1.2%)	1 (0.7%)
血中ビリルビン増加	0	0	1 (1.2%)	1 (0.7%)
肝硬変	0	0	1 (1.2%)	1 (0.7%)
脂肪肝	0	0	1 (1.2%)	1 (0.7%)
Ｂ型肝炎抗体異常	0	1 (3.0%)	0	1 (0.7%)
Ｃ型肝炎	0	1 (3.0%)	0	1 (0.7%)
黄疸眼	0	0	1 (1.2%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.2%)	1 (0.7%)
Total number of recurrent AESIs	2	4	14	20
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (25.0%)	10 (71.4%)	11 (55.0%)

TSFAEOL16E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Recovered or Resolved	2 (100.0%)	3 (75.0%)	3 (21.4%)	8 (40.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (7.1%)	1 (5.0%)
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (1.2%)	1 (0.7%)
肝硬変	0	0	1 (1.2%)	1 (0.7%)
門脈圧亢進症	0	0	1 (1.2%)	1 (0.7%)
食道静脈瘤	0	0	1 (1.2%)	1 (0.7%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (3.4%)	0	2 (2.4%)	3 (2.1%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (1.2%)	1 (0.7%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (1.2%)	1 (0.7%)
Ｂ型肝炎	1 (3.4%)	0	0	1 (0.7%)
トランスアミナーゼ上昇	0	0	1 (1.2%)	1 (0.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL16E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Sex: Male	6	10	25	41
Subjects with 1 or more AESIs	0	0	1 (4.0%)	1 (2.4%)
Severity[a]				
Mild	0	0	0	0
Moderate	0	0	1 (4.0%)	1 (2.4%)
Severe	0	0	0	0
Preferred term				
薬物性肝障害	0	0	1 (4.0%)	1 (2.4%)
Total number of recurrent AESIs	0	0	1	1
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	1 (100.0%)	1 (100.0%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (4.0%)	1 (2.4%)
薬物性肝障害	0	0	1 (4.0%)	1 (2.4%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL16E: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Sex; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL16E.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL16E.SAS] 02MAR2023, 10:29

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Race: White	20	29	66	115
Subjects with 1 or more AESIs	0	0	5 (7.6%)	5 (4.3%)
Severity[a]				
Mild	0	0	2 (3.0%)	2 (1.7%)
Moderate	0	0	2 (3.0%)	2 (1.7%)
Severe	0	0	1 (1.5%)	1 (0.9%)
Preferred term				
トランスアミナーゼ上昇	0	0	2 (3.0%)	2 (1.7%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
血中アルカリホスファターゼ増加	0	0	1 (1.5%)	1 (0.9%)
血中ビリルビン増加	0	0	1 (1.5%)	1 (0.9%)
薬物性肝障害	0	0	1 (1.5%)	1 (0.9%)
脂肪肝	0	0	1 (1.5%)	1 (0.9%)
Ｂ型肝炎	0	0	1 (1.5%)	1 (0.9%)
黄疸眼	0	0	1 (1.5%)	1 (0.9%)
Total number of recurrent AESIs	0	0	12	12
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	7 (58.3%)	7 (58.3%)
Recovered or Resolved	0	0	4 (33.3%)	4 (33.3%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	1 (8.3%)	1 (8.3%)
Unknown	0	0	0	0

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	3 (4.5%)	3 (2.6%)
アラニンアミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	1 (1.5%)	1 (0.9%)
薬物性肝障害	0	0	1 (1.5%)	1 (0.9%)
トランスアミナーゼ上昇	0	0	1 (1.5%)	1 (0.9%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

*Other=America Indian or Alaska native / Native Hawaiian or other Pacific Islander

Note: If race is not reported, the subjects are excluded.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.

Note: Adverse events are coded using MedDRA Version 25.1.

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Black or African American	1	2	2	5
Subjects with 1 or more AESIs	0	1 (50.0%)	0	1 (20.0%)
Severity[a]				
Mild	0	1 (50.0%)	0	1 (20.0%)
Moderate	0	0	0	0
Severe	0	0	0	0
Preferred term				
Ｂ型肝炎抗体異常	0	1 (50.0%)	0	1 (20.0%)
Total number of recurrent AESIs	0	1	0	1
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	1 (100.0%)	0	1 (100.0%)
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Asian	12	10	36	58
Subjects with 1 or more AESIs	1 (8.3%)	1 (10.0%)	1 (2.8%)	3 (5.2%)
Severity[a]				
Mild	1 (8.3%)	1 (10.0%)	0	2 (3.4%)
Moderate	0	0	1 (2.8%)	1 (1.7%)
Severe	0	0	0	0
Preferred term				
食道静脈瘤	1 (8.3%)	0	1 (2.8%)	2 (3.4%)
アラニンアミノトランスフェラーゼ増加	0	1 (10.0%)	0	1 (1.7%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (10.0%)	0	1 (1.7%)
肝硬変	0	0	1 (2.8%)	1 (1.7%)
Ｂ型肝炎	1 (8.3%)	0	0	1 (1.7%)
Ｃ型肝炎	0	1 (10.0%)	0	1 (1.7%)
門脈圧亢進症	0	0	1 (2.8%)	1 (1.7%)
Total number of recurrent AESIs	2	3	3	8
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	3 (100.0%)	3 (37.5%)
Recovered or Resolved	2 (100.0%)	3 (100.0%)	0	5 (62.5%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	0	0	1 (2.8%)	1 (1.7%)
肝硬変	0	0	1 (2.8%)	1 (1.7%)
門脈圧亢進症	0	0	1 (2.8%)	1 (1.7%)
食道静脈瘤	0	0	1 (2.8%)	1 (1.7%)

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	1 (8.3%)	0	0	1 (1.7%)
Ｂ型肝炎	1 (8.3%)	0	0	1 (1.7%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race: Other*	-	-	1	1
Subjects with 1 or more AESIs	-	-	0	0
Severity[a]				
Mild	-	-	0	0
Moderate	-	-	0	0
Severe	-	-	0	0
Preferred term				
No data to report	-	-	-	-
Total number of recurrent AESIs	-	-	0	0
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	0	0	0	0
Recovered or Resolved	0	0	0	0
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	0	0	0
Unknown	0	0	0	0
Subjects with 1 or more serious AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more fatal AESIs	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	-	-	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment interruption	-	-	0	0
No data to report	-	-	-	-

TSFAEOL16F: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Race; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total

[TSFAEOL16F.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL16F.SAS] 02MAR2023, 10:29

TSFAEOL16R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Analysis set: Combination Safety Set	77	81	26	185
Subjects with 1 or more AESIs	4 (5.2%)	4 (4.9%)	1 (3.8%)	9 (4.9%)
Severity[a]				
Mild	2 (2.6%)	2 (2.5%)	1 (3.8%)	5 (2.7%)
Moderate	1 (1.3%)	2 (2.5%)	0	3 (1.6%)
Severe	1 (1.3%)	0	0	1 (0.5%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AESI = Adverse event of special interest; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.

[a] In case of missing intensity, AESI is summarized as severe. Subjects are counted only once for the worst severity for any given event, regardless of the number of times they actually experienced the event.

[b] Percentages are counted with respect to the total number of recurrent AESIs.

Note: The treatment-emergent period for subjects from the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for subjects from the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. I.e. the table is covering treatment period with M/T FDC at any time during study.

Note: Adverse events are coded using MedDRA Version 25.1.

Note: One subject with missing baseline eGFR is only included in the Total column.

Note: 腎機能障害 is defined by severity at baseline: No impairment (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR 60 to <90 mL/min/1.73 m^2), moderate impairment (eGFR 30 to <60 mL/min/1.73 m^2), and severe impairment (eGFR <30 mL/min/1.73 m^2).

TSFAEOL16R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Preferred term				
アラニンアミノトランスフェラーゼ増加	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
アスパラギン酸アミノトランスフェラーゼ増加	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
Ｂ型肝炎	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
トランスアミナーゼ上昇	1 (1.3%)	1 (1.2%)	0	2 (1.1%)
食道静脈瘤	2 (2.6%)	0	0	2 (1.1%)
血中アルカリホスファターゼ増加	0	1 (1.2%)	0	1 (0.5%)
血中ビリルビン増加	0	1 (1.2%)	0	1 (0.5%)
薬物性肝障害	0	1 (1.2%)	0	1 (0.5%)
肝硬変	1 (1.3%)	0	0	1 (0.5%)
脂肪肝	0	1 (1.2%)	0	1 (0.5%)
Ｂ型肝炎抗体異常	0	0	1 (3.8%)	1 (0.5%)
Ｃ型肝炎	1 (1.3%)	0	0	1 (0.5%)
黄疸眼	0	1 (1.2%)	0	1 (0.5%)
門脈圧亢進症	1 (1.3%)	0	0	1 (0.5%)
Total number of recurrent AESIs	9	11	1	21
AESI outcome[b]				
Fatal	0	0	0	0
Not Recovered or Not Resolved	3 (33.3%)	7 (63.6%)	1 (100.0%)	11 (52.4%)
Recovered or Resolved	6 (66.7%)	3 (27.3%)	0	9 (42.9%)
Recovered or Resolved with Sequelae	0	0	0	0
Recovering or Resolving	0	1 (9.1%)	0	1 (4.8%)
Unknown	0	0	0	0

TSFAEOL16R: Number of Subjects With Treatment-emergent Adverse Events of Special Interest: Hepatic Disorders in the Combined Double-blind and Open-label Period by Preferred Term, Seriousness, Severity, Action Taken and Recurrence, by Renal Impairment Status at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	M/T FDC			
	No renal impairment	Mild renal impairment	Moderate renal impairment	Total
Subjects with 1 or more serious AESIs	1 (1.3%)	0	0	1 (0.5%)
肝硬変	1 (1.3%)	0	0	1 (0.5%)
門脈圧亢進症	1 (1.3%)	0	0	1 (0.5%)
食道静脈瘤	1 (1.3%)	0	0	1 (0.5%)
Subjects with 1 or more fatal AESIs	0	0	0	0
No data to report	-	-	-	-
Subjects with 1 or more AESIs leading to treatment discontinuation	2 (2.6%)	2 (2.5%)	0	4 (2.2%)
アラニンアミノトランスフェラーゼ増加	0	1 (1.2%)	0	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (1.2%)	0	1 (0.5%)
薬物性肝障害	0	1 (1.2%)	0	1 (0.5%)
Ｂ型肝炎	1 (1.3%)	0	0	1 (0.5%)
トランスアミナーゼ上昇	1 (1.3%)	0	0	1 (0.5%)
Subjects with 1 or more AESIs leading to treatment interruption	0	0	0	0
No data to report	-	-	-	-

[TSFAEOL16R.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSFAEOL16R.SAS] 20APR2023, 11:09

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with one or more concomitant medications	34 (97.1%)	43 (100.0%)	107 (100.0%)	184 (99.5%)
ATC Level 4 Standardized medication name				
SULFONAMIDES, PLAIN	21 (60.0%)	23 (53.5%)	67 (62.6%)	111 (60.0%)
FUROSEMIDE	17 (48.6%)	16 (37.2%)	53 (49.5%)	86 (46.5%)
TORASEMIDE	5 (14.3%)	7 (16.3%)	19 (17.8%)	31 (16.8%)
AZOSEMIDE	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
BUMETANIDE	0	0	4 (3.7%)	4 (2.2%)
INDAPAMIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
CHLORTALIDONE	0	0	1 (0.9%)	1 (0.5%)
METOLAZONE	0	0	1 (0.9%)	1 (0.5%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period; DB = Double-blind; OL = Open-label.
Note: Study Treatment-concomitant medications are defined as any therapy used on or after the same day as the first dose of M/T FDC study treatment in DB or OL period, including those that started before and continue on after the first dose of M/T FDC study treatment in DB or OL period, up to EOT (EOT-DB or EOT-OL).
Note: Medications are coded using WHO-DD Version Sep 2022 B3 Global.

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER VIRAL VACCINES	11 (31.4%)	17 (39.5%)	56 (52.3%)	84 (45.4%)
TOZINAMERAN	6 (17.1%)	8 (18.6%)	39 (36.4%)	53 (28.6%)
ELASOMERAN	4 (11.4%)	8 (18.6%)	8 (7.5%)	20 (10.8%)
COVID-19 VACCINE INACT (VERO) CZ02	1 (2.9%)	2 (4.7%)	9 (8.4%)	12 (6.5%)
COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19)	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
COVID-19 VACCINE NRVV AD26 (GAM-COVID-VAC);COVID-19 VACCINE NRVV AD5 (GAM-COVID-VAC)	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
COVID-19 VACCINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
COVID-19 VACCINE PROT. SUBUNIT (MVC-COV1901)	0	1 (2.3%)	0	1 (0.5%)
COVID-19 VACCINE PROT. SUBUNIT (NVX COV 2373)	0	1 (2.3%)	0	1 (0.5%)
COVID-19 VACCINE PROT. SUBUNIT (ZF 2001)	0	0	1 (0.9%)	1 (0.5%)
ALDOSTERONE ANTAGONISTS	18 (51.4%)	17 (39.5%)	48 (44.9%)	83 (44.9%)
SPIRONOLACTONE	17 (48.6%)	15 (34.9%)	45 (42.1%)	77 (41.6%)
EPLERENONE	1 (2.9%)	2 (4.7%)	3 (2.8%)	6 (3.2%)
POTASSIUM CANRENOATE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PROTON PUMP INHIBITORS	14 (40.0%)	22 (51.2%)	44 (41.1%)	80 (43.2%)
OMEPRAZOLE	7 (20.0%)	6 (14.0%)	15 (14.0%)	28 (15.1%)
PANTOPRAZOLE	2 (5.7%)	6 (14.0%)	9 (8.4%)	17 (9.2%)
ESOMEPRAZOLE MAGNESIUM	2 (5.7%)	1 (2.3%)	7 (6.5%)	10 (5.4%)
RABEPRAZOLE SODIUM	4 (11.4%)	1 (2.3%)	4 (3.7%)	9 (4.9%)
PANTOPRAZOLE SODIUM SESQUIHYDRATE	0	2 (4.7%)	6 (5.6%)	8 (4.3%)
ESOMEPRAZOLE	1 (2.9%)	4 (9.3%)	2 (1.9%)	7 (3.8%)
LANSOPRAZOLE	1 (2.9%)	0	4 (3.7%)	5 (2.7%)
DEXLANSOPRAZOLE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ESOMEPRAZOLE MAGNESIUM DIHYDRATE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
OMEPRAZOLE SODIUM	0	0	2 (1.9%)	2 (1.1%)
RABEPRAZOLE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
VONOPRAZAN FUMARATE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
GLUCOCORTICOIDS	10 (28.6%)	13 (30.2%)	41 (38.3%)	64 (34.6%)
PREDNISONE	2 (5.7%)	7 (16.3%)	9 (8.4%)	18 (9.7%)
PREDNISOLONE	3 (8.6%)	2 (4.7%)	11 (10.3%)	16 (8.6%)
METHYLPREDNISOLONE	1 (2.9%)	1 (2.3%)	12 (11.2%)	14 (7.6%)
DEXAMETHASONE	0	1 (2.3%)	5 (4.7%)	6 (3.2%)
HYDROCORTISONE	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
BUDESONIDE	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
PREDNISONE ACETATE	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
DEFLAZACORT	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
DEXAMETHASONE SODIUM PHOSPHATE	0	0	2 (1.9%)	2 (1.1%)
FLUTICASONE	0	0	2 (1.9%)	2 (1.1%)
PREDNISOLONE ACETATE	0	0	2 (1.9%)	2 (1.1%)
BECLOMETASONE DIPROPIONATE	0	1 (2.3%)	0	1 (0.5%)
BETAMETHASONE DIPROPIONATE	0	0	1 (0.9%)	1 (0.5%)
BETAMETHASONE DIPROPIONATE;BETAMETHASONE SODIUM PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
CICLESONIDE	1 (2.9%)	0	0	1 (0.5%)
CORTISONE	0	1 (2.3%)	0	1 (0.5%)
FLUTICASONE FUROATE	0	0	1 (0.9%)	1 (0.5%)
HYDROCORTISONE SODIUM SUCCINATE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ANILIDES	11 (31.4%)	11 (25.6%)	33 (30.8%)	55 (29.7%)
PARACETAMOL	10 (28.6%)	11 (25.6%)	29 (27.1%)	50 (27.0%)
AMANTADINE HYDROCHLORIDE;CAFFEINE;CHLORPHENAMINE MALEATE;COW BEZOAR;PARACETAMOL	0	0	2 (1.9%)	2 (1.1%)
AMANTADINE HYDROCHLORIDE;PARACETAMOL	0	0	1 (0.9%)	1 (0.5%)
AMINOPHENAZONE;CAFFEINE;CHLORPHENAMINE MALEATE;PARACETAMOL	0	0	1 (0.9%)	1 (0.5%)
ANILIDES MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
CAFFEINE;CHLORPHENAMINE;PARACETAMOL	0	0	1 (0.9%)	1 (0.5%)
CAFFEINE;PARACETAMOL	0	0	1 (0.9%)	1 (0.5%)
CAFFEINE;PARACETAMOL;PROPYPHENAZONE	1 (2.9%)	0	0	1 (0.5%)
HMG COA REDUCTASE INHIBITORS	10 (28.6%)	14 (32.6%)	19 (17.8%)	43 (23.2%)
ATORVASTATIN	2 (5.7%)	6 (14.0%)	9 (8.4%)	17 (9.2%)
ATORVASTATIN CALCIUM	2 (5.7%)	3 (7.0%)	4 (3.7%)	9 (4.9%)
ROSUVASTATIN	2 (5.7%)	2 (4.7%)	3 (2.8%)	7 (3.8%)
ROSUVASTATIN CALCIUM	3 (8.6%)	1 (2.3%)	0	4 (2.2%)
SIMVASTATIN	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
PITAVASTATIN CALCIUM	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
FLUVASTATIN	0	1 (2.3%)	0	1 (0.5%)
PRAVASTATIN	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	7 (20.0%)	13 (30.2%)	20 (18.7%)	40 (21.6%)
ACETYLSALICYLIC ACID	4 (11.4%)	12 (27.9%)	17 (15.9%)	33 (17.8%)
CLOPIDOGREL	0	1 (2.3%)	4 (3.7%)	5 (2.7%)
SELEXIPAG	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
TREPROSTINIL	2 (5.7%)	1 (2.3%)	0	3 (1.6%)
ILOPROST	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ACETYLSALICYLIC ACID;MAGNESIUM HYDROXIDE	0	0	1 (0.9%)	1 (0.5%)
ALPROSTADIL	0	0	1 (0.9%)	1 (0.5%)
CLOPIDOGREL BISULFATE	1 (2.9%)	0	0	1 (0.5%)
ILOPROST TROMETAMOL	0	0	1 (0.9%)	1 (0.5%)
PROPIONIC ACID DERIVATIVES	4 (11.4%)	6 (14.0%)	27 (25.2%)	37 (20.0%)
IBUPROFEN	2 (5.7%)	6 (14.0%)	19 (17.8%)	27 (14.6%)
DEXKETOPROFEN TROMETAMOL	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
DEXKETOPROFEN	0	0	2 (1.9%)	2 (1.1%)
FLURBIPROFEN	0	0	2 (1.9%)	2 (1.1%)
ASCORBIC ACID;IBUPROFEN;PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
CYANOCOBALAMIN;IBUPROFEN;PYRIDOXINE HYDROCHLORIDE;THIAMINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
FLURBIPROFEN AXETIL	1 (2.9%)	0	0	1 (0.5%)
KETOPROFEN	0	0	1 (0.9%)	1 (0.5%)
LOXOPROFEN	1 (2.9%)	0	0	1 (0.5%)
NAPROXEN	0	0	1 (0.9%)	1 (0.5%)
NAPROXEN SODIUM	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER IMMUNOSUPPRESSANTS	6 (17.1%)	6 (14.0%)	21 (19.6%)	33 (17.8%)
HYDROXYCHLOROQUINE	1 (2.9%)	3 (7.0%)	14 (13.1%)	18 (9.7%)
HYDROXYCHLOROQUINE SULFATE	1 (2.9%)	3 (7.0%)	5 (4.7%)	9 (4.9%)
AZATHIOPRINE	3 (8.6%)	1 (2.3%)	2 (1.9%)	6 (3.2%)
METHOTREXATE	3 (8.6%)	0	3 (2.8%)	6 (3.2%)
CHLOROQUINE	0	0	2 (1.9%)	2 (1.1%)
METHOTREXATE SODIUM	0	0	1 (0.9%)	1 (0.5%)
BETA BLOCKING AGENTS, SELECTIVE	5 (14.3%)	9 (20.9%)	17 (15.9%)	31 (16.8%)
BISOPROLOL	1 (2.9%)	2 (4.7%)	4 (3.7%)	7 (3.8%)
METOPROLOL SUCCINATE	2 (5.7%)	2 (4.7%)	3 (2.8%)	7 (3.8%)
METOPROLOL	0	3 (7.0%)	3 (2.8%)	6 (3.2%)
BISOPROLOL FUMARATE	1 (2.9%)	2 (4.7%)	2 (1.9%)	5 (2.7%)
METOPROLOL TARTRATE	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
NEBIVOLOL	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
NEBIVOLOL HYDROCHLORIDE	0	0	2 (1.9%)	2 (1.1%)
ATENOLOL	0	0	1 (0.9%)	1 (0.5%)
MEDICAL GASES	2 (5.7%)	12 (27.9%)	17 (15.9%)	31 (16.8%)
OXYGEN	2 (5.7%)	12 (27.9%)	17 (15.9%)	31 (16.8%)
DIHYDROPYRIDINE DERIVATIVES	4 (11.4%)	7 (16.3%)	19 (17.8%)	30 (16.2%)
AMLODIPINE	4 (11.4%)	4 (9.3%)	7 (6.5%)	15 (8.1%)
AMLODIPINE BESILATE	0	0	8 (7.5%)	8 (4.3%)
NIFEDIPINE	1 (2.9%)	3 (7.0%)	4 (3.7%)	8 (4.3%)
LERCANIDIPINE	0	0	1 (0.9%)	1 (0.5%)
NICARDIPINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
POTASSIUM	7 (20.0%)	3 (7.0%)	20 (18.7%)	30 (16.2%)
POTASSIUM CHLORIDE	7 (20.0%)	2 (4.7%)	14 (13.1%)	23 (12.4%)
MAGNESIUM ASPARTATE;POTASSIUM ASPARTATE	0	0	3 (2.8%)	3 (1.6%)
POTASSIUM	0	0	2 (1.9%)	2 (1.1%)
POTASSIUM GLUCONATE	0	0	2 (1.9%)	2 (1.1%)
ASCORBIC ACID;POTASSIUM BICARBONATE	0	1 (2.3%)	0	1 (0.5%)
CITRIC ACID;POTASSIUM BICARBONATE;POTASSIUM CITRATE	1 (2.9%)	0	0	1 (0.5%)
THYROID HORMONES	9 (25.7%)	9 (20.9%)	11 (10.3%)	29 (15.7%)
LEVOTHYROXINE	5 (14.3%)	8 (18.6%)	7 (6.5%)	20 (10.8%)
LEVOTHYROXINE SODIUM	4 (11.4%)	2 (4.7%)	4 (3.7%)	10 (5.4%)
DIGITALIS GLYCOSIDES	6 (17.1%)	4 (9.3%)	17 (15.9%)	27 (14.6%)
DIGOXIN	6 (17.1%)	4 (9.3%)	16 (15.0%)	26 (14.1%)
DIGITOXIN	0	0	1 (0.9%)	1 (0.5%)
VITAMIN D AND ANALOGUES	6 (17.1%)	6 (14.0%)	13 (12.1%)	25 (13.5%)
COLECALCIFEROL	5 (14.3%)	3 (7.0%)	5 (4.7%)	13 (7.0%)
ALFACALCIDOL	0	1 (2.3%)	4 (3.7%)	5 (2.7%)
CALCITRIOL	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
VITAMIN D NOS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
ELDECALCITOL	0	0	1 (0.9%)	1 (0.5%)
ERGOCALCIFEROL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
IRON BIVALENT, ORAL PREPARATIONS	7 (20.0%)	3 (7.0%)	14 (13.1%)	24 (13.0%)
FERROUS SULFATE	3 (8.6%)	2 (4.7%)	8 (7.5%)	13 (7.0%)
FERROUS FUMARATE	0	0	3 (2.8%)	3 (1.6%)
FERROUS GLYCINE SULFATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
IRON POLYSACCHARIDE COMPLEX	2 (5.7%)	0	0	2 (1.1%)
ASCORBIC ACID;FERRIC PYROPHOSPHATE	1 (2.9%)	0	0	1 (0.5%)
ASCORBIC ACID;FERROUS SULFATE	0	0	1 (0.9%)	1 (0.5%)
FERROUS GLUCONATE	0	0	1 (0.9%)	1 (0.5%)
FERROUS SODIUM CITRATE	1 (2.9%)	0	0	1 (0.5%)
IRON	0	0	1 (0.9%)	1 (0.5%)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS), PLAIN	5 (14.3%)	5 (11.6%)	11 (10.3%)	21 (11.4%)
LOSARTAN	1 (2.9%)	3 (7.0%)	3 (2.8%)	7 (3.8%)
OLMESARTAN MEDOXOMIL	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
TELMISARTAN	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
VALSARTAN	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
CANDESARTAN	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ALLISARTAN ISOPROXIL	1 (2.9%)	0	0	1 (0.5%)
IRBESARTAN	0	0	1 (0.9%)	1 (0.5%)
LOSARTAN POTASSIUM	0	1 (2.3%)	0	1 (0.5%)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	4 (11.4%)	7 (16.3%)	10 (9.3%)	21 (11.4%)
SALBUTAMOL	2 (5.7%)	5 (11.6%)	6 (5.6%)	13 (7.0%)
SALBUTAMOL SULFATE	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
FORMOTEROL	2 (5.7%)	0	0	2 (1.1%)
FENOTEROL HYDROBROMIDE	0	1 (2.3%)	0	1 (0.5%)
TERBUTALINE	0	0	1 (0.9%)	1 (0.5%)
VILANTEROL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SELECTIVE IMMUNOSUPPRESSANTS	3 (8.6%)	3 (7.0%)	15 (14.0%)	21 (11.4%)
MYCOPHENOLATE MOFETIL	3 (8.6%)	2 (4.7%)	11 (10.3%)	16 (8.6%)
LEFLUNOMIDE	0	0	2 (1.9%)	2 (1.1%)
MYCOPHENOLIC ACID	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BARICITINIB	0	0	1 (0.9%)	1 (0.5%)
MYCOPHENOLATE SODIUM	0	0	1 (0.9%)	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (8.6%)	6 (14.0%)	12 (11.2%)	21 (11.4%)
HERBAL PREPARATION	1 (2.9%)	0	4 (3.7%)	5 (2.7%)
ADINA PILULIFERA HERB;DYSPHANIA AMBROSIOIDES HERB	0	0	1 (0.9%)	1 (0.5%)
AESCULUS HIPPOCASTANUM EXTRACT	0	0	1 (0.9%)	1 (0.5%)
ALLIUM SATIVUM	0	1 (2.3%)	0	1 (0.5%)
CURCUMA LONGA	0	0	1 (0.9%)	1 (0.5%)
DRACAENA COCHINCHINENSIS RESIN	0	0	1 (0.9%)	1 (0.5%)
EUPHRASIA OFFICINALIS	0	1 (2.3%)	0	1 (0.5%)
GASTRODIA ELATA	0	0	1 (0.9%)	1 (0.5%)
ISATIS TINCTORIA LEAF;ISATIS TINCTORIA ROOT	0	0	1 (0.9%)	1 (0.5%)
LINUM USITATISSIMUM SEED OIL	0	1 (2.3%)	0	1 (0.5%)
MAGNOLIA SPP. BARK	1 (2.9%)	0	0	1 (0.5%)
OENOTHERA BIENNIS;VITAMIN E NOS	1 (2.9%)	0	0	1 (0.5%)
PERIPLANETA AMERICANA	0	1 (2.3%)	0	1 (0.5%)
PLANTAGO OVATA FIBRE	0	1 (2.3%)	0	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 3	0	0	1 (0.9%)	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 4	0	1 (2.3%)	0	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 5	0	0	1 (0.9%)	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 6	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 7	0	0	1 (0.9%)	1 (0.5%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE MULTI-INGREDIENT TERM 8	0	0	1 (0.9%)	1 (0.5%)
VACCINIUM MACROCARPON	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
VITAMIN K ANTAGONISTS	7 (20.0%)	4 (9.3%)	10 (9.3%)	21 (11.4%)
WARFARIN	3 (8.6%)	3 (7.0%)	7 (6.5%)	13 (7.0%)
WARFARIN SODIUM	4 (11.4%)	0	1 (0.9%)	5 (2.7%)
PHENPROCOUMON	0	0	2 (1.9%)	2 (1.1%)
ACENOCOUMAROL	0	1 (2.3%)	0	1 (0.5%)
AMIDES	1 (2.9%)	2 (4.7%)	17 (15.9%)	20 (10.8%)
LIDOCAINE HYDROCHLORIDE	0	0	10 (9.3%)	10 (5.4%)
LIDOCAINE	1 (2.9%)	2 (4.7%)	6 (5.6%)	9 (4.9%)
EPINEPHRINE BITARTRATE;LIDOCAINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
LIDOCAINE HYDROCHLORIDE MONOHYDRATE	0	0	1 (0.9%)	1 (0.5%)
MEPIVACAINE	0	1 (2.3%)	0	1 (0.5%)
ROPIVACAINE	0	1 (2.3%)	0	1 (0.5%)
BENZODIAZEPINE DERIVATIVES	5 (14.3%)	3 (7.0%)	11 (10.3%)	19 (10.3%)
ALPRAZOLAM	0	3 (7.0%)	3 (2.8%)	6 (3.2%)
LORAZEPAM	1 (2.9%)	0	5 (4.7%)	6 (3.2%)
MIDAZOLAM	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
BROMAZEPAM	1 (2.9%)	0	0	1 (0.5%)
CHLORDIAZEPOXIDE	0	0	1 (0.9%)	1 (0.5%)
CLONAZEPAM	1 (2.9%)	0	0	1 (0.5%)
DIAZEPAM	1 (2.9%)	0	0	1 (0.5%)
ESTAZOLAM	0	0	1 (0.9%)	1 (0.5%)
FLUNITRAZEPAM	0	0	1 (0.9%)	1 (0.5%)
OXAZOLAM	0	0	1 (0.9%)	1 (0.5%)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	4 (11.4%)	1 (2.3%)	14 (13.1%)	19 (10.3%)
ALLOPURINOL	3 (8.6%)	1 (2.3%)	12 (11.2%)	16 (8.6%)
FEBUXOSTAT	1 (2.9%)	0	2 (1.9%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ACE INHIBITORS, PLAIN	4 (11.4%)	5 (11.6%)	8 (7.5%)	17 (9.2%)
LISINOPRIL	2 (5.7%)	2 (4.7%)	2 (1.9%)	6 (3.2%)
RAMIPRIL	0	2 (4.7%)	3 (2.8%)	5 (2.7%)
PERINDOPRIL	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
ENALAPRIL	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	3 (8.6%)	2 (4.7%)	12 (11.2%)	17 (9.2%)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	1 (2.9%)	0	5 (4.7%)	6 (3.2%)
AMPICILLIN SODIUM;SULBACTAM SODIUM	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
AMOXICILLIN;CLAVULANIC ACID	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
PIPERACILLIN SODIUM;TAZOBACTAM SODIUM	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
AMOXICILLIN SODIUM;CLAVULANATE POTASSIUM	0	1 (2.3%)	0	1 (0.5%)
AMOXICILLIN;CLAVULANATE POTASSIUM	0	0	1 (0.9%)	1 (0.5%)
PIPERACILLIN SODIUM;SULBACTAM SODIUM	0	0	1 (0.9%)	1 (0.5%)
PIPERACILLIN;TAZOBACTAM	0	0	1 (0.9%)	1 (0.5%)
DIRECT FACTOR XA INHIBITORS	3 (8.6%)	4 (9.3%)	10 (9.3%)	17 (9.2%)
RIVAROXABAN	2 (5.7%)	2 (4.7%)	5 (4.7%)	9 (4.9%)
APIXABAN	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
EDOXABAN	0	1 (2.3%)	2 (1.9%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER CARDIAC PREPARATIONS	1 (2.9%)	2 (4.7%)	14 (13.1%)	17 (9.2%)
TRIMETAZIDINE	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
IVABRADINE	0	0	3 (2.8%)	3 (1.6%)
IVABRADINE HYDROCHLORIDE	0	0	3 (2.8%)	3 (1.6%)
ADENOSINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
UBIDECARENONE	0	0	2 (1.9%)	2 (1.1%)
IBUPROFEN	0	1 (2.3%)	0	1 (0.5%)
OTHER CARDIAC PREPARATIONS	0	0	1 (0.9%)	1 (0.5%)
RANOLAZINE	0	0	1 (0.9%)	1 (0.5%)
FLUOROQUINOLONES	3 (8.6%)	4 (9.3%)	9 (8.4%)	16 (8.6%)
LEVOFLOXACIN	1 (2.9%)	3 (7.0%)	6 (5.6%)	10 (5.4%)
CIPROFLOXACIN	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
MOXIFLOXACIN HYDROCHLORIDE	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
LEVOFLOXACIN HEMIHYDRATE	0	0	1 (0.9%)	1 (0.5%)
OFLOXACIN	0	1 (2.3%)	0	1 (0.5%)
PAZUFLOXACIN MESILATE	0	0	1 (0.9%)	1 (0.5%)
HEPARIN GROUP	1 (2.9%)	1 (2.3%)	13 (12.1%)	15 (8.1%)
ENOXAPARIN	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
HEPARIN SODIUM	0	0	5 (4.7%)	5 (2.7%)
ENOXAPARIN SODIUM	0	0	3 (2.8%)	3 (1.6%)
NADROPARIN CALCIUM	0	0	2 (1.9%)	2 (1.1%)
DALTEPARIN	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PIPERAZINE DERIVATIVES	2 (5.7%)	6 (14.0%)	7 (6.5%)	15 (8.1%)
CETIRIZINE HYDROCHLORIDE	1 (2.9%)	4 (9.3%)	2 (1.9%)	7 (3.8%)
CETIRIZINE	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
LEVOCETIRIZINE DIHYDROCHLORIDE	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
HYDROXYZINE EMBONATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
OXATOMIDE	0	0	1 (0.9%)	1 (0.5%)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	2 (5.7%)	2 (4.7%)	10 (9.3%)	14 (7.6%)
SODIUM CHLORIDE	1 (2.9%)	0	9 (8.4%)	10 (5.4%)
CALCIUM CHLORIDE;POTASSIUM CHLORIDE;SODIUM LACTATE	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
POTASSIUM CHLORIDE	0	0	3 (2.8%)	3 (1.6%)
CALCIUM CHLORIDE DIHYDRATE;POTASSIUM CHLORIDE;SODIUM CHLORIDE;SODIUM LACTATE	0	0	2 (1.9%)	2 (1.1%)
GLUCOSE;SODIUM CHLORIDE	0	0	2 (1.9%)	2 (1.1%)
CALCIUM CHLORIDE;MAGNESIUM CHLORIDE;POTASSIUM CHLORIDE;SODIUM ACETATE;SODIUM CHLORIDE	0	0	1 (0.9%)	1 (0.5%)
GLUCOSE;POTASSIUM CHLORIDE;SODIUM CHLORIDE;SODIUM LACTATE	1 (2.9%)	0	0	1 (0.5%)
GLUCOSE;SODIUM CHLORIDE;SODIUM LACTATE	0	0	1 (0.9%)	1 (0.5%)
MAGNESIUM SULFATE	0	0	1 (0.9%)	1 (0.5%)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE MULTI-INGREDIENT TERM 1	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	3 (8.6%)	3 (7.0%)	7 (6.5%)	13 (7.0%)
KETOROLAC	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
DICLOFENAC	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
DICLOFENAC SODIUM	0	0	2 (1.9%)	2 (1.1%)
KETOROLAC TROMETHAMINE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ACECLOFENAC	0	1 (2.3%)	0	1 (0.5%)
DICLOFENAC POTASSIUM	0	0	1 (0.9%)	1 (0.5%)
ETODOLAC	0	0	1 (0.9%)	1 (0.5%)
INDOMETACIN	0	0	1 (0.9%)	1 (0.5%)
ASCORBIC ACID (VITAMIN C), PLAIN	1 (2.9%)	2 (4.7%)	10 (9.3%)	13 (7.0%)
ASCORBIC ACID	1 (2.9%)	2 (4.7%)	10 (9.3%)	13 (7.0%)
H2-RECEPTOR ANTAGONISTS	2 (5.7%)	3 (7.0%)	8 (7.5%)	13 (7.0%)
FAMOTIDINE	2 (5.7%)	3 (7.0%)	7 (6.5%)	12 (6.5%)
CALCIUM CARBONATE;FAMOTIDINE;MAGNESIUM HYDROXIDE	0	0	1 (0.9%)	1 (0.5%)
CIMETIDINE	0	0	1 (0.9%)	1 (0.5%)
BIGUANIDES	4 (11.4%)	3 (7.0%)	5 (4.7%)	12 (6.5%)
METFORMIN	3 (8.6%)	3 (7.0%)	3 (2.8%)	9 (4.9%)
METFORMIN HYDROCHLORIDE	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
MACROLIDES	2 (5.7%)	3 (7.0%)	7 (6.5%)	12 (6.5%)
AZITHROMYCIN	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
ROXITHROMYCIN	0	0	2 (1.9%)	2 (1.1%)
AZITHROMYCIN DIHYDRATE	0	1 (2.3%)	0	1 (0.5%)
KITASAMYCIN	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
MUCOLYTICS	2 (5.7%)	2 (4.7%)	8 (7.5%)	12 (6.5%)
ACETYLCYSTEINE	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
AMBROXOL	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
AMBROXOL HYDROCHLORIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CARBOCISTEINE	0	0	2 (1.9%)	2 (1.1%)
BROMHEXINE	0	0	1 (0.9%)	1 (0.5%)
ERDOSTEINE	0	0	1 (0.9%)	1 (0.5%)
L-CARBOCISTEINE	0	0	1 (0.9%)	1 (0.5%)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	4 (11.4%)	3 (7.0%)	5 (4.7%)	12 (6.5%)
LORATADINE	4 (11.4%)	2 (4.7%)	1 (0.9%)	7 (3.8%)
DESLORATADINE	0	0	2 (1.9%)	2 (1.1%)
FEXOFENADINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BILASTINE	0	1 (2.3%)	0	1 (0.5%)
CYPROHEPTADINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
FEXOFENADINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
RUPATADINE FUMARATE	0	1 (2.3%)	0	1 (0.5%)
OTHER OPHTHALMOLOGICALS	3 (8.6%)	5 (11.6%)	4 (3.7%)	12 (6.5%)
OTHER OPHTHALMOLOGICALS	2 (5.7%)	1 (2.3%)	0	3 (1.6%)
HYALURONATE SODIUM	0	0	2 (1.9%)	2 (1.1%)
LIFITEGRAST	0	2 (4.7%)	0	2 (1.1%)
ASCORBIC ACID;CUPRIC OXIDE;DL-ALPHA TOCOPHERYL ACETATE;XANTOFYL;ZEAXANTHIN;ZINC OXIDE	0	1 (2.3%)	0	1 (0.5%)
ASCORBIC ACID;TOCOPHERYL ACETATE;XANTOFYL;ZEAXANTHIN;ZINC	0	0	1 (0.9%)	1 (0.5%)
CICLOSPORIN	1 (2.9%)	0	0	1 (0.5%)
CYANOCOBALAMIN	0	0	1 (0.9%)	1 (0.5%)
MACROGOL 400;PROPYLENE GLYCOL	0	1 (2.3%)	0	1 (0.5%)
OTHER OPHTHALMOLOGICALS MULTI-INGREDIENT TERM 1	0	1 (2.3%)	0	1 (0.5%)
PIRENOXINE	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PROGESTOGENS	5 (14.3%)	2 (4.7%)	5 (4.7%)	12 (6.5%)
DESOGESTREL	2 (5.7%)	1 (2.3%)	2 (1.9%)	5 (2.7%)
ETONOGESTREL	2 (5.7%)	0	2 (1.9%)	4 (2.2%)
DROSPIRENONE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
NORETHISTERONE	1 (2.9%)	0	0	1 (0.5%)
PROPULSIVES	4 (11.4%)	4 (9.3%)	4 (3.7%)	12 (6.5%)
DOMPERIDONE	1 (2.9%)	2 (4.7%)	1 (0.9%)	4 (2.2%)
MOSAPRIDE CITRATE	2 (5.7%)	1 (2.3%)	1 (0.9%)	4 (2.2%)
ITOPRIDE HYDROCHLORIDE	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
METOCLOPRAMIDE	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
METOCLOPRAMIDE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
FOLIC ACID AND DERIVATIVES	3 (8.6%)	0	8 (7.5%)	11 (5.9%)
FOLIC ACID	3 (8.6%)	0	8 (7.5%)	11 (5.9%)
OTHER ANTIDEPRESSANTS	1 (2.9%)	4 (9.3%)	6 (5.6%)	11 (5.9%)
DULOXETINE	0	0	2 (1.9%)	2 (1.1%)
LAMOTRIGINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
TRAZODONE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
VENLAFAXINE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
BUPROPION	0	1 (2.3%)	0	1 (0.5%)
BUPROPION HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
MIANSERIN	0	1 (2.3%)	0	1 (0.5%)
VENLAFAXINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
THIRD-GENERATION CEPHALOSPORINS	2 (5.7%)	4 (9.3%)	5 (4.7%)	11 (5.9%)
CEFIXIME	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
CEFTRIAXONE SODIUM	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
CEFTAZIDIME	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
CEFDINIR	0	0	1 (0.9%)	1 (0.5%)
CEFPODOXIME	0	1 (2.3%)	0	1 (0.5%)
CEFTRIAXONE	0	0	1 (0.9%)	1 (0.5%)
CEFTRIAXONE SODIUM SESQUATERHYDRATE	0	0	1 (0.9%)	1 (0.5%)
ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	2 (5.7%)	0	8 (7.5%)	10 (5.4%)
DICLOFENAC	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
DICLOFENAC SODIUM	0	0	1 (0.9%)	1 (0.5%)
ESFLURBIPROFEN	0	0	1 (0.9%)	1 (0.5%)
ETOFENAMATE	0	0	1 (0.9%)	1 (0.5%)
FELBINAC	1 (2.9%)	0	0	1 (0.5%)
FLURBIPROFEN	0	0	1 (0.9%)	1 (0.5%)
IBUPROFEN	0	0	1 (0.9%)	1 (0.5%)
INDOMETACIN	0	0	1 (0.9%)	1 (0.5%)
KETOPROFEN	1 (2.9%)	0	0	1 (0.5%)
LOXOPROFEN SODIUM	1 (2.9%)	0	0	1 (0.5%)
LOXOPROFEN SODIUM DIHYDRATE	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS	1 (2.9%)	6 (14.0%)	3 (2.8%)	10 (5.4%)
FLUTICASONE PROPIONATE	1 (2.9%)	3 (7.0%)	2 (1.9%)	6 (3.2%)
FLUTICASONE	0	2 (4.7%)	0	2 (1.1%)
MOMETASONE FUROATE	0	0	2 (1.9%)	2 (1.1%)
AZELASTINE HYDROCHLORIDE;FLUTICASONE PROPIONATE	0	1 (2.3%)	0	1 (0.5%)
TRIAMCINOLONE ACETONIDE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
MULTIVITAMINS, PLAIN	1 (2.9%)	5 (11.6%)	4 (3.7%)	10 (5.4%)
VITAMINS NOS	1 (2.9%)	5 (11.6%)	4 (3.7%)	10 (5.4%)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	3 (8.6%)	2 (4.7%)	5 (4.7%)	10 (5.4%)
CLONIXIN LYSINATE	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
NIMESULIDE	2 (5.7%)	0	0	2 (1.1%)
SULFASALAZINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BENZYDAMINE	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	0	0	1 (0.9%)	1 (0.5%)
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	3 (8.6%)	2 (4.7%)	5 (4.7%)	10 (5.4%)
DROSPIRENONE;ETHINYLESTRADIOL	2 (5.7%)	1 (2.3%)	3 (2.8%)	6 (3.2%)
CHLORMADINONE ACETATE;ETHINYLESTRADIOL	0	0	1 (0.9%)	1 (0.5%)
DIENOGEST;ETHINYLESTRADIOL	0	1 (2.3%)	0	1 (0.5%)
ETHINYLESTRADIOL;NORELGESTROMIN	0	0	1 (0.9%)	1 (0.5%)
ETHINYLESTRADIOL;NORGESTIMATE	1 (2.9%)	0	0	1 (0.5%)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	1 (2.9%)	6 (14.0%)	3 (2.8%)	10 (5.4%)
FLUOXETINE	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
SERTRALINE	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
CITALOPRAM HYDROBROMIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ESCITALOPRAM	0	1 (2.3%)	0	1 (0.5%)
ESCITALOPRAM OXALATE	0	1 (2.3%)	0	1 (0.5%)
PAROXETINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
BISPHOSPHONATES	2 (5.7%)	0	7 (6.5%)	9 (4.9%)
ALENDRONATE SODIUM	1 (2.9%)	0	4 (3.7%)	5 (2.7%)
MINODRONIC ACID	0	0	2 (1.9%)	2 (1.1%)
RISEDRONATE SODIUM	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
CALCIUM	2 (5.7%)	1 (2.3%)	6 (5.6%)	9 (4.9%)
CALCIUM CARBONATE	2 (5.7%)	0	3 (2.8%)	5 (2.7%)
CALCIUM	0	1 (2.3%)	0	1 (0.5%)
CALCIUM ACETATE	0	0	1 (0.9%)	1 (0.5%)
CALCIUM AMINO ACID CHELATE	0	0	1 (0.9%)	1 (0.5%)
CALCIUM GLUCONATE	0	0	1 (0.9%)	1 (0.5%)
FIRST-GENERATION CEPHALOSPORINS	2 (5.7%)	3 (7.0%)	4 (3.7%)	9 (4.9%)
CEFALEXIN	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
CEFADROXIL	0	0	2 (1.9%)	2 (1.1%)
CEFAZOLIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CEFAZOLIN SODIUM	1 (2.9%)	0	0	1 (0.5%)
CEFRADINE	0	0	1 (0.9%)	1 (0.5%)
NATURAL OPIUM ALKALOIDS	1 (2.9%)	3 (7.0%)	5 (4.7%)	9 (4.9%)
MORPHINE	0	0	4 (3.7%)	4 (2.2%)
OXYCODONE	0	2 (4.7%)	0	2 (1.1%)
CODEINE	1 (2.9%)	0	0	1 (0.5%)
CODEINE PHOSPHATE;MEPROBAMATE;PARACETAMOL	0	1 (2.3%)	0	1 (0.5%)
HYDROCODONE	0	0	1 (0.9%)	1 (0.5%)
HYDROMORPHONE	0	1 (2.3%)	0	1 (0.5%)
MORPHINE SULFATE	0	0	1 (0.9%)	1 (0.5%)
OXYCODONE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	0	6 (14.0%)	3 (2.8%)	9 (4.9%)
HYDROCODONE;PARACETAMOL	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
PARACETAMOL;TRAMADOL HYDROCHLORIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CAFFEINE;CODEINE PHOSPHATE;PARACETAMOL	0	1 (2.3%)	0	1 (0.5%)
CODEINE PHOSPHATE;IBUPROFEN	0	0	1 (0.9%)	1 (0.5%)
HYDROCODONE BITARTRATE;PARACETAMOL	0	1 (2.3%)	0	1 (0.5%)
OXYCODONE HYDROCHLORIDE;PARACETAMOL	0	1 (2.3%)	0	1 (0.5%)
OTHER ANALGESICS AND ANTIPYRETICS	2 (5.7%)	4 (9.3%)	3 (2.8%)	9 (4.9%)
PREGABALIN	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
AMITRIPTYLINE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
DULOXETINE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
GABAPENTIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	1 (2.9%)	3 (7.0%)	5 (4.7%)	9 (4.9%)
CYANOCOBALAMIN	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
MECOBALAMIN	0	0	2 (1.9%)	2 (1.1%)
VITAMIN B12 NOS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
VITAMIN B NOS	0	1 (2.3%)	0	1 (0.5%)
ADRENERGIC AND DOPAMINERGIC AGENTS	1 (2.9%)	1 (2.3%)	6 (5.6%)	8 (4.3%)
NOREPINEPHRINE	1 (2.9%)	0	4 (3.7%)	5 (2.7%)
PHENYLEPHRINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DOBUTAMINE	0	0	1 (0.9%)	1 (0.5%)
MIDODRINE	0	0	1 (0.9%)	1 (0.5%)
PHENYLEPHRINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ANTIHYPERTENSIVES FOR PULMONARY ARTERIAL HYPERTENSION	1 (2.9%)	3 (7.0%)	4 (3.7%)	8 (4.3%)
BOSENTAN	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
SILDENAFIL	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
SILDENAFIL CITRATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
MACITENTAN	0	0	1 (0.9%)	1 (0.5%)
MAGNESIUM SULFATE	0	0	1 (0.9%)	1 (0.5%)
TADALAFIL	0	1 (2.3%)	0	1 (0.5%)
IRON, PARENTERAL PREPARATIONS	0	4 (9.3%)	4 (3.7%)	8 (4.3%)
FERRIC CARBOXYMALTOSE	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
FERRIC HYDROXIDE POLYMALTOSE COMPLEX	0	1 (2.3%)	0	1 (0.5%)
IRON	0	1 (2.3%)	0	1 (0.5%)
IRON DEXTRAN	0	0	1 (0.9%)	1 (0.5%)
IRON;SUCROSE	0	1 (2.3%)	0	1 (0.5%)
OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	1 (2.9%)	1 (2.3%)	6 (5.6%)	8 (4.3%)
SUCRALFATE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
REBAMIPIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ALDIOXA	0	0	1 (0.9%)	1 (0.5%)
CALCIUM CARBONATE;MAGNESIUM CARBONATE;SODIUM ALGINATE	0	0	1 (0.9%)	1 (0.5%)
CALCIUM CARBONATE;SODIUM ALGINATE	0	0	1 (0.9%)	1 (0.5%)
SODIUM GUALENATE HYDRATE	0	0	1 (0.9%)	1 (0.5%)
TEPRENONE	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER OPIOIDS	2 (5.7%)	1 (2.3%)	5 (4.7%)	8 (4.3%)
TRAMADOL	2 (5.7%)	1 (2.3%)	3 (2.8%)	6 (3.2%)
TAPENTADOL	0	0	1 (0.9%)	1 (0.5%)
TRAMADOL HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
PREPARATIONS WITH NO EFFECT ON URIC ACID METABOLISM	3 (8.6%)	1 (2.3%)	4 (3.7%)	8 (4.3%)
COLCHICINE	3 (8.6%)	1 (2.3%)	4 (3.7%)	8 (4.3%)
SEROTONIN (5HT3) ANTAGONISTS	0	2 (4.7%)	6 (5.6%)	8 (4.3%)
ONDANSETRON	0	2 (4.7%)	5 (4.7%)	7 (3.8%)
GRANISETRON HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	1 (2.9%)	2 (4.7%)	4 (3.7%)	7 (3.8%)
BUDESONIDE;FORMOTEROL FUMARATE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
FLUTICASONE PROPIONATE;SALMETEROL XINAFOATE	0	0	2 (1.9%)	2 (1.1%)
BUDESONIDE;FORMOTEROL	0	1 (2.3%)	0	1 (0.5%)
FLUTICASONE FUROATE;VILANTEROL TRIFENATATE	0	0	1 (0.9%)	1 (0.5%)
INDACATEROL;MOMETASONE	0	0	1 (0.9%)	1 (0.5%)
BENZOTHIAZEPINE DERIVATIVES	2 (5.7%)	2 (4.7%)	3 (2.8%)	7 (3.8%)
DILTIAZEM HYDROCHLORIDE	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
DILTIAZEM	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	0	0	7 (6.5%)	7 (3.8%)
SULFAMETHOXAZOLE;TRIMETHOPRIM	0	0	7 (6.5%)	7 (3.8%)
INFLUENZA VACCINES	0	1 (2.3%)	6 (5.6%)	7 (3.8%)
INFLUENZA VACCINE	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
INFLUENZA VACCINE INACT	0	0	1 (0.9%)	1 (0.5%)
INFLUENZA VACCINE INACT SAG 4V	0	0	1 (0.9%)	1 (0.5%)
INFLUENZA VACCINE INACT SPLIT 4V	0	0	1 (0.9%)	1 (0.5%)
OSMOTICALLY ACTING LAXATIVES	3 (8.6%)	1 (2.3%)	3 (2.8%)	7 (3.8%)
MAGNESIUM OXIDE	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
ASCORBIC ACID;MACROGOL 4000;POTASSIUM CHLORIDE;SODIUM ASCORBATE;SODIUM CHLORIDE;SODIUM SULFATE ANHYDROUS	1 (2.9%)	0	0	1 (0.5%)
MACROGOL	1 (2.9%)	0	0	1 (0.5%)
MACROGOL 3350	0	1 (2.3%)	0	1 (0.5%)
MACROGOL 3350;POTASSIUM CHLORIDE;SODIUM BICARBONATE;SODIUM CHLORIDE	1 (2.9%)	0	0	1 (0.5%)
MACROGOL 3350;POTASSIUM CHLORIDE;SODIUM BICARBONATE;SODIUM CHLORIDE;SODIUM SULFATE ANHYDROUS	0	0	1 (0.9%)	1 (0.5%)
OTHER CENTRALLY ACTING AGENTS	0	2 (4.7%)	5 (4.7%)	7 (3.8%)
CYCLOBENZAPRINE HYDROCHLORIDE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
TIZANIDINE HYDROCHLORIDE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
CYCLOBENZAPRINE	0	0	2 (1.9%)	2 (1.1%)
FENYRAMIDOL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SALICYLIC ACID AND DERIVATIVES	2 (5.7%)	1 (2.3%)	4 (3.7%)	7 (3.8%)
ACETYLSALICYLIC ACID	2 (5.7%)	1 (2.3%)	4 (3.7%)	7 (3.8%)
SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	3 (8.6%)	2 (4.7%)	2 (1.9%)	7 (3.8%)
EMPAGLIFLOZIN	2 (5.7%)	0	1 (0.9%)	3 (1.6%)
DAPAGLIFLOZIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
ANTICHOLINERGICS	1 (2.9%)	3 (7.0%)	2 (1.9%)	6 (3.2%)
TIOTROPIUM BROMIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
IPRATROPIUM BROMIDE	0	1 (2.3%)	0	1 (0.5%)
TIOTROPIUM	0	1 (2.3%)	0	1 (0.5%)
TIOTROPIUM BROMIDE MONOHYDRATE	0	1 (2.3%)	0	1 (0.5%)
TROPICAMIDE	0	0	1 (0.9%)	1 (0.5%)
BENZODIAZEPINE RELATED DRUGS	2 (5.7%)	2 (4.7%)	2 (1.9%)	6 (3.2%)
ZOLPIDEM	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ZOLPIDEM TARTRATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ZOPICLONE	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
IRON IN OTHER COMBINATIONS	0	0	6 (5.6%)	6 (3.2%)
IRON IN OTHER COMBINATIONS MULTI-INGREDIENT TERM 1	0	0	3 (2.8%)	3 (1.6%)
ASCORBIC ACID;CYANOCOBALAMIN;FERROUS SULFATE;FOLIC ACID;LIVER;PROSULTIAMINE;RIBOFLAVIN	0	0	1 (0.9%)	1 (0.5%)
ASCORBIC ACID;FERROUS SULFATE	0	0	1 (0.9%)	1 (0.5%)
CYANOCOBALAMIN;FOLIC ACID;IRON PENTACARBONYL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
LEUKOTRIENE RECEPTOR ANTAGONISTS	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
MONTELUKAST	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
LEVOCETIRIZINE DIHYDROCHLORIDE;MONTELUKAST SODIUM	0	0	1 (0.9%)	1 (0.5%)
MONTELUKAST SODIUM	0	1 (2.3%)	0	1 (0.5%)
PRANLUKAST HYDRATE	0	0	1 (0.9%)	1 (0.5%)
MAGNESIUM	1 (2.9%)	2 (4.7%)	3 (2.8%)	6 (3.2%)
MAGNESIUM	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
MAGNESIUM OXIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
MAGNESIUM CITRATE	0	0	1 (0.9%)	1 (0.5%)
MAGNESIUM GLYCINATE	0	0	1 (0.9%)	1 (0.5%)
OPIUM ALKALOIDS AND DERIVATIVES	1 (2.9%)	3 (7.0%)	2 (1.9%)	6 (3.2%)
DEXTROMETHORPHAN HYDROBROMIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CHLORPHENAMINE;DEXTROMETHORPHAN	0	0	1 (0.9%)	1 (0.5%)
CODEINE PHOSPHATE	0	1 (2.3%)	0	1 (0.5%)
DEXTROMETHORPHAN	1 (2.9%)	0	0	1 (0.5%)
DEXTROMETHORPHAN HYDROBROMIDE;LYSOZYME HYDROCHLORIDE;POTASSIUM CRESOLSULFONATE	0	1 (2.3%)	0	1 (0.5%)
DIHYDROCODEINE	0	1 (2.3%)	0	1 (0.5%)
DIMEMORFAN	0	0	1 (0.9%)	1 (0.5%)
OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	2 (5.7%)	1 (2.3%)	3 (2.8%)	6 (3.2%)
DIMETICONE	2 (5.7%)	0	1 (0.9%)	3 (1.6%)
SIMETICONE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SOLUTIONS FOR PARENTERAL NUTRITION	1 (2.9%)	0	5 (4.7%)	6 (3.2%)
GLUCOSE	0	0	4 (3.7%)	4 (2.2%)
AMINO ACIDS NOS;COPPER;ELECTROLYTES NOS;GLUCOSE;IODINE;IRON;MANGANESE;VITAMINS NOS;ZINC	0	0	1 (0.9%)	1 (0.5%)
AMINO ACIDS NOS;ELECTROLYTES NOS;GLUCOSE;THIAMINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
THIAZIDES, PLAIN	3 (8.6%)	0	3 (2.8%)	6 (3.2%)
HYDROCHLOROTHIAZIDE	3 (8.6%)	0	2 (1.9%)	5 (2.7%)
TRICHLORMETHIAZIDE	0	0	1 (0.9%)	1 (0.5%)
BETA-LACTAMASE INHIBITORS	1 (2.9%)	1 (2.3%)	3 (2.8%)	5 (2.7%)
CLAVULANIC ACID	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
TAZOBACTAM	0	0	1 (0.9%)	1 (0.5%)
BILE ACIDS AND DERIVATIVES	2 (5.7%)	2 (4.7%)	1 (0.9%)	5 (2.7%)
URSODEOXYCHOLIC ACID	2 (5.7%)	2 (4.7%)	1 (0.9%)	5 (2.7%)
CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	1 (2.9%)	3 (7.0%)	1 (0.9%)	5 (2.7%)
CALCIUM CARBONATE;COLECALCIFEROL	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
CALCIUM;MAGNESIUM;VITAMIN D NOS	0	1 (2.3%)	0	1 (0.5%)
CALCIUM;VITAMIN D NOS	1 (2.9%)	0	0	1 (0.5%)
IMIDAZOLE DERIVATIVES	1 (2.9%)	2 (4.7%)	2 (1.9%)	5 (2.7%)
METRONIDAZOLE	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
KETOCONAZOLE	0	1 (2.3%)	0	1 (0.5%)
LIDOCAINE;TINIDAZOLE;TIOCONAZOLE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
INTRAUTERINE CONTRACEPTIVES	0	1 (2.3%)	4 (3.7%)	5 (2.7%)
LEVONORGESTREL	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
INTRAUTERINE CONTRACEPTIVE DEVICE	0	0	2 (1.9%)	2 (1.1%)
NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	0	0	5 (4.7%)	5 (2.7%)
LAMIVUDINE	0	0	3 (2.8%)	3 (1.6%)
TENOFOVIR	0	0	3 (2.8%)	3 (1.6%)
EMTRICITABINE	0	0	1 (0.9%)	1 (0.5%)
ENTECAVIR MONOHYDRATE	0	0	1 (0.9%)	1 (0.5%)
NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	0	0	5 (4.7%)	5 (2.7%)
REMDESIVIR	0	0	2 (1.9%)	2 (1.1%)
ACICLOVIR	0	0	1 (0.9%)	1 (0.5%)
MOLNUPIRAVIR	0	0	1 (0.9%)	1 (0.5%)
VALACICLOVIR HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
VALGANCICLOVIR HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
OTHER ANTIBIOTICS FOR TOPICAL USE	0	2 (4.7%)	3 (2.8%)	5 (2.7%)
NEOMYCIN SULFATE	0	0	2 (1.9%)	2 (1.1%)
BACITRACIN	0	1 (2.3%)	0	1 (0.5%)
FUSIDIC ACID	0	0	1 (0.9%)	1 (0.5%)
MUPIROCIN	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER ANXIOLYTICS	2 (5.7%)	2 (4.7%)	1 (0.9%)	5 (2.7%)
DULOXETINE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
PREGABALIN	0	0	1 (0.9%)	1 (0.5%)
PROPRANOLOL HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
SERTRALINE	0	1 (2.3%)	0	1 (0.5%)
SERTRALINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
OTHER COUGH SUPPRESSANTS	1 (2.9%)	3 (7.0%)	1 (0.9%)	5 (2.7%)
BENZONATATE	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
BENPROPERINE PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
PENTOXYVERINE CITRATE	0	1 (2.3%)	0	1 (0.5%)
OTHER GENERAL ANESTHETICS	1 (2.9%)	3 (7.0%)	1 (0.9%)	5 (2.7%)
PROPOFOL	1 (2.9%)	3 (7.0%)	1 (0.9%)	5 (2.7%)
KETAMINE	0	1 (2.3%)	0	1 (0.5%)
PENICILLINS WITH EXTENDED SPECTRUM	2 (5.7%)	1 (2.3%)	2 (1.9%)	5 (2.7%)
AMOXICILLIN	2 (5.7%)	1 (2.3%)	1 (0.9%)	4 (2.2%)
AMOXICILLIN TRIHYDRATE	0	0	1 (0.9%)	1 (0.5%)
SUBSTITUTED ALKYLAMINES	0	0	5 (4.7%)	5 (2.7%)
CHLORPHENAMINE	0	0	2 (1.9%)	2 (1.1%)
CHLORPHENAMINE MALEATE	0	0	1 (0.9%)	1 (0.5%)
DEXCHLORPHENIRAMINE	0	0	1 (0.9%)	1 (0.5%)
PHENIRAMINE MALEATE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
VITAMIN B1, PLAIN	1 (2.9%)	0	4 (3.7%)	5 (2.7%)
PROSULTIAMINE	0	0	1 (0.9%)	1 (0.5%)
THIAMINE DISULFIDE PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
THIAMINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
THIAMINE MONONITRATE	1 (2.9%)	0	0	1 (0.5%)
VITAMIN B1 NOS	0	0	1 (0.9%)	1 (0.5%)
WATERSOLUBLE, NEPHROTROPIC, LOW OSMOLAR X-RAY CONTRAST MEDIA	2 (5.7%)	1 (2.3%)	2 (1.9%)	5 (2.7%)
IOPAMIDOL	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
IOHEXOL	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ANTIBIOTICS	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
NYSTATIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CHLORAMPHENICOL	0	1 (2.3%)	0	1 (0.5%)
ERYTHROMYCIN	0	0	1 (0.9%)	1 (0.5%)
ANTIDIARRHEAL MICROORGANISMS	0	3 (7.0%)	1 (0.9%)	4 (2.2%)
LACTOBACILLUS RHAMNOSUS	0	2 (4.7%)	0	2 (1.1%)
ANTIDIARRHEAL MICROORGANISMS MULTI-INGREDIENT TERM 1	0	1 (2.3%)	0	1 (0.5%)
BIFIDOBACTERIUM NOS	0	0	1 (0.9%)	1 (0.5%)
ANTIPROPULSIVES	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
LOPERAMIDE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
LOPERAMIDE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
CALCINEURIN INHIBITORS	0	0	4 (3.7%)	4 (2.2%)
CICLOSPORIN	0	0	3 (2.8%)	3 (1.6%)
TACROLIMUS	0	0	1 (0.9%)	1 (0.5%)
COMBINATIONS AND COMPLEXES OF ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
HYDROTALCITE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ALUMINIUM HYDROXIDE;CALCIUM CARBONATE;MAGNESIUM HYDROXIDE	0	1 (2.3%)	0	1 (0.5%)
MAGALDRATE	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS, PLAIN	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
FLUOROMETHOLONE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BETAMETHASONE SODIUM PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
DEXAMETHASONE	1 (2.9%)	0	0	1 (0.5%)
PREDNISOLONE ACETATE	0	0	1 (0.9%)	1 (0.5%)
EXPECTORANTS	1 (2.9%)	2 (4.7%)	1 (0.9%)	4 (2.2%)
GUAIFENESIN	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
CHLORPHENAMINE MALEATE;METHYLEPHEDRINE HYDROCHLORIDE-DL;SODIUM DIBUNATE	0	1 (2.3%)	0	1 (0.5%)
HERBAL ANTIVIRALS FOR SYSTEMIC USE	0	0	4 (3.7%)	4 (2.2%)
HERBAL ANTIVIRALS FOR SYSTEMIC USE MULTI-INGREDIENT TERM 2	0	0	3 (2.8%)	3 (1.6%)
HERBAL ANTIVIRALS FOR SYSTEMIC USE MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
INSULIN GLARGINE	0	0	2 (1.9%)	2 (1.1%)
INSULIN DEGLUDEC	1 (2.9%)	0	0	1 (0.5%)
INSULIN DETEMIR	0	0	1 (0.9%)	1 (0.5%)
IRON PREPARATIONS	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
IRON	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
IRON POLYSACCHARIDE COMPLEX	0	0	2 (1.9%)	2 (1.1%)
LIVER THERAPY	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
SILYBUM MARIANUM	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
PHOSPHOLIPIDS	0	0	1 (0.9%)	1 (0.5%)
OPIOID ANESTHETICS	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
FENTANYL CITRATE	0	0	2 (1.9%)	2 (1.1%)
FENTANYL	0	1 (2.3%)	0	1 (0.5%)
REMIFENTANIL HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
OPIUM DERIVATIVES AND EXPECTORANTS	1 (2.9%)	2 (4.7%)	1 (0.9%)	4 (2.2%)
ANTIMONY POTASSIUM TARTRATE;GLYCYRRHIZA SPP.;PAPAVER SOMNIFERUM TINCTURE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CAMPHOR;GLYCYRRHIZA SPP. ROOT WITH RHIZOME;ILLICIUM VERUM OIL;PAPAVER SOMNIFERUM LATEX;SODIUM BENZOATE	1 (2.9%)	0	0	1 (0.5%)
DEXTROMETHORPHAN HYDROBROMIDE;GUAIFENESIN	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER ANTIEMETICS	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
DIFENIDOL	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
DOMPERIDONE	0	0	1 (0.9%)	1 (0.5%)
TRIMETHOBENZAMIDE	0	0	1 (0.9%)	1 (0.5%)
OTHER ANTIPSYCHOTICS	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
ARIPIPRAZOLE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CARIPRAZINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
VALPROATE SEMISODIUM	0	0	1 (0.9%)	1 (0.5%)
OTHER BLOOD PRODUCTS	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
BLOOD CELLS, PACKED HUMAN	0	0	2 (1.9%)	2 (1.1%)
BLOOD, WHOLE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BLOOD PLASMA	0	1 (2.3%)	0	1 (0.5%)
RED BLOOD CELLS, CONCENTRATED	0	0	1 (0.9%)	1 (0.5%)
OTHER DERMATOLOGICALS	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
COLLAGEN	0	0	1 (0.9%)	1 (0.5%)
DICLOFENAC	0	0	1 (0.9%)	1 (0.5%)
ESTRADIOL	0	0	1 (0.9%)	1 (0.5%)
TRETINOIN	0	1 (2.3%)	0	1 (0.5%)
OTHER EMOLLIENTS AND PROTECTIVES	0	0	4 (3.7%)	4 (2.2%)
HEPARINOID	0	0	2 (1.9%)	2 (1.1%)
CAMPHOR;MENTHOL	0	0	1 (0.9%)	1 (0.5%)
COLECALCIFEROL;DL-ALPHA TOCOPHERYL ACETATE;RETINOL	0	0	1 (0.9%)	1 (0.5%)
TOCOPHEROL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER PLAIN VITAMIN PREPARATIONS	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
BIOTIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
PYRIDOXINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
TOCOPHEROL	0	0	1 (0.9%)	1 (0.5%)
VITAMIN B NOS	0	0	1 (0.9%)	1 (0.5%)
PHENOTHIAZINE DERIVATIVES	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
MEQUITAZINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
PROMETHAZINE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
PHENYLPIPERIDINE DERIVATIVES	1 (2.9%)	0	3 (2.8%)	4 (2.2%)
FENTANYL	0	0	3 (2.8%)	3 (1.6%)
FENTANYL CITRATE	1 (2.9%)	0	0	1 (0.5%)
PYRAZOLONES	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
METAMIZOLE SODIUM	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
METAMIZOLE MAGNESIUM	0	0	1 (0.9%)	1 (0.5%)
SECOND-GENERATION CEPHALOSPORINS	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
CEFUROXIME	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
SYMPATHOMIMETICS	1 (2.9%)	1 (2.3%)	2 (1.9%)	4 (2.2%)
PSEUDOEPHEDRINE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
CHLORPHENAMINE MALEATE;IBUPROFEN;PSEUDOEPHEDRINE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SYNTHETIC ANTICHOLINERGICS, ESTERS WITH TERTIARY AMINO GROUP	0	1 (2.3%)	3 (2.8%)	4 (2.2%)
TRIMEBUTINE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
PIPETHANATE ETHOBROMIDE	0	0	1 (0.9%)	1 (0.5%)
TETRACYCLINES	0	3 (7.0%)	1 (0.9%)	4 (2.2%)
DOXYCYCLINE	0	3 (7.0%)	1 (0.9%)	4 (2.2%)
ALL OTHER NON-THERAPEUTIC PRODUCTS	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
ALL OTHER NON-THERAPEUTIC PRODUCTS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
MEDICAL DEVICES, WITHOUT SUBSTANCES	0	1 (2.3%)	0	1 (0.5%)
ALPHA AND BETA BLOCKING AGENTS	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
CARVEDILOL	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
AMINO ACIDS	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
TRANEXAMIC ACID	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
AMINOALKYL ETHERS	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
DIPHENHYDRAMINE HYDROCHLORIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DIPHENHYDRAMINE	1 (2.9%)	0	0	1 (0.5%)
AMINOSALICYLIC ACID AND SIMILAR AGENTS	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
MESALAZINE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND CALCIUM CHANNEL BLOCKERS	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
AMLODIPINE BESILATE;OLMESARTAN MEDOXOMIL	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
AMLODIPINE BESILATE;AZILSARTAN	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ANTACIDS WITH SODIUM BICARBONATE	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
ALGELDRATE;ALGINIC ACID;MAGNESIUM TRISILICATE;SODIUM BICARBONATE	0	0	1 (0.9%)	1 (0.5%)
CITRIC ACID;SODIUM BICARBONATE;SODIUM CITRATE;TARTARIC ACID	1 (2.9%)	0	0	1 (0.5%)
SODIUM ALGINATE;SODIUM BICARBONATE	0	1 (2.3%)	0	1 (0.5%)
ANTIARRHYTHMICS, CLASS IC	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
PROPAFENONE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
ANTIDOTES	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
FLUMAZENIL	0	0	1 (0.9%)	1 (0.5%)
NALOXONE	0	1 (2.3%)	0	1 (0.5%)
SUGAMMADEX SODIUM	1 (2.9%)	0	0	1 (0.5%)
ANTIINFLAMMATORY AGENTS, NON-STEROIDS	0	0	3 (2.8%)	3 (1.6%)
BROMFENAC SODIUM	0	0	1 (0.9%)	1 (0.5%)
NAPROXEN	0	0	1 (0.9%)	1 (0.5%)
NEPAFENAC	0	0	1 (0.9%)	1 (0.5%)
ANTIVERTIGO PREPARATIONS	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
BETAHISTINE MESILATE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
MECLOZINE	0	0	1 (0.9%)	1 (0.5%)
AZASPIRODECANEDIONE DERIVATIVES	0	0	3 (2.8%)	3 (1.6%)
BUSPIRONE HYDROCHLORIDE	0	0	2 (1.9%)	2 (1.1%)
BUSPIRONE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
BETA BLOCKING AGENTS, NON-SELECTIVE	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
PROPRANOLOL	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
SOTALOL	0	0	1 (0.9%)	1 (0.5%)
CD20 (CLUSTERS OF DIFFERENTIATION 20) INHIBITORS	0	0	3 (2.8%)	3 (1.6%)
RITUXIMAB	0	0	3 (2.8%)	3 (1.6%)
CONTACT LAXATIVES	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
SENNOSIDE A+B	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
BISACODYL;SENNOSIDE B	0	0	1 (0.9%)	1 (0.5%)
CITRIC ACID;MAGNESIUM OXIDE;SODIUM PICOSULFATE	0	0	1 (0.9%)	1 (0.5%)
SENNOSIDE A+B CALCIUM	1 (2.9%)	0	0	1 (0.5%)
COXIBS	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
CELECOXIB	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
ETORICOXIB	0	0	1 (0.9%)	1 (0.5%)
DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	0	0	3 (2.8%)	3 (1.6%)
SITAGLIPTIN	0	0	2 (1.9%)	2 (1.1%)
SITAGLIPTIN PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
IMIDAZOLE AND TRIAZOLE DERIVATIVES	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
ISOCONAZOLE NITRATE	0	0	1 (0.9%)	1 (0.5%)
KETOCONAZOLE	1 (2.9%)	0	0	1 (0.5%)
LULICONAZOLE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	0	0	3 (2.8%)	3 (1.6%)
INSULIN	0	0	1 (0.9%)	1 (0.5%)
INSULIN ASPART	0	0	1 (0.9%)	1 (0.5%)
INSULIN HUMAN	0	0	1 (0.9%)	1 (0.5%)
INSULIN LISPRO	0	0	1 (0.9%)	1 (0.5%)
INTEGRASE INHIBITORS	0	0	3 (2.8%)	3 (1.6%)
DOLUTEGRAVIR	0	0	1 (0.9%)	1 (0.5%)
DOLUTEGRAVIR SODIUM	0	0	1 (0.9%)	1 (0.5%)
RALTEGRAVIR	0	0	1 (0.9%)	1 (0.5%)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
ESTRADIOL	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
ETHINYLESTRADIOL	0	0	1 (0.9%)	1 (0.5%)
NICOTINIC ACID AND DERIVATIVES	0	0	3 (2.8%)	3 (1.6%)
TOCOPHERYL NICOTINATE	0	0	2 (1.9%)	2 (1.1%)
NICAMETATE DIHYDROGEN CITRATE	0	0	1 (0.9%)	1 (0.5%)
NITROGEN MUSTARD ANALOGUES	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
CYCLOPHOSPHAMIDE	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	0	0	3 (2.8%)	3 (1.6%)
CLOSTRIDIUM BUTYRICUM	0	0	3 (2.8%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER ANTIBACTERIALS	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
D-MANNOSE	1 (2.9%)	0	0	1 (0.5%)
DAPTOMYCIN	0	1 (2.3%)	0	1 (0.5%)
FOSFOMYCIN	0	0	1 (0.9%)	1 (0.5%)
LINEZOLID	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIVIRALS	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
UMIFENOVIR	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
PHOSPHAZID	0	0	1 (0.9%)	1 (0.5%)
OTHER COMBINATIONS OF NUTRIENTS	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
FISH OIL	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
OTHER LIPID MODIFYING AGENTS	0	0	3 (2.8%)	3 (1.6%)
EZETIMIBE	0	0	2 (1.9%)	2 (1.1%)
SALMON OIL	0	0	1 (0.9%)	1 (0.5%)
OTHER NASAL PREPARATIONS	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
SODIUM CHLORIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
SODIUM BICARBONATE;SODIUM CHLORIDE	0	1 (2.3%)	0	1 (0.5%)
OTHER PROTEIN KINASE INHIBITORS	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
NINTEDANIB	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
OXICAMS	0	0	3 (2.8%)	3 (1.6%)
MELOXICAM	0	0	2 (1.9%)	2 (1.1%)
TENOXICAM	0	0	1 (0.9%)	1 (0.5%)
PHENYLALKYLAMINE DERIVATIVES	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
VERAPAMIL	0	1 (2.3%)	2 (1.9%)	3 (1.6%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SULFONYLUREAS	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
GLIBENCLAMIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
GLICLAZIDE	0	0	1 (0.9%)	1 (0.5%)
SYMPATHOMIMETICS, PLAIN	0	1 (2.3%)	2 (1.9%)	3 (1.6%)
XYLOMETAZOLINE HYDROCHLORIDE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
OXYMETAZOLINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (2.9%)	2 (4.7%)	0	3 (1.6%)
PROBIOTICS NOS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
UBIDECARENONE	0	1 (2.3%)	0	1 (0.5%)
VITAMIN B-COMPLEX, PLAIN	0	3 (7.0%)	0	3 (1.6%)
VITAMIN B COMPLEX	0	3 (7.0%)	0	3 (1.6%)
VITAMIN B1 IN COMBINATION WITH VITAMIN B6 AND/OR VITAMIN B12	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
CYANOCOBALAMIN;PYRIDOXINE HYDROCHLORIDE;THIAMINE HYDROCHLORIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
BENFOTIAMINE;CYANOCOBALAMIN;PYRIDOXINE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
ZINC	1 (2.9%)	0	2 (1.9%)	3 (1.6%)
ZINC	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ZINC GLUCONATE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS INCL. TRIPLE COMBINATIONS WITH CORTICOSTEROIDS	0	0	2 (1.9%)	2 (1.1%)
IPRATROPIUM BROMIDE MONOHYDRATE;SALBUTAMOL SULFATE	0	0	1 (0.9%)	1 (0.5%)
UMECLIDINIUM;VILANTEROL	0	0	1 (0.9%)	1 (0.5%)
ALPHA-ADRENORECEPTOR ANTAGONISTS	0	0	2 (1.9%)	2 (1.1%)
DOXAZOSIN	0	0	1 (0.9%)	1 (0.5%)
PRAZOSIN	0	0	1 (0.9%)	1 (0.5%)
PRAZOSIN HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND DIURETICS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
HYDROCHLOROTHIAZIDE;LOSARTAN	0	1 (2.3%)	0	1 (0.5%)
HYDROCHLOROTHIAZIDE;LOSARTAN POTASSIUM	1 (2.9%)	0	0	1 (0.5%)
ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	0	2 (4.7%)	0	2 (1.1%)
AZELASTINE HYDROCHLORIDE	0	2 (4.7%)	0	2 (1.1%)
ANTINEOVASCULARISATION AGENTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
AFLIBERCEPT	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ANTISEPTICS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
BENZYDAMINE HYDROCHLORIDE;CHLORHEXIDINE GLUCONATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ANTIVIRAL MONOCLONAL ANTIBODIES	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CASIRIVIMAB;IMDEVIMAB	0	1 (2.3%)	0	1 (0.5%)
SOTROVIMAB	0	0	1 (0.9%)	1 (0.5%)
ANTIVIRALS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ACICLOVIR	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ANTIVIRALS FOR TREATMENT OF HCV INFECTIONS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
GLECAPREVIR;PIBRENTASVIR	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBINATIONS	0	2 (4.7%)	0	2 (1.1%)
ABACAVIR;LAMIVUDINE	0	1 (2.3%)	0	1 (0.5%)
BICTEGRAVIR SODIUM;EMTRICITABINE;TENOFOVIR ALAFENAMIDE FUMARATE	0	1 (2.3%)	0	1 (0.5%)
BIOFLAVONOIDS	0	0	2 (1.9%)	2 (1.1%)
DIOSMIN;HESPERIDIN	0	0	2 (1.9%)	2 (1.1%)
CARBAPENEMS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ERTAPENEM	1 (2.9%)	0	0	1 (0.5%)
MEROPENEM TRIHYDRATE	0	0	1 (0.9%)	1 (0.5%)
CARBONIC ANHYDRASE INHIBITORS	0	0	2 (1.9%)	2 (1.1%)
ACETAZOLAMIDE	0	0	1 (0.9%)	1 (0.5%)
BRINZOLAMIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
EMPAGLIFLOZIN;METFORMIN HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
METFORMIN HYDROCHLORIDE;VILDAGLIPTIN	1 (2.9%)	0	0	1 (0.5%)
COMBINATIONS OF VITAMINS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
COLECALCIFEROL;MENAQUINONE	0	1 (2.3%)	0	1 (0.5%)
VITAMINS NOS	1 (2.9%)	0	0	1 (0.5%)
CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	0	2 (4.7%)	0	2 (1.1%)
BETAMETHASONE SODIUM PHOSPHATE;NEOMYCIN SULFATE	0	1 (2.3%)	0	1 (0.5%)
DEXAMETHASONE;GENTAMICIN SULFATE	0	1 (2.3%)	0	1 (0.5%)
CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
HYDROCORTISONE BUTYRATE	1 (2.9%)	0	0	1 (0.5%)
TRIAMCINOLONE	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS, POTENT (GROUP III)	0	0	2 (1.9%)	2 (1.1%)
BETAMETHASONE BUTYRATE PROPIONATE	0	0	1 (0.9%)	1 (0.5%)
BETAMETHASONE VALERATE	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS, VERY POTENT (GROUP IV)	0	0	2 (1.9%)	2 (1.1%)
CLOBETASOL PROPIONATE	0	0	2 (1.9%)	2 (1.1%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
CORTICOSTEROIDS, WEAK (GROUP I)	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
HYDROCORTISONE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DETOXIFYING AGENTS FOR ANTINEOPLASTIC TREATMENT	0	0	2 (1.9%)	2 (1.1%)
CALCIUM LEVOFOLINATE	0	0	1 (0.9%)	1 (0.5%)
MESNA	0	0	1 (0.9%)	1 (0.5%)
DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	0	0	2 (1.9%)	2 (1.1%)
QUETIAPINE	0	0	1 (0.9%)	1 (0.5%)
QUETIAPINE FUMARATE	0	0	1 (0.9%)	1 (0.5%)
FIBRATES	0	0	2 (1.9%)	2 (1.1%)
CIPROFIBRATE	0	0	1 (0.9%)	1 (0.5%)
FENOFIBRATE	0	0	1 (0.9%)	1 (0.5%)
GLYCOPEPTIDE ANTIBACTERIALS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
VANCOMYCIN	0	0	1 (0.9%)	1 (0.5%)
VANCOMYCIN HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
IRON TRIVALENT, ORAL PREPARATIONS	0	0	2 (1.9%)	2 (1.1%)
ASCORBIC ACID;FERROUS SULFATE	0	0	1 (0.9%)	1 (0.5%)
SACCHARATED IRON OXIDE	0	0	1 (0.9%)	1 (0.5%)
LINCOSAMIDES	0	0	2 (1.9%)	2 (1.1%)
CLINDAMYCIN	0	0	2 (1.9%)	2 (1.1%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
MAGNESIUM COMPOUNDS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
MAGNESIUM HYDROXIDE	0	0	1 (0.9%)	1 (0.5%)
MAGNESIUM OXIDE	1 (2.9%)	0	0	1 (0.5%)
MELATONIN RECEPTOR AGONISTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
MELATONIN	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
MULTIVITAMINS, OTHER COMBINATIONS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
FERROUS SULFATE;VITAMINS NOS	1 (2.9%)	0	0	1 (0.5%)
MULTIVITAMINS, OTHER COMBINATIONS MULTI-INGREDIENT TERM 1	0	1 (2.3%)	0	1 (0.5%)
NITROFURAN DERIVATIVES	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
NITROFURANTOIN	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
EFAVIRENZ	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
OTHER ANTIALLERGICS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
BEPOTASTINE BESILATE	0	1 (2.3%)	0	1 (0.5%)
OLOPATADINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
OTHER ANTIINFECTIVES AND ANTISEPTICS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
LACTOBACILLUS ACIDOPHILUS	0	1 (2.3%)	0	1 (0.5%)
LACTOBACILLUS RHAMNOSUS	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER ANTIMIGRAINE PREPARATIONS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
FLUNARIZINE DIHYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
TOPIRAMATE	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIOBESITY DRUGS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
LIRAGLUTIDE	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIOBESITY DRUGS MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
OTHER COLD PREPARATIONS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
OTHER COLD PREPARATIONS	0	0	1 (0.9%)	1 (0.5%)
OTHER COLD PREPARATIONS MULTI-INGREDIENT TERM 1	0	1 (2.3%)	0	1 (0.5%)
OTHER COUGH SUPPRESSANTS AND EXPECTORANTS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
CHLORPHENAMINE MALEATE;FICUS MICROCARPA LEAF	1 (2.9%)	0	0	1 (0.5%)
OTHER COUGH SUPPRESSANTS AND EXPECTORANTS MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
OTHER HYPNOTICS AND SEDATIVES	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DEXMEDETOMIDINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
VALERIANA OFFICINALIS	0	1 (2.3%)	0	1 (0.5%)
OTHER INTESTINAL ADSORBENTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DIOSMECTITE	0	0	1 (0.9%)	1 (0.5%)
MONTMORILLONITE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER MINERAL SUPPLEMENTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
MAGNESIUM OXIDE;ZINC SULFATE	0	0	1 (0.9%)	1 (0.5%)
OTHER MINERAL SUPPLEMENTS	0	1 (2.3%)	0	1 (0.5%)
OTHER QUATERNARY AMMONIUM COMPOUNDS	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
ROCURONIUM BROMIDE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
OTHER SYSTEMIC HEMOSTATICS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CARBAZOCHROME SODIUM SULFONATE	0	0	1 (0.9%)	1 (0.5%)
ETAMSILATE	0	1 (2.3%)	0	1 (0.5%)
OTHER THERAPEUTIC PRODUCTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ADENOSINE	0	0	1 (0.9%)	1 (0.5%)
LACTOBACILLUS RHAMNOSUS	0	1 (2.3%)	0	1 (0.5%)
OTHER THROAT PREPARATIONS	1 (2.9%)	1 (2.3%)	0	2 (1.1%)
BENZYDAMINE	1 (2.9%)	0	0	1 (0.5%)
BENZYDAMINE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
CARBOMER;HYALURONATE SODIUM;XANTHAN GUM	0	1 (2.3%)	0	1 (0.5%)
OXAZOL, THIAZINE, AND TRIAZINE DERIVATIVES	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
CAFFEINE;CHLORZOXAZONE;PARACETAMOL;PROSULTIA MINE	0	1 (2.3%)	0	1 (0.5%)
CHLORZOXAZONE;PARACETAMOL	0	0	1 (0.9%)	1 (0.5%)
PNEUMOCOCCAL VACCINES	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
PNEUMOCOCCAL VACCINE	1 (2.9%)	0	0	1 (0.5%)
PNEUMOCOCCAL VACCINE POLYSACCH 23V	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PREGNADIEN DERIVATIVES	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
DIENOGEST	0	0	1 (0.9%)	1 (0.5%)
DYDROGESTERONE	0	1 (2.3%)	0	1 (0.5%)
PROGESTOGENS AND ESTROGENS, SEQUENTIAL PREPARATIONS	0	0	2 (1.9%)	2 (1.1%)
DIENOGEST;ESTRADIOL VALERATE	0	0	1 (0.9%)	1 (0.5%)
ESTRADIOL;NORGESTREL	0	0	1 (0.9%)	1 (0.5%)
PROTEASE INHIBITORS	0	2 (4.7%)	0	2 (1.1%)
NIRMATRELVIR;RITONAVIR	0	2 (4.7%)	0	2 (1.1%)
SELECTIVE SEROTONIN (5HT1) AGONISTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
FROVATRIPTAN	0	0	1 (0.9%)	1 (0.5%)
SUMATRIPTAN	0	1 (2.3%)	0	1 (0.5%)
SUBSTITUTED ETHYLENE DIAMINES	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
CHLOROPYRAMINE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
SULFONAMIDES	0	0	2 (1.9%)	2 (1.1%)
SULFADIAZINE SILVER	0	0	2 (1.9%)	2 (1.1%)
SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
BRIMONIDINE	1 (2.9%)	0	1 (0.9%)	2 (1.1%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SYMPATHOMIMETICS USED AS DECONGESTANTS	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
ANTAZOLINE HYDROCHLORIDE;TETRYZOLINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
ANTAZOLINE PHOSPHATE;CHLORHEXIDINE GLUCONATE;TETRYZOLINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
CHONDROITIN SULFATE SODIUM;NAPHAZOLINE HYDROCHLORIDE	0	1 (2.3%)	0	1 (0.5%)
SULFAMETHOXAZOLE SODIUM;TETRYZOLINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
VASOPRESSIN ANTAGONISTS	0	0	2 (1.9%)	2 (1.1%)
TOLVAPTAN	0	0	2 (1.9%)	2 (1.1%)
XANTHINES	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
AMINOPHYLLINE	0	1 (2.3%)	0	1 (0.5%)
DIPROPHYLLINE	0	1 (2.3%)	0	1 (0.5%)
GUAIFENESIN;THEOPHYLLINE SODIUM AMINOACETATE	0	1 (2.3%)	0	1 (0.5%)
THEOPHYLLINE	0	0	1 (0.9%)	1 (0.5%)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	0	0	1 (0.9%)	1 (0.5%)
TRANDOLAPRIL;VERAPAMIL HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
ADRENERGICS AND OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1 (2.9%)	0	0	1 (0.5%)
IPRATROPIUM BROMIDE MONOHYDRATE;SALBUTAMOL SULFATE	1 (2.9%)	0	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES	0	0	1 (0.9%)	1 (0.5%)
QUINFAMIDE	0	0	1 (0.9%)	1 (0.5%)
ALPHA GLUCOSIDASE INHIBITORS	0	0	1 (0.9%)	1 (0.5%)
ACARBOSE	0	0	1 (0.9%)	1 (0.5%)
ALUMINIUM COMPOUNDS	0	0	1 (0.9%)	1 (0.5%)
ALUMINIUM PHOSPHATE	0	0	1 (0.9%)	1 (0.5%)
AMINO ACIDS AND DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
ACETYLCYSTEINE	0	0	1 (0.9%)	1 (0.5%)
AMINOQUINOLINES	0	0	1 (0.9%)	1 (0.5%)
HYDROXYCHLOROQUINE	0	0	1 (0.9%)	1 (0.5%)
AMPHENICOLS	0	0	1 (0.9%)	1 (0.5%)
THIAMPHENICOL	0	0	1 (0.9%)	1 (0.5%)
ANESTHETICS FOR TOPICAL USE	0	0	1 (0.9%)	1 (0.5%)
CINCHOCAINE HYDROCHLORIDE;DIPHENHYDRAMINE;ZINC OXIDE	0	0	1 (0.9%)	1 (0.5%)
ANESTHETICS, LOCAL	1 (2.9%)	0	0	1 (0.5%)
BENZOCAINE	1 (2.9%)	0	0	1 (0.5%)
ANTACIDS	0	0	1 (0.9%)	1 (0.5%)
GI COCKTAIL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
ANTACIDS WITH ANTIFLATULENTS	0	0	1 (0.9%)	1 (0.5%)
ALUMINIUM HYDROXIDE;MAGNESIUM HYDROXIDE;SIMETICONE	0	0	1 (0.9%)	1 (0.5%)
ANTACIDS, OTHER COMBINATIONS	0	0	1 (0.9%)	1 (0.5%)
ANTACIDS, OTHER COMBINATIONS	0	0	1 (0.9%)	1 (0.5%)
ANTI-ESTROGENS	1 (2.9%)	0	0	1 (0.5%)
TAMOXIFEN	1 (2.9%)	0	0	1 (0.5%)
ANTIARRHYTHMICS, CLASS III	0	0	1 (0.9%)	1 (0.5%)
AMIODARONE	0	0	1 (0.9%)	1 (0.5%)
ANTIFUNGALS FOR SYSTEMIC USE	0	0	1 (0.9%)	1 (0.5%)
TERBINAFINE	0	0	1 (0.9%)	1 (0.5%)
ANTIHISTAMINES FOR TOPICAL USE	0	0	1 (0.9%)	1 (0.5%)
DIMETINDENE MALEATE	0	0	1 (0.9%)	1 (0.5%)
ANTIINFECTIVES/ANTISEPTICS IN COMBINATION WITH CORTICOSTEROIDS	0	0	1 (0.9%)	1 (0.5%)
NEOMYCIN SULFATE;NYSTATIN;PREDNISOLONE METASULFOBENZOATE SODIUM;TERNIDAZOLE	0	0	1 (0.9%)	1 (0.5%)
BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	0	0	1 (0.9%)	1 (0.5%)
HYOSCINE BUTYLBROMIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
BELLADONNA AND DERIVATIVES IN COMBINATION WITH PSYCHOLEPTICS	0	0	1 (0.9%)	1 (0.5%)
HYOSCINE BUTYLBROMIDE;MEDAZEPAM	0	0	1 (0.9%)	1 (0.5%)
BENZAMIDES	0	0	1 (0.9%)	1 (0.5%)
SULPIRIDE	0	0	1 (0.9%)	1 (0.5%)
BENZIMIDAZOLE DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
ALBENDAZOLE	0	0	1 (0.9%)	1 (0.5%)
BETA BLOCKING AGENTS	0	0	1 (0.9%)	1 (0.5%)
TIMOLOL	0	0	1 (0.9%)	1 (0.5%)
BILE ACID SEQUESTRANTS	0	1 (2.3%)	0	1 (0.5%)
COLESTIPOL	0	1 (2.3%)	0	1 (0.5%)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	0	0	1 (0.9%)	1 (0.5%)
CARBOHYDRATES NOS;POTASSIUM CHLORIDE;SODIUM CHLORIDE;SODIUM LACTATE	0	0	1 (0.9%)	1 (0.5%)
BLOOD TRANSFUSION, AUXILIARY PRODUCTS	0	0	1 (0.9%)	1 (0.5%)
BLOOD TRANSFUSION, AUXILIARY PRODUCTS	0	0	1 (0.9%)	1 (0.5%)
CALCIUM COMPOUNDS	0	1 (2.3%)	0	1 (0.5%)
CALCIUM CARBONATE	0	1 (2.3%)	0	1 (0.5%)
CARBAMIC ACID ESTERS	0	0	1 (0.9%)	1 (0.5%)
METHOCARBAMOL	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
COLONY STIMULATING FACTORS	0	0	1 (0.9%)	1 (0.5%)
FILGRASTIM	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS	0	0	1 (0.9%)	1 (0.5%)
GRAMICIDIN;NEOMYCIN;NYSTATIN;TRIAMCINOLONE	0	0	1 (0.9%)	1 (0.5%)
CORTICOSTEROIDS, WEAK, OTHER COMBINATIONS	0	0	1 (0.9%)	1 (0.5%)
CROTAMITON;HYDROCORTISONE	0	0	1 (0.9%)	1 (0.5%)
HYDROCORTISONE ACETATE;UREA	0	0	1 (0.9%)	1 (0.5%)
HYDROCORTISONE;UREA	0	0	1 (0.9%)	1 (0.5%)
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE	0	0	1 (0.9%)	1 (0.5%)
ANTAZOLINE HYDROCHLORIDE;CINEOLE;EPHEDRINE HYDROCHLORIDE;MENTHOL;NAPHAZOLINE HYDROCHLORIDE	0	0	1 (0.9%)	1 (0.5%)
DIPHENYLMETHANE DERIVATIVES	1 (2.9%)	0	0	1 (0.5%)
HYDROXYZINE HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
DIRECT ACTING ANTIVIRALS	0	0	1 (0.9%)	1 (0.5%)
AMANTADINE	0	0	1 (0.9%)	1 (0.5%)
DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	0	0	1 (0.9%)	1 (0.5%)
OXYBUTYNIN	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
DRUGS USED IN NICOTINE DEPENDENCE	0	0	1 (0.9%)	1 (0.5%)
VARENICLINE TARTRATE	0	0	1 (0.9%)	1 (0.5%)
DRUGS USED IN OPIOID DEPENDENCE	0	1 (2.3%)	0	1 (0.5%)
LEVOMETHADONE	0	1 (2.3%)	0	1 (0.5%)
ELECTROLYTE SOLUTIONS	0	0	1 (0.9%)	1 (0.5%)
POTASSIUM CHLORIDE	0	0	1 (0.9%)	1 (0.5%)
ENZYMES	0	0	1 (0.9%)	1 (0.5%)
PAPAIN	0	0	1 (0.9%)	1 (0.5%)
ESTERS OF AMINOBENZOIC ACID	0	0	1 (0.9%)	1 (0.5%)
PROCAINE	0	0	1 (0.9%)	1 (0.5%)
ESTREN DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
LEVONORGESTREL	0	0	1 (0.9%)	1 (0.5%)
ETHERS, CHEMICALLY CLOSE TO ANTIHISTAMINES	0	0	1 (0.9%)	1 (0.5%)
ORPHENADRINE	0	0	1 (0.9%)	1 (0.5%)
GINKGO REMEDIES	0	0	1 (0.9%)	1 (0.5%)
GINKGO BILOBA LEAF	0	0	1 (0.9%)	1 (0.5%)
GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	0	0	1 (0.9%)	1 (0.5%)
SEMAGLUTIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
GLYCOGENOLYTIC HORMONES	1 (2.9%)	0	0	1 (0.5%)
GLUCAGON HYDROCHLORIDE	1 (2.9%)	0	0	1 (0.5%)
HEPARINS OR HEPARINOIDS FOR TOPICAL USE	0	0	1 (0.9%)	1 (0.5%)
HEPARINOID	0	0	1 (0.9%)	1 (0.5%)
HEPATITIS VACCINES	0	0	1 (0.9%)	1 (0.5%)
HEPATITIS A VACCINE INACT;HEPATITIS B VACCINE RHBSAG (YEAST)	0	0	1 (0.9%)	1 (0.5%)
HERBAL ANTIANEMIC PREPARATIONS	0	0	1 (0.9%)	1 (0.5%)
ASINI CORII COLLA;ASTRAGALUS MONGHOLICUS ROOT;CRATAEGUS PINNATIFIDA FRUIT;FERROUS SULFATE HEPTAHYDRATE;ZIZIPHUS JUJUBA FRUIT	0	0	1 (0.9%)	1 (0.5%)
HERBAL ANTIINFLAMMATORY AND ANTIRHEUMATIC REMEDIES	0	0	1 (0.9%)	1 (0.5%)
GLYCYRRHIZA SPP. ROOT;PAEONIA LACTIFLORA ROOT	0	0	1 (0.9%)	1 (0.5%)
HERBAL COUGH AND COLD REMEDIES, OTHER	0	0	1 (0.9%)	1 (0.5%)
HERBAL COUGH AND COLD REMEDIES, OTHER	0	0	1 (0.9%)	1 (0.5%)
HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	0	1 (2.3%)	0	1 (0.5%)
GENTIANA LUTEA ROOT;PRIMULA SPP.;RUMEX SPP.;SAMBUCUS NIGRA FLOWER;VERBENA OFFICINALIS	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
HERBAL DIGESTIVES, OTHER	1 (2.9%)	0	0	1 (0.5%)
ATRACTYLODES LANCEA RHIZOME	1 (2.9%)	0	0	1 (0.5%)
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	0	0	1 (0.9%)	1 (0.5%)
CONTRACEPTIVES	0	0	1 (0.9%)	1 (0.5%)
IMMUNOGLOBULINS, NORMAL HUMAN	0	0	1 (0.9%)	1 (0.5%)
IMMUNOGLOBULIN HUMAN NORMAL	0	0	1 (0.9%)	1 (0.5%)
INTERLEUKIN INHIBITORS	0	0	1 (0.9%)	1 (0.5%)
TOCILIZUMAB	0	0	1 (0.9%)	1 (0.5%)
IRON IN COMBINATION WITH FOLIC ACID	0	0	1 (0.9%)	1 (0.5%)
ANGELICA SINENSIS;ASTRAGALUS SPP.;ATRACTYLODES MACROCEPHALA;FERROUS SULFATE;FOLIC ACID;YEAST DRIED	0	0	1 (0.9%)	1 (0.5%)
IRRIGATING SOLUTIONS	0	0	1 (0.9%)	1 (0.5%)
ELECTROLYTES NOS	0	0	1 (0.9%)	1 (0.5%)
LOCAL ANESTHETICS	0	0	1 (0.9%)	1 (0.5%)
LIDOCAINE	0	0	1 (0.9%)	1 (0.5%)
LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	0	1 (0.9%)	1 (0.5%)
AMILORIDE HYDROCHLORIDE;HYDROCHLOROTHIAZIDE	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
NASAL DECONGESTANTS FOR SYSTEMIC USE	0	0	1 (0.9%)	1 (0.5%)
NASAL DECONGESTANTS FOR SYSTEMIC USE MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
NEURAMINIDASE INHIBITORS	1 (2.9%)	0	0	1 (0.5%)
OSELTAMIVIR	1 (2.9%)	0	0	1 (0.5%)
ORIPAVINE DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
BUPRENORPHINE	0	0	1 (0.9%)	1 (0.5%)
OTHER AGENTS FOR LOCAL ORAL TREATMENT	0	0	1 (0.9%)	1 (0.5%)
BENZYDAMINE	0	0	1 (0.9%)	1 (0.5%)
OTHER AMINOGLYCOSIDES	0	0	1 (0.9%)	1 (0.5%)
RIBOSTAMYCIN SULFATE	0	0	1 (0.9%)	1 (0.5%)
OTHER ANTIANEMIC PREPARATIONS	0	0	1 (0.9%)	1 (0.5%)
ERYTHROPOIETIN	0	0	1 (0.9%)	1 (0.5%)
OTHER ANTIDIARRHEALS	0	1 (2.3%)	0	1 (0.5%)
CROFELEMER	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIEPILEPTICS	0	1 (2.3%)	0	1 (0.5%)
LAMOTRIGINE	0	1 (2.3%)	0	1 (0.5%)
OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	1 (0.9%)	1 (0.5%)
METHYL SALICYLATE;TOLNAFTATE	0	0	1 (0.9%)	1 (0.5%)
OTHER BETA-LACTAM ANTIBACTERIALS	0	0	1 (0.9%)	1 (0.5%)
CEPHALOSPORIN NOS	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	0	0	1 (0.9%)	1 (0.5%)
REPAGLINIDE	0	0	1 (0.9%)	1 (0.5%)
OTHER CICATRIZANTS	0	0	1 (0.9%)	1 (0.5%)
ALPROSTADIL ALFADEX	0	0	1 (0.9%)	1 (0.5%)
OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	0	1 (2.3%)	0	1 (0.5%)
DENOSUMAB	0	1 (2.3%)	0	1 (0.5%)
OTHER DRUGS FOR ACID RELATED DISORDERS	0	0	1 (0.9%)	1 (0.5%)
ALUMINIUM SILICATE;OXETACAINE	0	0	1 (0.9%)	1 (0.5%)
OTHER HEMATOLOGICAL AGENTS	0	1 (2.3%)	0	1 (0.5%)
HYDROXYCARBAMIDE	0	1 (2.3%)	0	1 (0.5%)
OTHER IMMUNOSTIMULANTS	0	1 (2.3%)	0	1 (0.5%)
NALTREXONE	0	1 (2.3%)	0	1 (0.5%)
OTHER NERVOUS SYSTEM DRUGS	0	1 (2.3%)	0	1 (0.5%)
BUTYLPHTHALIDE	0	1 (2.3%)	0	1 (0.5%)
CINNARIZINE;PANAX NOTOGINSENG ROOT TOTAL SAPONIN EXTRACT;PYRIDOXINE HYDROCHLORIDE;VITAMIN E NOS	0	1 (2.3%)	0	1 (0.5%)
OTHER PSYCHOSTIMULANTS AND NOOTROPICS	0	1 (2.3%)	0	1 (0.5%)
VINPOCETINE	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
OTHER QUINOLONES	0	0	1 (0.9%)	1 (0.5%)
NEMONOXACIN MALATE	0	0	1 (0.9%)	1 (0.5%)
OTHER TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	0	0	1 (0.9%)	1 (0.5%)
HEPARINOID	0	0	1 (0.9%)	1 (0.5%)
OTHER UROLOGICALS	0	0	1 (0.9%)	1 (0.5%)
PHENAZOPYRIDINE	0	0	1 (0.9%)	1 (0.5%)
PAPAVERINE AND DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
DROTAVERINE	0	0	1 (0.9%)	1 (0.5%)
PARASYMPATHOMIMETICS	0	0	1 (0.9%)	1 (0.5%)
NEOSTIGMINE METILSULFATE	0	0	1 (0.9%)	1 (0.5%)
PENICILLAMINE AND SIMILAR AGENTS	0	0	1 (0.9%)	1 (0.5%)
PENICILLAMINE	0	0	1 (0.9%)	1 (0.5%)
PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	0	0	1 (0.9%)	1 (0.5%)
NALDEMEDINE TOSILATE	0	0	1 (0.9%)	1 (0.5%)
PERTUSSIS VACCINES	0	0	1 (0.9%)	1 (0.5%)
DIPHTHERIA VACCINE TOXOID;PERTUSSIS VACCINE ACELLULAR;TETANUS VACCINE TOXOID	0	0	1 (0.9%)	1 (0.5%)
PHENOL AND DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
CRESOL;FORMALDEHYDE SOLUTION	0	0	1 (0.9%)	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PHOSPHODIESTERASE INHIBITORS	0	0	1 (0.9%)	1 (0.5%)
BUCLADESINE CALCIUM	0	0	1 (0.9%)	1 (0.5%)
PLATINUM COMPOUNDS	0	0	1 (0.9%)	1 (0.5%)
CARBOPLATIN	0	0	1 (0.9%)	1 (0.5%)
PREGNEN (4) DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
PROGESTERONE	0	0	1 (0.9%)	1 (0.5%)
PROSTAGLANDINS	0	0	1 (0.9%)	1 (0.5%)
MISOPROSTOL	0	0	1 (0.9%)	1 (0.5%)
PURINE DERIVATIVES	1 (2.9%)	0	0	1 (0.5%)
PENTOXIFYLLINE	1 (2.9%)	0	0	1 (0.5%)
QUATERNARY AMMONIUM COMPOUNDS	1 (2.9%)	0	0	1 (0.5%)
BENZETHONIUM CHLORIDE	1 (2.9%)	0	0	1 (0.5%)
RETINOIDS FOR TOPICAL USE IN ACNE	0	0	1 (0.9%)	1 (0.5%)
ERYTHROMYCIN;TRETINOIN	0	0	1 (0.9%)	1 (0.5%)
SALT SOLUTIONS	0	0	1 (0.9%)	1 (0.5%)
SODIUM BICARBONATE	0	0	1 (0.9%)	1 (0.5%)
SODIUM	0	0	1 (0.9%)	1 (0.5%)
SODIUM CHLORIDE	0	0	1 (0.9%)	1 (0.5%)
SOFTENERS, EMOLLIENTS	0	1 (2.3%)	0	1 (0.5%)
DOCUSATE SODIUM	0	1 (2.3%)	0	1 (0.5%)

TSICMOL01: Study Treatment-concomitant Medications in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
SOLVENTS AND DILUTING AGENTS, INCL. IRRIGATING SOLUTIONS	0	0	1 (0.9%)	1 (0.5%)
WATER FOR INJECTION	0	0	1 (0.9%)	1 (0.5%)
TRIAZOLE AND TETRAZOLE DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
FLUCONAZOLE	0	0	1 (0.9%)	1 (0.5%)
TRIMETHOPRIM AND DERIVATIVES	0	0	1 (0.9%)	1 (0.5%)
TRIMETHOPRIM	0	0	1 (0.9%)	1 (0.5%)
VASOPRESSIN AND ANALOGUES	0	1 (2.3%)	0	1 (0.5%)
DESMOPRESSIN ACETATE	0	1 (2.3%)	0	1 (0.5%)
VITAMIN A AND D IN COMBINATION	1 (2.9%)	0	0	1 (0.5%)
ERGOCALCIFEROL;RETINOL	1 (2.9%)	0	0	1 (0.5%)
VITAMINS	0	0	1 (0.9%)	1 (0.5%)
VITAMINS MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)
VITAMINS, OTHER COMBINATIONS	0	0	1 (0.9%)	1 (0.5%)
VITAMINS, OTHER COMBINATIONS MULTI-INGREDIENT TERM 1	0	0	1 (0.9%)	1 (0.5%)

[TSICMOL01.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSICMOL01.SAS] 02MAR2023, 07:50

TSICMOL04: PAH-specific Medications at Baseline; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Subjects with one or more PAH-specific study treatment-concomitant medications	1 (2.9%)	2 (4.7%)	3 (2.8%)	6 (3.2%)
Special interest category Standardized medication name				
PDE-5i	0	2 (4.7%)	2 (1.9%)	4 (2.2%)
SILDENAFIL CITRATE	0	1 (2.3%)	1 (0.9%)	2 (1.1%)
SILDENAFIL	0	0	1 (0.9%)	1 (0.5%)
TADALAFIL	0	1 (2.3%)	0	1 (0.5%)
ERA	1 (2.9%)	0	1 (0.9%)	2 (1.1%)
BOSENTAN	1 (2.9%)	0	0	1 (0.5%)
MACITENTAN	0	0	1 (0.9%)	1 (0.5%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination.
Note: Medication at baseline is any medication taken during the first day of M/T FDC study treatment.

[TSICMOL04.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSICMOL04.SAS] 02MAR2023, 07:50

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Age, years				
N	35	43	107	185
Mean (SD)	51.3 (15.85)	53.2 (13.83)	48.7 (15.78)	50.2 (15.40)
Median	51.0	56.0	48.0	50.0
Range	(20; 80)	(19; 78)	(18; 79)	(18; 80)
18-25	3 (8.6%)	1 (2.3%)	10 (9.3%)	14 (7.6%)
26-50	14 (40.0%)	17 (39.5%)	52 (48.6%)	83 (44.9%)
51-64	10 (28.6%)	15 (34.9%)	25 (23.4%)	50 (27.0%)
>= 65	8 (22.9%)	10 (23.3%)	20 (18.7%)	38 (20.5%)
Sex				
N	35	43	107	185
Female	29 (82.9%)	33 (76.7%)	82 (76.6%)	144 (77.8%)
Male	6 (17.1%)	10 (23.3%)	25 (23.4%)	41 (22.2%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; SD = Standard deviation; WHO FC = World Health Organization Functional Classification; PAH = Pulmonary arterial hypertension; PVR = Pulmonary vascular resistance; CO = Cardiac output; mPAP = Mean pulmonary artery pressure; PAWP = Pulmonary artery wedge pressure; 6MWD = 6-minute walk distance.

[a] Proportion of baseline PVR assessments based on Fick CO and Thermodilutation CO.

Note: N's for each parameter reflect non-missing values. Baseline is defined as the last observation prior to the first intake of M/T FDC study treatment either in DB or OL period.

Note: Weight, Body mass index, WHO FC, Time since diagnosis, PVR, CO method, mPAP, PAWP, 6MWD are derived from analysis set baseline. Other parameters were assessed at enrollment into study.

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Race				
N	35	43	107	185
American Indian or Alaska Native	0	0	1 (0.9%)	1 (0.5%)
Asian	12 (34.3%)	10 (23.3%)	36 (33.6%)	58 (31.4%)
Japanese	1 (2.9%)	1 (2.3%)	6 (5.6%)	8 (4.3%)
Other Asian	11 (31.4%)	9 (20.9%)	30 (28.0%)	50 (27.0%)
Black or African American	1 (2.9%)	2 (4.7%)	2 (1.9%)	5 (2.7%)
White	20 (57.1%)	29 (67.4%)	66 (61.7%)	115 (62.2%)
Not reported	2 (5.7%)	2 (4.7%)	2 (1.9%)	6 (3.2%)
Ethnicity				
N	35	43	107	185
Hispanic or Latino	2 (5.7%)	5 (11.6%)	8 (7.5%)	15 (8.1%)
Not Hispanic or Latino	30 (85.7%)	38 (88.4%)	95 (88.8%)	163 (88.1%)
Not reported	3 (8.6%)	0	4 (3.7%)	7 (3.8%)
Region				
N	35	43	107	185
US	4 (11.4%)	13 (30.2%)	13 (12.1%)	30 (16.2%)
Non-US	31 (88.6%)	30 (69.8%)	94 (87.9%)	155 (83.8%)
Geographical region				
N	35	43	107	185
North America	4 (11.4%)	14 (32.6%)	14 (13.1%)	32 (17.3%)
Latin America	7 (20.0%)	5 (11.6%)	10 (9.3%)	22 (11.9%)
Asia	11 (31.4%)	11 (25.6%)	49 (45.8%)	71 (38.4%)
Eastern Europe	4 (11.4%)	4 (9.3%)	19 (17.8%)	27 (14.6%)
South and Western Europe	6 (17.1%)	7 (16.3%)	14 (13.1%)	27 (14.6%)
Oceania	0	0	0	0
Africa	3 (8.6%)	2 (4.7%)	1 (0.9%)	6 (3.2%)

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Weight, kg				
N	35	43	107	185
Mean (SD)	66.69 (14.096)	73.69 (18.226)	69.38 (16.564)	69.87 (16.615)
Median	65.00	73.00	68.00	68.80
Range	(41.0; 100.4)	(35.0; 130.0)	(34.5; 117.7)	(34.5; 130.0)
Height, cm				
N	35	43	107	185
Mean (SD)	160.97 (8.102)	164.53 (9.112)	162.02 (8.417)	162.41 (8.569)
Median	160.00	163.00	162.00	162.00
Range	(146.7; 186.0)	(145.0; 186.0)	(143.8; 183.0)	(143.8; 186.0)
Body mass index, kg/m^2				
N	35	43	107	185
Mean (SD)	25.9 (5.43)	27.0 (5.58)	26.3 (5.23)	26.4 (5.34)
Median	24.0	28.0	26.0	26.0
Range	(17; 38)	(15; 42)	(16; 39)	(15; 42)
Underweight <18.5	2 (5.7%)	4 (9.3%)	6 (5.6%)	12 (6.5%)
Normal 18.5-<25	16 (45.7%)	10 (23.3%)	39 (36.4%)	65 (35.1%)
Overweight 25-<30	9 (25.7%)	16 (37.2%)	38 (35.5%)	63 (34.1%)
Obese >=30	8 (22.9%)	13 (30.2%)	24 (22.4%)	45 (24.3%)
WHO FC				
N	35	43	107	185
Class I	3 (8.6%)	3 (7.0%)	0	6 (3.2%)
Class II	19 (54.3%)	25 (58.1%)	65 (60.7%)	109 (58.9%)
Class III	13 (37.1%)	15 (34.9%)	42 (39.3%)	70 (37.8%)
Class IV	0	0	0	0

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
PAH etiology				
N	35	43	107	185
Idiopathic	16 (45.7%)	19 (44.2%)	58 (54.2%)	93 (50.3%)
Heritable	3 (8.6%)	2 (4.7%)	4 (3.7%)	9 (4.9%)
Drug- and- toxin induced	0	2 (4.7%)	1 (0.9%)	3 (1.6%)
PAH associated with connective tissue disease	13 (37.1%)	16 (37.2%)	36 (33.6%)	65 (35.1%)
PAH associated with HIV infection	0	2 (4.7%)	4 (3.7%)	6 (3.2%)
PAH associated with portal hypertension	1 (2.9%)	1 (2.3%)	1 (0.9%)	3 (1.6%)
PAH associated with congenital heart disease	2 (5.7%)	1 (2.3%)	3 (2.8%)	6 (3.2%)
PAH associated with schistosomiasis	0	0	0	0
Long-term responders to calcium channel blockers	0	0	0	0
With overt features of venous/capillaries (PVOD/PCH) involvement	0	0	0	0
Time since diagnosis, years				
N	35	43	107	185
Mean (SD)	3.497 (6.1458)	1.259 (2.2776)	1.828 (2.8016)	2.012 (3.6410)
Median	0.452	0.663	0.411	0.465
Range	(0.33; 27.96)	(0.33; 13.13)	(0.02; 14.84)	(0.02; 27.96)
PVR calculated by central reader, dyn.sec/cm^5				
N	35	43	107	185
Mean (SD)	635.75 (357.594)	632.08 (391.826)	881.58 (627.193)	777.08 (548.044)
Median	592.59	629.21	723.46	650.30
Range	(159.2; 1606.0)	(180.7; 2241.9)	(194.3; 3888.2)	(159.2; 3888.2)

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
CO method used for PVR calculation by central reader[a]				
N	35	43	107	185
Fick CO	13 (37.1%)	21 (48.8%)	54 (50.5%)	88 (47.6%)
Thermodilution CO	22 (62.9%)	22 (51.2%)	53 (49.5%)	97 (52.4%)
mPAP calculated by central reader, mmHg				
N	35	43	107	185
Mean (SD)	42.90 (14.202)	43.36 (15.494)	48.00 (16.006)	45.96 (15.666)
Median	42.33	41.33	46.00	43.33
Range	(21.3; 82.7)	(19.7; 88.3)	(25.0; 98.7)	(19.7; 98.7)
PAWP calculated by central reader, mmHg				
N	32	42	97	171
Mean (SD)	10.91 (5.089)	11.50 (4.769)	10.56 (3.503)	10.85 (4.158)
Median	10.00	11.00	11.00	11.00
Range	(3.0; 27.0)	(3.0; 25.0)	(3.0; 23.0)	(3.0; 27.0)
LVEDP calculated by central reader, mmHg				
N	7	3	20	30
Mean (SD)	10.9 (6.44)	14.3 (5.13)	10.8 (3.55)	11.1 (4.45)
Median	10.0	13.0	10.0	10.0
Range	(4; 23)	(10; 20)	(4; 22)	(4; 23)
Thermodilution CO calculated by central reader, L/min				
N	22	22	53	97
Mean (SD)	4.8 (0.97)	4.7 (1.50)	4.5 (1.18)	4.6 (1.21)
Median	5.1	4.3	4.3	4.4
Range	(3; 7)	(2; 9)	(2; 7)	(2; 9)

TSIDEMOL01C: Summary of Demographics and Baseline Characteristics; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Fick CO calculated by central reader, L/min				
N	13	21	54	88
Mean (SD)	3.8 (1.14)	4.4 (1.71)	3.5 (1.33)	3.8 (1.43)
Median	3.7	4.1	3.4	3.6
Range	(2; 6)	(2; 9)	(1; 8)	(1; 9)
6MWD, m				
N	35	43	107	185
Mean (SD)	385.1 (87.32)	382.3 (77.96)	352.3 (96.07)	365.5 (91.40)
Median	370.0	408.0	373.0	380.0
Range	(140; 540)	(133; 490)	(2; 550)	(2; 550)

[TSIDEMOL01C.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSIDEMOL01C.SAS] 02MAR2023, 07:50

TSIEXOL01C: Summary of Combined Double-blind and Open-label Treatment; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
Analysis set: Combination Safety Set	35	43	107	185
Total duration of treatment (weeks) for CSS[a]				
N	35	43	107	185
Mean (SD)	58.37 (32.841)	60.17 (35.502)	65.96 (39.940)	63.18 (37.643)
Median	58.57	61.43	59.86	59.86
Range	(4.7; 113.1)	(1.0; 129.7)	(0.6; 151.6)	(0.6; 151.6)
Total duration of treatment (weeks) for CSS[a]				
< 4	0	2 (4.7%)	10 (9.3%)	12 (6.5%)
4 - < 16	2 (5.7%)	2 (4.7%)	4 (3.7%)	8 (4.3%)
16 - < 42	12 (34.3%)	14 (32.6%)	18 (16.8%)	44 (23.8%)
42 - < 68	7 (20.0%)	5 (11.6%)	29 (27.1%)	41 (22.2%)
68 - < 94	6 (17.1%)	10 (23.3%)	12 (11.2%)	28 (15.1%)
94 - < 120	8 (22.9%)	9 (20.9%)	23 (21.5%)	40 (21.6%)
>= 120	0	1 (2.3%)	11 (10.3%)	12 (6.5%)
Total duration of treatment - interruptions excluded (weeks) for CSS[b]				
N	35	43	107	185
Mean (SD)	58.31 (32.872)	60.13 (35.514)	65.83 (39.962)	63.08 (37.660)
Median	58.57	61.43	59.86	59.86
Range	(4.7; 113.1)	(1.0; 129.7)	(0.6; 151.0)	(0.6; 151.0)
Total duration of treatment - interruptions excluded (weeks) for CSS[b]				
< 4	0	2 (4.7%)	10 (9.3%)	12 (6.5%)
4 - < 16	2 (5.7%)	2 (4.7%)	5 (4.7%)	9 (4.9%)
16 - < 42	12 (34.3%)	14 (32.6%)	19 (17.8%)	45 (24.3%)
42 - < 68	7 (20.0%)	5 (11.6%)	27 (25.2%)	39 (21.1%)
68 - < 94	6 (17.1%)	10 (23.3%)	12 (11.2%)	28 (15.1%)
94 - < 120	8 (22.9%)	9 (20.9%)	25 (23.4%)	42 (22.7%)
>= 120	0	1 (2.3%)	9 (8.4%)	10 (5.4%)
Cumulative duration of treatment (weeks)[a]				
>=4	35 (100.0%)	41 (95.3%)	97 (90.7%)	173 (93.5%)
>=16	33 (94.3%)	39 (90.7%)	93 (86.9%)	165 (89.2%)
>=42	21 (60.0%)	25 (58.1%)	75 (70.1%)	121 (65.4%)

TSIEXOL01C: Summary of Combined Double-blind and Open-label Treatment; Combination Safety Set (Study AC-077A301) [Cutoff Date: 31DEC2022]

	OL Period (M/T FDC)		DB/OL Period M/T FDC	M/T FDC
	DB-Macitentan	DB-Tadalafil	DB-M/T FDC	Total
>=68	14 (40.0%)	20 (46.5%)	46 (43.0%)	80 (43.2%)
>=94	8 (22.9%)	10 (23.3%)	34 (31.8%)	52 (28.1%)
>=120	0	1 (2.3%)	11 (10.3%)	12 (6.5%)

Key:
[a] Total duration of treatment is defined as (date of EOT – date of first dose of study treatment +1)/7.
[b] Total duration of treatment with interruptions is defined as (date of EOT – date of first dose of study treatment – days without study treatment administration + 1)/7.
Note: First dose of study treatment refers to first dose of M/T FDC (or LC macitentan and tadalafil) in DB or OL.

[TSIEXOL01C.RTF] [JNJ-68150420/AC-077A301/DBR_IA2/RE_IA2/PROD/TSIEXOL01C.SAS] 02MAR2023, 10:01

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
Treatment-naive/ Macitentan 10mg	[redacted]	[redacted]	[redacted] / M/ [redacted]	NA/10mg/-100	[redacted]	[redacted]	[redacted]	[redacted] / 19	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	
		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/87	右室不全/ Right Heart Failure	87	[redacted]	[redacted] / 11	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/284	亜イレウス/ Subileus	284	[redacted]	[redacted] / 5	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/335	右室不全/ Right Heart Failure With Hydropic Decompensation	335	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/437	低酸素症/ Hypoxia	437	[redacted]	[redacted] / 9	Recovered/ Resolved/ Not Applicable	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/455	全身性強皮症/ Systemic Scleroderma	455	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Mild/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/33	肺動脈性肺高血圧症/ Pah Worsening	33	[redacted]	[redacted] / 4	Recovered/ Resolved/ Drug Withdrawn	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/143	乳癌/ Breast Cancer	143	[redacted]	[redacted] / 4	Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/205	憩室炎/ Acute Diverticulitis Exacerbation	205	[redacted]	[redacted] / 7	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	NA/10mg/-74	[redacted]	[redacted]	[redacted]	[redacted] / 6	Recovered/ Resolved/ Drug Interrupted	Severe/ Not Related	
				NA/10mg/-40	[redacted]	[redacted]	[redacted]	[redacted] / 7	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	
				40mg/10mg/45	パラインフルエンザウイルス感染/ Parainfluenza (Hpiv)	45	[redacted]	[redacted] / 8	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
Treatment-naive/ Tadalafil 40 mg		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/304	子宮ポリープ/ Polipus Uteri	304	[redacted]	[redacted] / 28	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted]	40mg/NA/-58	[redacted]	[redacted]	[redacted]	[redacted] / 10	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
				40mg/NA/-57	/ Cerebral Infarction				Recovering/ Resolving/ Dose Not Changed	Severe/ Not Related	
			/ M/	40mg/NA/-81				/ 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	
				40mg/10mg/133	基底細胞癌/ Solid Basal Cell Carcinoma On The Left	133	2021-06-14	2021-06-16/ 3	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	Y
			/ F/		/ (No Further Information)			/ 6	Recovered/ Resolved/ Not Applicable	Moderate/ Not Related	
				40mg/10mg/8	洞結節機能不全/ Sick Sinus Syndrom	8		/ 16	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/278	虚血性大腸炎/ Ischemic Colitis	278		/ 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/288	裂孔ヘルニア/ Hiatus Hernia	288		/ 8	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/	40mg/10mg/214	心房粗動/ Atrial Flutter With Rapid Ventricular Response	214		/ 5	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/272	卵巣嚢胞破裂/ Ruptured Hemorrhagic Ovarian Cyst (Right)	272		/ 2	Recovered/ Resolved With Sequelae/ Dose Not Changed	Severe/ Not Related	Y
			/ F/	20mg/NA/-104				/ 5	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	
			/ F/	40mg/10mg/550	ウイルス性肺炎/ Bilateral Multifocal Viral Pneumonia	550			Recovering/ Resolving/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/	40mg/10mg/555	網膜静脈閉塞/ Retinal Vein Occlusion	555			Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Related	Y
			/ F/	40mg/10mg/97	気胸/ Pneumothorax	97		/ 5	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
[redacted]	[redacted]	[redacted]	[redacted] / F/ [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] / 5	Recovered/ Resolved/ Not Applicable	Mild/ Not Related	
Treatment-naive/ M/T FDC		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/ 104	COVID-19肺炎/ Covid 19 Pneumonia	104	[redacted]	[redacted] / 39	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 126	低血圧/ Hypotension	126	[redacted]	[redacted] / 13	Recovered/ Resolved/ Drug Interrupted	Moderate/ Not Related	Y
				40mg/10mg/ 434	大腿骨骨折/ Right Proximal Femoral Fracture	434	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 434	上腕骨骨折/ Right Proximal Humeral Fracture Dislocation	434	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 679	胃炎/ Gastritis	679	[redacted]	[redacted] / 2	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/ 95	COVID-19/ Covid-19	95	[redacted]	[redacted] / 29	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 543	前立腺癌/ Prostata Carcinome	543	[redacted]	[redacted] / 60	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 118	ホルネル症候群/ Horner Syndrome	118	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Mild/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 291	心房細動/ Atrial Fibrillation	295	[redacted]	[redacted] / 6	Recovered/ Resolved/ Not Applicable	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 18	左室不全/ Mild Decompensation Of The Left Heart	18	[redacted]	[redacted] / 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/ 51	冠動脈疾患/ Single Vessel Disease	51	[redacted]	[redacted] / 3	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 728	右室不全/ Right Heart Failure	728	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
			/ M/	40mg/10mg/ 29	右室不全/ Right Heart Failure	29			Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Related	Y
				40mg/10mg/ 47	肺静脈閉塞性疾患/ Pulmonary Veno-Occlusive Disease	47			Not Recovered/ Not Resolved/ Drug Withdrawn	Severe/ Not Related	Y
			/ F/	40mg/10mg/ 15	心不全/ Heart Failure	15		/ 19	Recovered/ Resolved/ Dose Reduced	Severe/ Related	Y
				20mg/10mg/ 22	貧血/ Anemia	22		/ 172	Recovered/ Resolved/ Drug Withdrawn	Moderate/ Related	Y
			/ F/	40mg/10mg/ 218	硬膜下血腫/ Acute Subdural Hematoma	218		/ 14	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ M/	40mg/10mg/ 278	呼吸困難/ Shortness Of Breath	278			Not Recovered/ Not Resolved/ Not Applicable	Severe/ Not Related	Y
				40mg/10mg/ 278	呼吸不全/ Respiratory Failure	278			Fatal/ Not Applicable	Severe/ Not Related	Y
			/ F/			-3		/ 76	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	
			/ F/	40mg/10mg/ 14	呼吸困難/ Dyspnoe	14		/ 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	末梢腫脹/ Swelling Of The Limbs	14		/ 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	顔面腫脹/ Swelling Of The Face	14		/ 10	Recovered/ Resolved/ Drug Withdrawn	Severe/ Related	Y
				40mg/10mg/ 14	心不全/ Heart Failure	86		/ 14	Recovered/ Resolved/ Not Applicable	Severe/ Not Related	
				40mg/10mg/ 14	COVID-19肺炎/ Pneumonia Due To Covid-19	100			Fatal/ Not Applicable	Severe/ Not Related	
				40mg/10mg/ 14	急性呼吸不全/ Acute Respiratory Failure	111			Not Recovered/ Not Resolved/ Not Applicable	Severe/ Not Related	
			/ F/	40mg/10mg/ 247	月経中間期出血/ Metrorrhagia	247		/ 11	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
			/ M/	40mg/10mg/ 809	ウイルス性肺炎/ Viral Pneumonia	809		/ 12	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/	40mg/10mg/ 355	COVID-19/ Covid-19	355		/ 5	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 418	膜性糸球体腎炎/ Membranous Glomerulopathy	418		/ 231	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ M/	40mg/10mg/ 450	肺炎/ Pneumonia	450		/ 17	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 506	低酸素症/ Hypoxia	506		/ 9	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
			/ M/	40mg/10mg/ 583	前立腺癌/ Prostate Adenocarcinoma	583		/ 3	Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ M/	40mg/10mg/ 160	痔出血/ Gi Bleed Secondary To Hemorrhoids	160		/ 3	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 160	ウイルス性上気道感染/ Upper Respiratory Viral Infection	160		/ 3	Recovered/ Resolved With Sequelae/ Dose Not Changed	Severe/ Not Related	Y
			/ F/	40mg/10mg/ 185	パラインフルエンザウイルス感染/ Parainfluenza Infection	185		/ 9	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
			/ F/					/ 4	Recovered/ Resolved/ Not Applicable	Moderate/ Not Related	
Prior ERA/ Macitentan 10mg			/ M/	NA/10mg/- 97	/			/ 15	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	
			/ M/	40mg/10mg/ 319	椎間板突出/ Worsening Of Lumbar Disc Herniation	319		/ 61	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
Prior ERA/ M/T FDC			/ F/	20mg/10mg/ 4	心不全/ Worsening Of Hf Bronchopneumonia	19			Fatal/ Not Applicable	Severe/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
Prior PDE-5i/ Tadalafil 40 mg	[redacted]	193	[redacted] F/ [redacted]	40mg/10mg/ 77	インフルエンザ/ Flu Syndrome	[redacted]	[redacted]	[redacted] / 13	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		382	[redacted] F/ [redacted]	40mg/10mg/ 259	COVID-19/ Covid-19	259	[redacted]	[redacted] / 9	Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 267	COVID-19/ Covid-19	267	[redacted]	[redacted] / 30	Recovered/ Resolved/ Drug Withdrawn	Severe/ Not Related	Y
		257	[redacted] F/ [redacted]	40mg/10mg/ 79	骨壊死/ Ostonecrosis	79	[redacted]	[redacted] / 126	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 86	舌嚢胞/ Tongue Root Cyst	86	[redacted]	[redacted] / 3	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 303	舌嚢胞/ Tongue Root Cyst	303	[redacted]	[redacted] / 8	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 450	肺炎/ Pneumonia	450	[redacted]	[redacted] / 98	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
		221	[redacted] F/ [redacted]	40mg/10mg/ 140	上室性頻脈/ Supraventricular Tachycardia	140	[redacted]	[redacted] / 1	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
		407	[redacted] F/ [redacted]	40mg/10mg/ 15	肺性心/ Cor Pulmonale	15	[redacted]	[redacted] / 58	Recovered/ Resolved/ Dose Not Changed	Moderate/ Related	Y
		310	[redacted] F/ [redacted]	40mg/NA/- 18	[redacted]	[redacted]	[redacted]	[redacted] / 81	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	
				40mg/10mg/ 76	過量投与/ Treprostinil Overdose	76	[redacted]	[redacted] / 6	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 193	右室不全/ Exacerbation Of Right Ventricular Heart Failure	193	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
		162	[redacted] F/ [redacted]	40mg/10mg/ 683	肺炎/ Pneumonia	683	[redacted]	[redacted] / 9	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
Prior PDE-5i/ M/T FDC		393	[redacted] M/ [redacted]	40mg/10mg/ 104	クロストリジウム菌性胃腸炎/ Gastoenteritis C. Difficile	104	[redacted]		Fatal/ Dose Not Changed	Severe/ Not Related	Y
		124	[redacted] F/ [redacted]	40mg/10mg/ 53	心房粗動/ Atrial Flutter	53*	[redacted]	[redacted] / 110	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y

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LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
[redacted]	[redacted]	[redacted]	[redacted]	40mg/10mg/ 127	右室不全/ Right Heart Failure	127	[redacted]	[redacted]/ 11	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 151	右室不全/ Right Heart Failure	151	[redacted]	[redacted]/ 13	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 384	上部消化管出血/ Upper Gastrointestinal Bleeding	384	[redacted]	[redacted]/ 17	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 389	右室不全/ Right Heart Failure	389	[redacted]	[redacted]/ 12	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 415	右室不全/ Right Heart Failure	415	[redacted]	[redacted]/ 14	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 428	肝硬変/ Liver Cirrhosis (Congestive Hepatopathy)	428	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 428	門脈圧亢進症/ Portal Hypertension	428	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 428	食道静脈瘤/ Esophageal Varices	428	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 523	右室不全/ Right Heart Failure Due To Worsening Pah	523	[redacted]	[redacted]/ 18	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 538	COVID-19/ Recent Covid-19 Infection	538	[redacted]	[redacted]/ 3	Recovered/ Resolved/ Dose Not Changed	Mild/ Not Related	Y
				40mg/10mg/ 569	右室不全/ Right Heart Failure	569	[redacted]	[redacted]/ 19	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 582	肺炎/ Community Acquired Pneumonia	582	[redacted]	[redacted]/ 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 587	右室不全/ Right Heart Failure	587	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 608	急性腎障害/ Acute Kidney Injury	608	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
[redacted]	[redacted]	[redacted]	[redacted]	40mg/10mg/ 622	右室不全/ Advanced Right Heart Failure	622	2021-11-21	[redacted]	Fatal/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 377	COVID-19肺炎/ Covid-19 Pneumonia	377	[redacted]	[redacted] 16	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 76	胸痛/ Acute Episode Of Chest Pain (No Further Information)	76	[redacted]	[redacted] 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	呼吸困難/ Acute Episode Of Dyspnoea	76	[redacted]	[redacted] 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	不全片麻痺/ Transient Hemiparesis Of Uncertain Mechanism	76	[redacted]	[redacted] 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
				40mg/10mg/ 76	動悸/ Acute Episode Of Palpitation	76	[redacted]	[redacted] 1	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / M/ [redacted]	40mg/10mg/ 174	正色素性貧血/ Normochromic Anemia	175	[redacted]	[redacted] 67	Recovered/ Resolved/ Drug Interrupted	Severe/ Related	Y
				40mg/10mg/ 706	胃腸炎/ Acute Gastroenteritis	706	[redacted]	[redacted] 5	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 710	COVID-19/ Covid 19	710	[redacted]	[redacted] 6	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 27	子宮内膜症/ Endometriosis	27	[redacted]	[redacted] 6	Recovered/ Resolved/ Dose Not Changed	Severe/ Not Related	Y
				40mg/10mg/ 42	卵巣粘液性嚢胞腺癌/ Ovarian Mucinous Carcinoma G2	42	[redacted]		Not Recovered/ Not Resolved/ Dose Not Changed	Severe/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 334	子宮ポリープ/ Endometrial Polyp	334	[redacted]	[redacted] 5	Recovered/ Resolved/ Dose Not Changed	Moderate/ Not Related	Y
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 6	心房中隔欠損症/ Confirmed Patent Foramen Ovale 2.0 Mm With Left-Right Reset.	85	[redacted]	[redacted] 6	Recovered/ Resolved/ Not Applicable	Mild/ Not Related	
		[redacted]	[redacted] / F/ [redacted]	40mg/10mg/ 161	肺動脈性肺高血圧症/ Pah Worsening	190	[redacted]	[redacted] 2	Recovered/ Resolved With Sequelae/ Not Applicable	Severe/ Not Related	Y

LSFAEOL02: Listing of Serious Adverse Events in the Combined Double-blind and Open-label Period; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

Stratum/ DB Treatment Group	Site ID	Subject ID	Age (years)/ Sex/Race/ Region	Onset Tadalafil/Macitentan Dose (unit)/Day of Last Dose[a,b]	Preferred Term/ Reported Term	Day of AE Onset[b]	Start Date	End Date/ Duration (days)	Outcome/ Action Taken With Study Treatment	Severity/ Relationship to Study Treatment[c]	Treatment-emergent Flag
40mg/10mg/ 161	[redacted]				脳血管発作/ Stroke	552	[redacted]		Fatal/ Not Applicable	Severe/ Not Related	

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period; * = imputed date, day, or duration.

[a] Day of last administration of study treatment prior to AE onset.

[b] Day of last administration of study treatment (prior to the AE) and Day of AE Onset are in reference to the first macitentan 10 mg and tadalafil (20 mg or 40 mg) study treatment administration in DB or OL.

[c] Relationship to study treatment is assessed by the investigator.

Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days.

Note: Adverse events are coded using MedDRA Version 25.1.

[LSFAEOL02.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/LSFAEOL02.SAS] 08JUN2023, 11:54

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Analysis set: Combination Safety Set	185	185	180	174	161	138
Subjects with 1 or more AEs	173 (93.5%)	142 (76.8%)	70 (38.9%)	60 (34.5%)	48 (29.8%)	57 (41.3%)
System organ class Preferred term						
Infections and infestations	95 (51.4%)	38 (20.5%)	22 (12.2%)	20 (11.5%)	28 (17.4%)	30 (21.7%)
COVID-19	43 (23.2%)	5 (2.7%)	4 (2.2%)	12 (6.9%)	14 (8.7%)	11 (8.0%)
Upper respiratory tract infection	13 (7.0%)	2 (1.1%)	5 (2.8%)	2 (1.1%)	2 (1.2%)	3 (2.2%)
Urinary tract infection	10 (5.4%)	4 (2.2%)	2 (1.1%)	2 (1.1%)	1 (0.6%)	2 (1.4%)
Pneumonia	8 (4.3%)	2 (1.1%)	0	0	2 (1.2%)	4 (2.9%)
Nasopharyngitis	7 (3.8%)	4 (2.2%)	1 (0.6%)	0	3 (1.9%)	3 (2.2%)
Influenza	5 (2.7%)	2 (1.1%)	0	0	1 (0.6%)	3 (2.2%)
Cellulitis	4 (2.2%)	1 (0.5%)	0	0	0	3 (2.2%)
Sinusitis	4 (2.2%)	2 (1.1%)	0	0	0	2 (1.4%)
COVID-19 pneumonia	3 (1.6%)	1 (0.5%)	0	0	2 (1.2%)	0
Oral herpes	3 (1.6%)	3 (1.6%)	0	0	0	0
Bronchitis	2 (1.1%)	0	0	0	0	2 (1.4%)
Conjunctivitis	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Hepatitis B	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Localised infection	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Oesophageal candidiasis	2 (1.1%)	0	0	0	1 (0.6%)	1 (0.7%)
Parainfluenzae virus infection	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	0	0
Pneumonia viral	2 (1.1%)	0	0	0	0	2 (1.4%)
Rhinitis	2 (1.1%)	2 (1.1%)	0	0	0	0
Suspected COVID-19	2 (1.1%)	0	2 (1.1%)	0	0	0
Acute sinusitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Anal fungal infection	1 (0.5%)	0	0	1 (0.6%)	0	0
Bacterial infection	1 (0.5%)	1 (0.5%)	1 (0.6%)	0	0	0
Body tinea	1 (0.5%)	0	0	0	0	1 (0.7%)
Bronchitis bacterial	1 (0.5%)	0	1 (0.6%)	0	0	0
Candida infection	1 (0.5%)	0	1 (0.6%)	0	0	0
Cervicitis	1 (0.5%)	0	0	1 (0.6%)	0	0

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Chronic tonsillitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Cystitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Cytomegalovirus chorioretinitis	1 (0.5%)	1 (0.5%)	0	0	0	0
Diverticulitis	1 (0.5%)	0	1 (0.6%)	0	0	0
Ear infection	1 (0.5%)	0	0	0	1 (0.6%)	0
Endometritis	1 (0.5%)	0	0	0	0	1 (0.7%)
Gastroenteritis	1 (0.5%)	0	0	0	0	1 (0.7%)
Gastroenteritis clostridial	1 (0.5%)	1 (0.5%)	0	0	0	0
Gastrointestinal infection	1 (0.5%)	0	1 (0.6%)	0	0	0
Genital herpes	1 (0.5%)	0	0	0	0	1 (0.7%)
Gingivitis	1 (0.5%)	1 (0.5%)	0	0	0	0
Haematological infection	1 (0.5%)	0	0	1 (0.6%)	0	0
Hepatitis C	1 (0.5%)	0	0	1 (0.6%)	0	0
Herpes zoster	1 (0.5%)	1 (0.5%)	0	0	0	0
Otitis externa	1 (0.5%)	0	0	0	0	1 (0.7%)
Otitis media	1 (0.5%)	1 (0.5%)	0	0	0	0
Otosalpingitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Pericoronitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Pharyngitis	1 (0.5%)	1 (0.5%)	0	0	0	0
Pharyngitis bacterial	1 (0.5%)	0	0	0	1 (0.6%)	0
Pharyngotonsillitis	1 (0.5%)	0	1 (0.6%)	0	0	0
Pneumonia bacterial	1 (0.5%)	0	0	1 (0.6%)	0	0
Pneumonia pseudomonal	1 (0.5%)	0	0	0	1 (0.6%)	0
Pneumonia staphylococcal	1 (0.5%)	0	1 (0.6%)	0	0	0
Post-acute COVID-19 syndrome	1 (0.5%)	0	0	0	0	1 (0.7%)
Respiratory tract infection	1 (0.5%)	0	0	1 (0.6%)	0	0
Respiratory tract infection viral	1 (0.5%)	0	1 (0.6%)	0	0	1 (0.7%)
Salpingo-oophoritis	1 (0.5%)	0	0	0	0	1 (0.7%)
Tooth abscess	1 (0.5%)	1 (0.5%)	0	0	0	0
Vaginal infection	1 (0.5%)	0	1 (0.6%)	0	0	0
Viral infection	1 (0.5%)	0	0	0	1 (0.6%)	0
Viral upper respiratory tract infection	1 (0.5%)	0	1 (0.6%)	0	0	0
Vulvovaginal mycotic infection	1 (0.5%)	0	0	0	0	1 (0.7%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Respiratory, thoracic and mediastinal disorders	54 (29.2%)	35 (18.9%)	8 (4.4%)	6 (3.4%)	7 (4.3%)	14 (10.1%)
Cough	15 (8.1%)	8 (4.3%)	2 (1.1%)	1 (0.6%)	1 (0.6%)	4 (2.9%)
Dyspnoea	13 (7.0%)	8 (4.3%)	0	3 (1.7%)	2 (1.2%)	0
Nasal congestion	9 (4.9%)	8 (4.3%)	0	0	0	1 (0.7%)
Pulmonary arterial hypertension	8 (4.3%)	4 (2.2%)	2 (1.1%)	0	2 (1.2%)	1 (0.7%)
Dyspnoea exertional	4 (2.2%)	3 (1.6%)	1 (0.6%)	0	0	1 (0.7%)
Epistaxis	4 (2.2%)	3 (1.6%)	0	0	0	1 (0.7%)
Hypoxia	3 (1.6%)	0	1 (0.6%)	0	0	2 (1.4%)
Bronchial hyperreactivity	2 (1.1%)	0	0	1 (0.6%)	0	1 (0.7%)
Oropharyngeal pain	2 (1.1%)	2 (1.1%)	0	0	0	0
Pulmonary veno-occlusive disease	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Rhinitis allergic	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Rhinorrhoea	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Allergic sinusitis	1 (0.5%)	0	0	0	0	1 (0.7%)
Asthma	1 (0.5%)	1 (0.5%)	0	0	0	0
Bronchial secretion retention	1 (0.5%)	0	0	0	1 (0.6%)	0
Chronic respiratory failure	1 (0.5%)	0	0	0	0	1 (0.7%)
Haemoptysis	1 (0.5%)	0	1 (0.6%)	0	0	0
Nasal septum deviation	1 (0.5%)	0	0	0	0	1 (0.7%)
Orthopnoea	1 (0.5%)	1 (0.5%)	0	0	0	0
Pharyngeal swelling	1 (0.5%)	0	1 (0.6%)	0	0	0
Pneumothorax	1 (0.5%)	1 (0.5%)	0	0	0	0
Productive cough	1 (0.5%)	1 (0.5%)	0	0	0	0
Pulmonary embolism	1 (0.5%)	1 (0.5%)	0	0	0	0
Pulmonary oedema	1 (0.5%)	0	0	0	0	1 (0.7%)
Respiratory failure	1 (0.5%)	0	0	1 (0.6%)	0	0
Sleep apnoea syndrome	1 (0.5%)	0	0	0	1 (0.6%)	0
Throat irritation	1 (0.5%)	0	0	0	0	1 (0.7%)
Tracheal inflammation	1 (0.5%)	0	0	0	1 (0.6%)	0
Metabolism and nutrition disorders	30 (16.2%)	16 (8.6%)	4 (2.2%)	4 (2.3%)	6 (3.7%)	3 (2.2%)
Hypokalaemia	6 (3.2%)	2 (1.1%)	0	2 (1.1%)	2 (1.2%)	0
Iron deficiency	4 (2.2%)	2 (1.1%)	0	0	0	2 (1.4%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Vitamin B12 deficiency	4 (2.2%)	2 (1.1%)	1 (0.6%)	0	1 (0.6%)	1 (0.7%)
Hyperuricaemia	3 (1.6%)	3 (1.6%)	0	0	0	0
Decreased appetite	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	0	0
Gout	2 (1.1%)	2 (1.1%)	0	0	0	0
Hyperlipidaemia	2 (1.1%)	0	0	1 (0.6%)	0	1 (0.7%)
Hyponatraemia	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Dehydration	1 (0.5%)	0	1 (0.6%)	0	0	0
Diabetes mellitus	1 (0.5%)	0	0	0	1 (0.6%)	0
Dyslipidaemia	1 (0.5%)	1 (0.5%)	0	0	0	0
Hyperglycaemia	1 (0.5%)	0	0	0	1 (0.6%)	0
Hyperkalaemia	1 (0.5%)	1 (0.5%)	0	0	0	0
Hypervolaemia	1 (0.5%)	1 (0.5%)	0	0	0	0
Impaired fasting glucose	1 (0.5%)	0	0	0	1 (0.6%)	0
Type 2 diabetes mellitus	1 (0.5%)	0	1 (0.6%)	0	0	0
Vitamin D deficiency	1 (0.5%)	1 (0.5%)	0	0	0	0
Gastrointestinal disorders	57 (30.8%)	36 (19.5%)	12 (6.7%)	8 (4.6%)	5 (3.1%)	13 (9.4%)
Nausea	9 (4.9%)	7 (3.8%)	1 (0.6%)	1 (0.6%)	0	1 (0.7%)
Vomiting	9 (4.9%)	5 (2.7%)	4 (2.2%)	1 (0.6%)	1 (0.6%)	1 (0.7%)
Diarrhoea	7 (3.8%)	5 (2.7%)	1 (0.6%)	0	0	1 (0.7%)
Gastritis	7 (3.8%)	3 (1.6%)	2 (1.1%)	0	1 (0.6%)	1 (0.7%)
Abdominal discomfort	4 (2.2%)	3 (1.6%)	1 (0.6%)	0	0	0
Abdominal pain	4 (2.2%)	2 (1.1%)	0	0	0	2 (1.4%)
Dyspepsia	4 (2.2%)	4 (2.2%)	0	1 (0.6%)	0	1 (0.7%)
Gastrooesophageal reflux disease	4 (2.2%)	3 (1.6%)	0	0	0	1 (0.7%)
Haemorrhoidal haemorrhage	4 (2.2%)	2 (1.1%)	1 (0.6%)	0	0	1 (0.7%)
Abdominal pain upper	3 (1.6%)	0	2 (1.1%)	0	0	1 (0.7%)
Constipation	3 (1.6%)	2 (1.1%)	0	0	1 (0.6%)	0
Dry mouth	3 (1.6%)	3 (1.6%)	0	0	0	0
Haemorrhoids	3 (1.6%)	1 (0.5%)	1 (0.6%)	0	0	1 (0.7%)
Enteritis	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Flatulence	2 (1.1%)	1 (0.5%)	0	0	1 (0.6%)	0
Oesophagitis	2 (1.1%)	2 (1.1%)	1 (0.6%)	0	0	0
Toothache	2 (1.1%)	0	0	0	0	2 (1.4%)
Varices oesophageal	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Abdominal distension	1 (0.5%)	1 (0.5%)	0	0	0	0
Anal haemorrhage	1 (0.5%)	1 (0.5%)	0	0	0	0
Chronic gastritis	1 (0.5%)	1 (0.5%)	0	0	0	0
Colitis	1 (0.5%)	0	1 (0.6%)	0	0	0
Colitis ischaemic	1 (0.5%)	0	0	1 (0.6%)	0	0
Colon dysplasia	1 (0.5%)	0	1 (0.6%)	0	0	0
Frequent bowel movements	1 (0.5%)	1 (0.5%)	0	0	0	0
Gastric disorder	1 (0.5%)	1 (0.5%)	0	0	0	0
Gastrointestinal disorder	1 (0.5%)	1 (0.5%)	0	0	0	0
Haematochezia	1 (0.5%)	0	0	1 (0.6%)	0	0
Hiatus hernia	1 (0.5%)	0	0	1 (0.6%)	0	0
Intussusception	1 (0.5%)	0	0	0	0	1 (0.7%)
Lumbar hernia	1 (0.5%)	1 (0.5%)	0	0	0	0
Mouth ulceration	1 (0.5%)	0	0	1 (0.6%)	0	0
Oesophageal stenosis	1 (0.5%)	0	0	0	0	1 (0.7%)
Subileus	1 (0.5%)	0	0	1 (0.6%)	0	0
Tongue cyst	1 (0.5%)	1 (0.5%)	0	1 (0.6%)	0	0
Upper gastrointestinal haemorrhage	1 (0.5%)	0	0	0	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	55 (29.7%)	32 (17.3%)	10 (5.6%)	10 (5.7%)	5 (3.1%)	9 (6.5%)
Myalgia	12 (6.5%)	8 (4.3%)	2 (1.1%)	1 (0.6%)	0	1 (0.7%)
Arthralgia	11 (5.9%)	8 (4.3%)	2 (1.1%)	1 (0.6%)	0	1 (0.7%)
Back pain	10 (5.4%)	7 (3.8%)	1 (0.6%)	2 (1.1%)	0	0
Pain in extremity	8 (4.3%)	4 (2.2%)	0	0	1 (0.6%)	3 (2.2%)
Intervertebral disc protrusion	3 (1.6%)	2 (1.1%)	0	1 (0.6%)	1 (0.6%)	0
Osteoarthritis	3 (1.6%)	0	0	3 (1.7%)	0	0
Systemic scleroderma	3 (1.6%)	1 (0.5%)	0	1 (0.6%)	0	1 (0.7%)
Musculoskeletal chest pain	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Musculoskeletal pain	2 (1.1%)	2 (1.1%)	0	0	0	0
Osteonecrosis	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	1 (0.6%)	0
Arthritis	1 (0.5%)	0	1 (0.6%)	0	0	0
Bursitis	1 (0.5%)	0	1 (0.6%)	0	0	0
Limb discomfort	1 (0.5%)	0	0	1 (0.6%)	0	0

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Muscular weakness	1 (0.5%)	1 (0.5%)	0	0	0	0
Musculoskeletal discomfort	1 (0.5%)	0	1 (0.6%)	0	0	0
Osteochondritis	1 (0.5%)	0	1 (0.6%)	0	0	0
Osteopenia	1 (0.5%)	0	1 (0.6%)	0	0	0
Osteoporosis	1 (0.5%)	0	0	0	1 (0.6%)	0
Pain in jaw	1 (0.5%)	1 (0.5%)	0	0	0	0
Plantar fasciitis	1 (0.5%)	0	0	0	1 (0.6%)	0
Sacroiliitis	1 (0.5%)	0	0	1 (0.6%)	0	0
Sjogren's syndrome	1 (0.5%)	1 (0.5%)	0	0	0	0
Spinal osteoarthritis	1 (0.5%)	0	0	0	0	1 (0.7%)
Systemic lupus erythematosus	1 (0.5%)	0	0	0	0	1 (0.7%)
Cardiac disorders	33 (17.8%)	24 (13.0%)	7 (3.9%)	5 (2.9%)	4 (2.5%)	5 (3.6%)
Palpitations	11 (5.9%)	7 (3.8%)	3 (1.7%)	2 (1.1%)	0	0
Right ventricular failure	7 (3.8%)	2 (1.1%)	2 (1.1%)	0	4 (2.5%)	2 (1.4%)
Angina pectoris	4 (2.2%)	3 (1.6%)	0	0	0	1 (0.7%)
Cardiac failure	4 (2.2%)	4 (2.2%)	0	0	0	0
Tachycardia	4 (2.2%)	2 (1.1%)	0	1 (0.6%)	0	2 (1.4%)
Atrial flutter	3 (1.6%)	1 (0.5%)	1 (0.6%)	1 (0.6%)	0	0
Coronary artery disease	2 (1.1%)	2 (1.1%)	0	0	0	0
Atrial fibrillation	1 (0.5%)	0	0	1 (0.6%)	0	0
Bradycardia	1 (0.5%)	0	0	1 (0.6%)	0	0
Cardiovascular disorder	1 (0.5%)	1 (0.5%)	0	0	0	0
Cor pulmonale	1 (0.5%)	1 (0.5%)	0	0	0	0
Left ventricular failure	1 (0.5%)	1 (0.5%)	0	0	0	0
Pericardial effusion	1 (0.5%)	0	1 (0.6%)	0	0	0
Sinus arrest	1 (0.5%)	1 (0.5%)	0	0	0	0
Sinus node dysfunction	1 (0.5%)	1 (0.5%)	0	0	0	0
Supraventricular tachycardia	1 (0.5%)	0	1 (0.6%)	0	0	0
Ventricular extrasystoles	1 (0.5%)	0	1 (0.6%)	0	0	0
Blood and lymphatic system disorders	38 (20.5%)	18 (9.7%)	8 (4.4%)	6 (3.4%)	2 (1.2%)	11 (8.0%)
Anaemia	20 (10.8%)	9 (4.9%)	2 (1.1%)	3 (1.7%)	1 (0.6%)	5 (3.6%)
Iron deficiency anaemia	8 (4.3%)	4 (2.2%)	1 (0.6%)	0	1 (0.6%)	2 (1.4%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Leukopenia	4 (2.2%)	2 (1.1%)	1 (0.6%)	0	0	1 (0.7%)
Neutropenia	4 (2.2%)	1 (0.5%)	2 (1.1%)	0	0	1 (0.7%)
Thrombocytopenia	3 (1.6%)	0	2 (1.1%)	0	0	1 (0.7%)
Leukocytosis	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	0	0
Lymphopenia	2 (1.1%)	0	1 (0.6%)	0	0	1 (0.7%)
Pancytopenia	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Anaemia of chronic disease	1 (0.5%)	1 (0.5%)	0	0	0	0
Blood loss anaemia	1 (0.5%)	0	0	1 (0.6%)	0	0
Bone marrow oedema	1 (0.5%)	1 (0.5%)	0	0	0	0
Hypersplenism	1 (0.5%)	0	1 (0.6%)	0	0	0
Lymphadenopathy	1 (0.5%)	0	0	1 (0.6%)	0	0
Lymphocytosis	1 (0.5%)	0	0	0	0	1 (0.7%)
Monocytopenia	1 (0.5%)	0	0	0	0	1 (0.7%)
Normochromic anaemia	1 (0.5%)	1 (0.5%)	1 (0.6%)	0	0	1 (0.7%)
General disorders and administration site conditions	49 (26.5%)	41 (22.2%)	6 (3.3%)	5 (2.9%)	2 (1.2%)	7 (5.1%)
Oedema peripheral	21 (11.4%)	18 (9.7%)	1 (0.6%)	1 (0.6%)	0	4 (2.9%)
Pyrexia	10 (5.4%)	6 (3.2%)	3 (1.7%)	1 (0.6%)	1 (0.6%)	0
Peripheral swelling	9 (4.9%)	8 (4.3%)	1 (0.6%)	0	0	0
Fatigue	5 (2.7%)	3 (1.6%)	1 (0.6%)	1 (0.6%)	0	1 (0.7%)
Chest discomfort	3 (1.6%)	2 (1.1%)	0	1 (0.6%)	0	0
Chest pain	3 (1.6%)	1 (0.5%)	0	0	0	2 (1.4%)
Non-cardiac chest pain	3 (1.6%)	3 (1.6%)	0	0	0	0
Chills	2 (1.1%)	0	0	1 (0.6%)	1 (0.6%)	0
Oedema	2 (1.1%)	2 (1.1%)	0	0	0	0
Pain	2 (1.1%)	2 (1.1%)	0	0	0	0
Swelling face	2 (1.1%)	2 (1.1%)	0	0	0	0
Asthenia	1 (0.5%)	1 (0.5%)	0	0	0	0
Face oedema	1 (0.5%)	1 (0.5%)	0	0	0	0
Generalised oedema	1 (0.5%)	1 (0.5%)	0	0	0	0
Malaise	1 (0.5%)	1 (0.5%)	0	0	0	0
Multiple organ dysfunction syndrome	1 (0.5%)	0	0	0	0	1 (0.7%)
Polyp	1 (0.5%)	0	1 (0.6%)	0	0	0

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Swelling	1 (0.5%)	1 (0.5%)	0	0	0	0
Thirst	1 (0.5%)	1 (0.5%)	0	0	0	0
Investigations	43 (23.2%)	22 (11.9%)	15 (8.3%)	6 (3.4%)	2 (1.2%)	3 (2.2%)
Haemoglobin decreased	17 (9.2%)	10 (5.4%)	4 (2.2%)	2 (1.1%)	1 (0.6%)	1 (0.7%)
Weight increased	4 (2.2%)	2 (1.1%)	1 (0.6%)	1 (0.6%)	0	0
Aspartate aminotransferase increased	3 (1.6%)	0	3 (1.7%)	1 (0.6%)	0	0
N-terminal prohormone brain natriuretic peptide increased	3 (1.6%)	1 (0.5%)	1 (0.6%)	0	0	1 (0.7%)
SARS-CoV-2 test positive	3 (1.6%)	0	1 (0.6%)	2 (1.1%)	0	0
Weight decreased	3 (1.6%)	1 (0.5%)	1 (0.6%)	1 (0.6%)	0	0
Alanine aminotransferase increased	2 (1.1%)	0	2 (1.1%)	1 (0.6%)	0	0
Blood glucose increased	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Transaminases increased	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	0	0
Blood alkaline phosphatase increased	1 (0.5%)	0	1 (0.6%)	0	0	0
Blood bilirubin increased	1 (0.5%)	0	1 (0.6%)	0	0	0
Blood creatinine increased	1 (0.5%)	1 (0.5%)	0	0	0	0
Blood pressure increased	1 (0.5%)	0	1 (0.6%)	0	0	0
Blood uric acid abnormal	1 (0.5%)	1 (0.5%)	0	0	0	0
Blood uric acid increased	1 (0.5%)	0	1 (0.6%)	0	0	0
Body temperature increased	1 (0.5%)	1 (0.5%)	0	0	0	0
Brain natriuretic peptide increased	1 (0.5%)	0	0	0	1 (0.6%)	0
Cardiac murmur	1 (0.5%)	1 (0.5%)	0	0	0	0
Heart rate increased	1 (0.5%)	1 (0.5%)	0	0	0	0
Hepatitis B antibody abnormal	1 (0.5%)	0	1 (0.6%)	0	0	0
Neutrophil count decreased	1 (0.5%)	1 (0.5%)	0	0	0	0
Oxygen saturation decreased	1 (0.5%)	1 (0.5%)	0	0	0	0
Platelet count decreased	1 (0.5%)	1 (0.5%)	0	0	0	0
Renal and urinary disorders	11 (5.9%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	2 (1.2%)	5 (3.6%)
Renal impairment	3 (1.6%)	1 (0.5%)	0	1 (0.6%)	0	1 (0.7%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Acute kidney injury	2 (1.1%)	0	0	1 (0.6%)	0	1 (0.7%)
Chronic kidney disease	2 (1.1%)	0	0	0	0	2 (1.4%)
Dysuria	1 (0.5%)	0	0	0	1 (0.6%)	0
Glomerulonephritis membranous	1 (0.5%)	0	0	0	0	1 (0.7%)
Haematuria	1 (0.5%)	0	1 (0.6%)	0	0	0
Lupus nephritis	1 (0.5%)	0	1 (0.6%)	0	0	0
Proteinuria	1 (0.5%)	0	0	0	1 (0.6%)	0
Urinary retention	1 (0.5%)	0	1 (0.6%)	0	0	0
Reproductive system and breast disorders	12 (6.5%)	5 (2.7%)	2 (1.1%)	7 (4.0%)	2 (1.2%)	1 (0.7%)
Heavy menstrual bleeding	4 (2.2%)	2 (1.1%)	2 (1.1%)	1 (0.6%)	1 (0.6%)	0
Uterine polyp	4 (2.2%)	0	0	4 (2.3%)	1 (0.6%)	0
Adenomyosis	2 (1.1%)	0	0	2 (1.1%)	0	0
Intermenstrual bleeding	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Ovarian cyst	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Vaginal haemorrhage	2 (1.1%)	1 (0.5%)	0	1 (0.6%)	0	0
Breast mass	1 (0.5%)	1 (0.5%)	0	0	0	0
Cervical cyst	1 (0.5%)	0	0	1 (0.6%)	0	0
Ectropion of cervix	1 (0.5%)	0	0	1 (0.6%)	0	0
Endometrial hyperplasia	1 (0.5%)	0	0	1 (0.6%)	0	0
Endometriosis	1 (0.5%)	1 (0.5%)	0	0	0	0
Gynaecomastia	1 (0.5%)	0	0	1 (0.6%)	0	0
Ovarian cyst ruptured	1 (0.5%)	0	0	1 (0.6%)	0	0
Pelvic adhesions	1 (0.5%)	0	0	0	0	1 (0.7%)
Polymenorrhagia	1 (0.5%)	0	0	1 (0.6%)	0	0
Ear and labyrinth disorders	2 (1.1%)	0	1 (0.6%)	1 (0.6%)	1 (0.6%)	0
Hyperacusis	1 (0.5%)	0	1 (0.6%)	0	0	0
Vertigo	1 (0.5%)	0	0	1 (0.6%)	0	0
Vertigo positional	1 (0.5%)	0	0	0	1 (0.6%)	0
Hepatobiliary disorders	4 (2.2%)	0	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.7%)
Drug-induced liver injury	1 (0.5%)	0	1 (0.6%)	0	0	0
Hepatic cirrhosis	1 (0.5%)	0	0	0	0	1 (0.7%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Hepatic steatosis	1 (0.5%)	0	0	0	1 (0.6%)	0
Ocular icterus	1 (0.5%)	0	0	1 (0.6%)	0	0
Portal hypertension	1 (0.5%)	0	0	0	0	1 (0.7%)
Injury, poisoning and procedural complications	17 (9.2%)	6 (3.2%)	6 (3.3%)	2 (1.1%)	1 (0.6%)	6 (4.3%)
Fall	2 (1.1%)	0	0	1 (0.6%)	0	1 (0.7%)
Humerus fracture	2 (1.1%)	0	0	1 (0.6%)	0	1 (0.7%)
Procedural pain	2 (1.1%)	0	1 (0.6%)	0	0	1 (0.7%)
Contusion	1 (0.5%)	0	1 (0.6%)	0	1 (0.6%)	0
Epicondylitis	1 (0.5%)	0	1 (0.6%)	0	0	0
Femur fracture	1 (0.5%)	0	0	0	0	1 (0.7%)
Foot fracture	1 (0.5%)	0	0	0	0	1 (0.7%)
Ligament rupture	1 (0.5%)	1 (0.5%)	0	0	0	0
Ligament sprain	1 (0.5%)	0	0	0	0	1 (0.7%)
Overdose	1 (0.5%)	1 (0.5%)	0	0	0	0
Post vaccination syndrome	1 (0.5%)	1 (0.5%)	1 (0.6%)	0	0	1 (0.7%)
Radiation fibrosis - lung	1 (0.5%)	0	1 (0.6%)	0	0	0
Rib fracture	1 (0.5%)	1 (0.5%)	0	0	0	0
Subdural haematoma	1 (0.5%)	0	0	1 (0.6%)	0	0
Thermal burn	1 (0.5%)	0	1 (0.6%)	0	0	0
Tooth fracture	1 (0.5%)	1 (0.5%)	0	0	0	0
Traumatic haematoma	1 (0.5%)	1 (0.5%)	0	0	0	0
Wound	1 (0.5%)	0	0	0	0	1 (0.7%)
Nervous system disorders	42 (22.7%)	36 (19.5%)	6 (3.3%)	0	1 (0.6%)	5 (3.6%)
Headache	27 (14.6%)	24 (13.0%)	2 (1.1%)	0	1 (0.6%)	1 (0.7%)
Dizziness	6 (3.2%)	4 (2.2%)	2 (1.1%)	0	0	0
Hypoaesthesia	3 (1.6%)	2 (1.1%)	0	0	0	1 (0.7%)
Syncope	3 (1.6%)	1 (0.5%)	2 (1.1%)	0	0	1 (0.7%)
Dizziness exertional	2 (1.1%)	2 (1.1%)	0	0	0	0
Dizziness postural	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Exertional headache	1 (0.5%)	1 (0.5%)	0	0	0	0
Facial paralysis	1 (0.5%)	0	1 (0.6%)	0	0	0
Hemiparesis	1 (0.5%)	1 (0.5%)	0	0	0	0

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Horner's syndrome	1 (0.5%)	1 (0.5%)	0	0	0	0
Lethargy	1 (0.5%)	1 (0.5%)	0	0	0	0
Migraine	1 (0.5%)	1 (0.5%)	0	0	0	0
Post herpetic neuralgia	1 (0.5%)	1 (0.5%)	0	0	0	0
Presyncope	1 (0.5%)	0	0	0	0	1 (0.7%)
Somnolence	1 (0.5%)	1 (0.5%)	0	0	0	0
Psychiatric disorders	5 (2.7%)	2 (1.1%)	0	2 (1.1%)	1 (0.6%)	0
Insomnia	4 (2.2%)	1 (0.5%)	0	2 (1.1%)	1 (0.6%)	0
Anxiety	1 (0.5%)	1 (0.5%)	0	0	0	0
Skin and subcutaneous tissue disorders	21 (11.4%)	14 (7.6%)	4 (2.2%)	4 (2.3%)	1 (0.6%)	6 (4.3%)
Rash	6 (3.2%)	5 (2.7%)	0	2 (1.1%)	0	0
Erythema	3 (1.6%)	1 (0.5%)	1 (0.6%)	0	0	1 (0.7%)
Skin hyperpigmentation	3 (1.6%)	2 (1.1%)	0	1 (0.6%)	0	0
Angioedema	2 (1.1%)	1 (0.5%)	0	0	1 (0.6%)	0
Pruritus	2 (1.1%)	1 (0.5%)	1 (0.6%)	0	0	0
Acne	1 (0.5%)	0	0	0	0	1 (0.7%)
Alopecia	1 (0.5%)	1 (0.5%)	0	0	0	0
Cold sweat	1 (0.5%)	0	0	1 (0.6%)	0	0
Dermatitis contact	1 (0.5%)	0	0	1 (0.6%)	0	0
Dry skin	1 (0.5%)	1 (0.5%)	0	0	0	0
Ecchymosis	1 (0.5%)	1 (0.5%)	0	0	0	0
Excessive granulation tissue	1 (0.5%)	0	1 (0.6%)	0	0	0
Hyperkeratosis	1 (0.5%)	0	0	0	0	1 (0.7%)
Ingrowing nail	1 (0.5%)	0	0	0	0	1 (0.7%)
Onycholysis	1 (0.5%)	0	0	0	0	1 (0.7%)
Papule	1 (0.5%)	0	1 (0.6%)	0	0	0
Rash papular	1 (0.5%)	0	0	0	0	1 (0.7%)
Skin hypopigmentation	1 (0.5%)	0	0	1 (0.6%)	0	0
Skin lesion	1 (0.5%)	1 (0.5%)	0	0	0	0
Skin ulcer	1 (0.5%)	1 (0.5%)	0	0	0	0
Vascular disorders	20 (10.8%)	16 (8.6%)	3 (1.7%)	2 (1.1%)	1 (0.6%)	1 (0.7%)

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Hypotension	12 (6.5%)	8 (4.3%)	3 (1.7%)	2 (1.1%)	0	0
Flushing	4 (2.2%)	3 (1.6%)	0	0	0	1 (0.7%)
Hot flush	2 (1.1%)	2 (1.1%)	0	0	0	0
Haematoma	1 (0.5%)	1 (0.5%)	0	0	0	0
Hypertension	1 (0.5%)	0	0	0	1 (0.6%)	0
Peripheral venous disease	1 (0.5%)	1 (0.5%)	0	0	0	0
Varicose vein	1 (0.5%)	1 (0.5%)	0	0	0	0
Endocrine disorders	1 (0.5%)	0	0	1 (0.6%)	0	0
Goitre	1 (0.5%)	0	0	1 (0.6%)	0	0
Eye disorders	20 (10.8%)	12 (6.5%)	2 (1.1%)	3 (1.7%)	0	3 (2.2%)
Cataract	4 (2.2%)	0	1 (0.6%)	2 (1.1%)	0	1 (0.7%)
Vision blurred	3 (1.6%)	3 (1.6%)	0	0	0	0
Eye pain	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Eyelid oedema	2 (1.1%)	2 (1.1%)	0	0	0	0
Ocular hyperaemia	2 (1.1%)	2 (1.1%)	0	0	0	0
Periorbital oedema	2 (1.1%)	2 (1.1%)	0	0	0	0
Eye irritation	1 (0.5%)	0	1 (0.6%)	0	0	0
Eye swelling	1 (0.5%)	1 (0.5%)	0	0	0	0
Hypermetropia	1 (0.5%)	1 (0.5%)	0	0	0	0
Macular degeneration	1 (0.5%)	0	0	0	0	1 (0.7%)
Retinal haemorrhage	1 (0.5%)	1 (0.5%)	0	0	0	0
Retinal vein occlusion	1 (0.5%)	0	0	0	0	1 (0.7%)
Visual impairment	1 (0.5%)	0	0	1 (0.6%)	0	0
Immune system disorders	2 (1.1%)	1 (0.5%)	0	0	0	1 (0.7%)
Allergy to arthropod sting	1 (0.5%)	0	0	0	0	1 (0.7%)
Hypersensitivity	1 (0.5%)	1 (0.5%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (4.9%)	2 (1.1%)	5 (2.8%)	1 (0.6%)	0	2 (1.4%)
Breast cancer	2 (1.1%)	1 (0.5%)	2 (1.1%)	0	0	0
Prostate cancer	2 (1.1%)	0	0	0	0	2 (1.4%)
Basal cell carcinoma	1 (0.5%)	0	1 (0.6%)	0	0	0

TSFAE02A: Number of Subjects With Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)					
	All	0 - 3 months	4 - 6 months	7 - 9 months	10 - 12 months	13 months -
Colorectal adenoma	1 (0.5%)	0	1 (0.6%)	0	0	0
Fibroma	1 (0.5%)	0	1 (0.6%)	0	0	0
Mucinous cystadenocarcinoma ovary	1 (0.5%)	1 (0.5%)	0	0	0	0
Myelofibrosis	1 (0.5%)	0	1 (0.6%)	0	0	0
Uterine leiomyoma	1 (0.5%)	0	0	1 (0.6%)	0	0

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

[TSFAE02A.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_JCTD/PROD/TSFAE02A.SAS] 30AUG2023, 00:38

TSFAE02PIG3: Number of Subjects With Related Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)
	All
Analysis set: Combination Safety Set	185
Subjects with 1 or more Related AEs	69 (37.3%)
System organ class Preferred term	
血液およびリンパ系障害	13 (7.0%)
貧血	12 (6.5%)
白血球減少症	1 (0.5%)
心臓障害	7 (3.8%)
動悸	2 (1.1%)
心不全	1 (0.5%)
心血管障害	1 (0.5%)
肺性心	1 (0.5%)
右室不全	1 (0.5%)
頻脈	1 (0.5%)
眼障害	7 (3.8%)
霧視	3 (1.6%)
眼瞼浮腫	2 (1.1%)
眼窩周囲浮腫	2 (1.1%)
網膜静脈閉塞	1 (0.5%)
胃腸障害	15 (8.1%)
悪心	7 (3.8%)
下痢	3 (1.6%)
嘔吐	3 (1.6%)
消化不良	2 (1.1%)
腹部不快感	1 (0.5%)
腹部膨満	1 (0.5%)

TSFAE02PIG3: Number of Subjects With Related Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)
	All
口内乾燥	1 (0.5%)
胃障害	1 (0.5%)
胃食道逆流性疾患	1 (0.5%)
痔出血	1 (0.5%)
食道炎	1 (0.5%)
一般・全身障害および投与部位の状態	20 (10.8%)
Edema/fluid retention	17 (9.2%)
疼痛	2 (1.1%)
顔面腫脹	2 (1.1%)
胸部不快感	1 (0.5%)
顔面浮腫	1 (0.5%)
疲労	1 (0.5%)
非心臓性胸痛	1 (0.5%)
発熱	1 (0.5%)
口渇	1 (0.5%)
肝胆道系障害	2 (1.1%)
薬物性肝障害	1 (0.5%)
黄疸眼	1 (0.5%)
免疫系障害	2 (1.1%)
血管浮腫	1 (0.5%)
過敏症	1 (0.5%)
感染症および寄生虫症	3 (1.6%)
細菌感染	1 (0.5%)
結膜炎	1 (0.5%)
上気道感染	1 (0.5%)
臨床検査	5 (2.7%)
トランスアミナーゼ上昇	2 (1.1%)

TSFAE02PIG3: Number of Subjects With Related Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)
	All
アラニンアミノトランスフェラーゼ増加	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.5%)
血中アルカリホスファターゼ増加	1 (0.5%)
血中ビリルビン増加	1 (0.5%)
心拍数増加	1 (0.5%)
体重増加	1 (0.5%)
代謝および栄養障害	1 (0.5%)
食欲減退	1 (0.5%)
筋骨格系および結合組織障害	9 (4.9%)
筋肉痛	6 (3.2%)
四肢痛	2 (1.1%)
筋力低下	1 (0.5%)
筋骨格痛	1 (0.5%)
神経系障害	21 (11.4%)
頭痛	19 (10.3%)
労作性めまい	1 (0.5%)
体位性めまい	1 (0.5%)
腎および尿路障害	1 (0.5%)
腎機能障害	1 (0.5%)
呼吸器、胸郭および縦隔障害	11 (5.9%)
鼻閉	7 (3.8%)
呼吸困難	5 (2.7%)
咳嗽	2 (1.1%)
鼻出血	1 (0.5%)
皮膚および皮下組織障害	2 (1.1%)
発疹	2 (1.1%)

TSFAE02PIG3: Number of Subjects With Related Treatment-emergent Adverse Events in the Combined Double-blind and Open-label Period by System Organ Class and Preferred Term; Combination Safety Set (Study AC-077A301) [Cutoff Date: 28APR2023]

	M/T FDC (Total)
	All
血管障害	7 (3.8%)
低血圧	5 (2.7%)
潮紅	3 (1.6%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1..

[TSFAE02PIG3.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_JCTD/PROD/TSFAE02PIG3.SAS] 28AUG2023, 22:15

2.7.5 参考文献

2.7 臨床概要の参考文献の掲載先を以下に示す。

2.7.1 生物薬剤学試験及び関連する分析法：「参考文献」の項

2.7.2 臨床薬理試験：「参考文献」の項

2.7.3 臨床的有効性：「参考文献」の項

2.7.4 臨床的安全性：「参考文献」の項

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全臨床試験一覧表 3
2.7.6.1 海外臨床第1相試験（67896062PAH1006試験，評価資料：5.3.1.2.1-1, 5.3.1.2.1-2） 5
2.7.6.2 国際共同臨床第3相試験（AC-077A301試験，評価資料：5.3.5.1.1-1，5.3.5.1.1-2） 24

略号一覧表

略号又は略称	名称及び内容
6MWD	6-minute walk distance（6 分間歩行距離）
AUC	area under the curve（血漿中濃度－時間曲線下面積）
AUC_t	area under the plasma concentration-time curve from zero to t h after drug administration（0 時間から t 時間までの血漿中濃度－時間曲線下面積）
AUC_∞	area under the plasma concentration-time curve from zero to infinity（0 時間から無限大時間までの血漿中濃度－時間曲線下面積）
AUC_{last}	area under the plasma concentration-time curve from zero to last （0 時間から最終測定時までの血漿中濃度－時間曲線下面積）
BMI	body mass index（体格指数）
CI	confidence interval（信頼区間）
CL	confidence limit（信頼限界）
C_{last}	last observed concentration（定量可能な最終血漿中濃度）
CL/F	apparent total body clearance after oral administration（見かけの経口クリアランス）
C_{max}	maximum observed concentration（最高血漿中濃度）
COVID-19	coronavirus disease 2019（新型コロナウイルス感染症）
CV	coefficient of variation（変動係数）
ECG	electrocardiogram（心電図）
EDBT	end of double-blind treatment
ERA	endothelin receptor antagonist（エンドセリン受容体拮抗薬）
FAS	Full analysis set
LS	least square（最小二乗）
MedDRA	Medical Dictionary for Regulatory Activities（国際医薬用語集）
M/M	morbidity/mortality
n	number of patient （被験者数）
NT-proBNP	N-terminal pro-brain natriuretic peptide（BNP 前駆体の N 端側フラグメント）
PAH	pulmonary arterial hypertension（肺動脈性肺高血圧症）
PAH-SYMPACT®	pulmonary arterial hypertension – symptoms and impact questionnaire（肺動脈性肺高血圧症－症状及び影響に関する質問票）
PDE5	phosphodiesterase type 5（ホスホジエステラーゼ 5）
PDE5i	phosphodiesterase type 5 inhibitor（ホスホジエステラーゼ 5 阻害薬）
PH	pulmonary hypertension（肺高血圧症）
PK	pharmacokinetics（薬物動態）
PT	preferred term（基本語）
PVR	pulmonary vascular resistance（肺血管抵抗）
SD	standard deviation （標準偏差）
SOC	system organ class（器官別大分類）
$t_{1/2}$	apparent elimination half-life（見かけの消失半減期）
TEAE	treatment-emergent adverse event（治験薬投与後に発現した有害事象）
t_{max}	time to reach the maximum plasma concentration（最高血漿中濃度到達時間）
Vd_z/F	apparent volume of distribution after oral administration（見かけの分布容積）
WHO FC	World Health Organization functional class（世界保健機関機能分類）
λ_z	elimination rate constant （見かけの消失速度定数）

Confidential

2.7.6　個々の試験のまとめ

全臨床試験一覧表

試験の種類（開発の相）／試験番号	試験報告書添付場所	試験の目的	試験デザイン及び対照の種類	被験薬及び対照薬 投与方法・経路・期間	健康被験者又は患者の診断名／被験者数	試験の進行状況
薬物動態 安全性 （第 1 相） ／67896062 PAH1006	5.3.1.2.1-1 5.3.1.2.1-2	グループ 1 **主要目的** ・健康成人被験者を対象に，マシテンタン 10 mg 及びタダラフィル 40 mg を配合剤（マシテンタン 10 mg／タダラフィル 40 mg 配合剤，以下，本配合剤）として投与又は各単味製剤として併用投与したときのタダラフィルの生物学的同等性を，タダラフィルの主要な PK パラメータに基づき検証する **副次目的** ・健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として投与又は各単味製剤として併用投与したときの，タダラフィルの副次 PK パラメータ並びにマシテンタンの主要及び副次 PK パラメータを評価する ・健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として投与又は各単味製剤として併用投与したときの安全性及び忍容性を評価する グループ 2 **主要目的** ・健康成人被験者を対象に，本配合剤を単回投与したときの，マシテンタン及びタダラフィルの主要 PK パラメータに対する食事の影響を評価する **副次目的** ・健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときの，マシテンタン及びタダラフィルの副次 PK パラメータを評価する ・健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときの安全性及び忍容性を評価する	ランダム化，単施設，非盲検，2 期クロスオーバー，単回投与試験	グループ 1 Treatment A：空腹時に本配合剤を単回経口投与 Treatment B：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg の単味製剤を単回経口併用投与 グループ 2 Treatment C：本配合剤を高脂肪食摂取直後に単回経口投与 Treatment D：本配合剤を空腹時に単回経口投与	健康成人／ グループ 1：46 例 グループ 2：16 例	完了

試験の種類（開発の相）／試験番号	試験報告書添付場所	試験の目的	試験デザイン及び対照の種類	被験薬及び対照薬 投与方法・経路・期間	健康被験者又は患者の診断名／被験者数	試験の進行状況
有効性 安全性 （第 3 相）／ AC-077A301	5.3.5.1.1-1 5.3.5.1.1-2	**主要目的** ・未治療又は ERA 既治療の PAH 患者を対象に，本配合剤が EDBT 時の PVR に与える効果をマシテンタン単剤と比較・評価する ・未治療又は PDE5i 既治療の PAH 患者を対象に，本配合剤が EDBT 時の PVR に与える効果をタダラフィル単剤と比較・評価する **副次目的** 以下の項目を本配合剤と各単剤とで比較する ・運動耐容能 ・心肺機能及び心血管機能に関する PAH 症状 ・WHO FC ・安全性及び忍容性	オープンラベル投与期を有する，ランダム化，国際共同，多施設共同，二重盲検，実薬対照，トリプルダミー試験	二重盲検投与期 本配合剤[*1]，マシテンタン 10 mg，又はタダラフィル 40 mg [*1] を 1 日 1 回投与 投与期間：16 週間 オープンラベル投与期 本配合剤を 1 日 1 回投与[*2] 投与期間：2 年間	PAH 患者／186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例）	継続中

*1 二重盲検投与期の治験薬投与開始後 2 週間でタダラフィルを漸増し，その後維持投与した。詳細は，【2.7.6.2】表 2.7.6.2-1 参照。

*2 二重盲検投与期にマシテンタン単剤投与群に割り付けられた被験者は，オープンラベル投与期の治験薬投与開始後 2 週間でタダラフィルを漸増し，その後維持投与した。詳細は，【2.7.6.2】表 2.7.6.2-2 参照。

Confidential

2.7.6.1　海外臨床第 1 相試験（67896062PAH1006 試験，評価資料：5.3.1.2.1-1，5.3.1.2.1-2）

2.7.6.1.1　概要

2.7.6.1.1.1　計画

(1) 治験の標題

健康成人被験者を対象に，マシテンタン及びタダラフィルを配合剤（マシテンタン 10 mg／タダラフィル 40 mg 配合剤）として投与，又は各単味製剤［マシテンタン 10 mg（オプスミット錠®）及びタダラフィル 40 mg（アドシルカ錠®）］として併用投与したときのタダラフィルの生物学的同等性，並びにマシテンタン 10 mg／タダラフィル 40 mg 配合剤投与時の薬物動態に対する食事の影響を評価するランダム化，単施設，非盲検，2 期クロスオーバー，単回投与試験

(2) 治験実施医療機関

米国（1 施設）

(3) 治験実施期間

2020 年 1 月 20 日～2020 年 7 月 17 日

(4) 開発の相

第 1 相

(5) 目的

グループ 1（生物学的同等性グループ）

主要目的

- 健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を配合剤（マシテンタン 10 mg／タダラフィル 40 mg 配合剤，以下，本配合剤）として投与，又は各単味製剤［マシテンタン 10 mg（オプスミット錠®）及びタダラフィル 40 mg 錠（アドシルカ錠®）］として併用投与したときのタダラフィルの生物学的同等性を，タダラフィルの主要な PK パラメータ（C_{max}，AUC_{last}，AUC_{∞}）に基づき検証する。

副次目的

- 健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として投与，又は各単味製剤として併用投与したときの，タダラフィルの副次 PK パラメータ（t_{max}，C_{last}，AUC_{72h}，$t_{1/2}$，λ_z，CL/F，Vd_z/F）並びにマシテンタンの主要及び副次 PK パラメータを評価する。
- 健康成人被験者を対象に，空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として投与又は各単味製剤として併用投与したときの安全性及び忍容性を評価する。

グループ 2（食事の影響グループ）

主要目的

・ 健康成人被験者を対象に，本配合剤を単回投与したときのマシテンタン及びタダラフィルの主要 PK パラメータに対する食事の影響を評価する。

副次目的

・ 健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときのマシテンタン及びタダラフィルの副次 PK パラメータを評価する。

・ 健康成人被験者を対象に，本配合剤を空腹時又は食後に単回投与したときの安全性及び忍容性を評価する。

(6) 治験方法

本試験は，健康成人被験者を対象とした，2 つのグループから成るランダム化，単施設，非盲検，2 期クロスオーバー，単回投与試験である。被験者はいずれかのグループにのみ参加可能であり，最初の 46 例をグループ 1 に，続く 16 例をグループ 2 に組み入れた。

グループ 1（生物学的同等性グループ）

適格性が確認された被験者は，Day −1 に治験実施医療機関に入院し，投与期 1 の Day 1 に，2 つの投与順序（投与順序は AB 又は BA）のいずれかにランダム化された（表 2.7.6.1-1）。全ての被験者は，投与期 1 及び 2 の Day 1 に Treatment A 又は B いずれかの治験薬が投与された。

表 2.7.6.1-1 被験者の各投与順序へのランダム割付け（グループ 1）

投与順序	投与期 1	投与期 2
AB	Treatment A	Treatment B
BA	Treatment B	Treatment A

- Treatment A（試験製剤）：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として単回経口投与
- Treatment B（標準製剤）：空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg を各単味製剤として単回経口併用投与

被験者は各投与期の Day 4（治験薬投与から約 72 時間後）の評価後に退院し，Day 4 以降は治験実施計画書で規定したスケジュールに従い，Day 6，8，10 に来院することとした。投与期 1 及び 2 の各治験薬投与の間には 10 日間以上の washout 期間を設けた。各投与期の治験薬投与後 216 時間まで，マシテンタン，その活性代謝物の ACT-132577／JNJ-68212820（以下，ACT-132577），及びタダラフィルの PK プロファイルを評価することとした。試験終了時の評価は，投与期 2 の Day 10（途中脱落した場合は治験薬の最終投与から 10〜13 日後）に実施した。試験期間を通して安全性を評価し，治験薬の最終投与から 30〜33 日後に電話にて追跡調査（脱落例も含む）することとした。

2020 年 3 月 19 日に COVID-19 感染拡大の影響により治験実施医療機関が閉鎖され，本試験は中断された。この時点でグループ 1 に登録されていた 46 例のうち 33 例は両投与期（Treatment A 及び B）を完了し，3 例は試験を中止していた。残りの 10 例は投与期 1 の投与を完了していた

が，安全性確保のため，投与期 2 へ移行せず試験を中止した。これら 10 例の投与期 1 の最終安全性検査は完了しており，最終調査は電話で実施した。

グループ 2（食事の影響グループ）

適格性が確認された被験者は，Day −1 に治験実施医療機関に入院し，投与期 1 の Day 1 に，2 つの投与順序（投与順序は CD 又は DC）のいずれかにランダム化された（表 2.7.6.1-2）。全ての被験者は，投与期 1 及び 2 の Day 1 に Treatment C 又は D いずれかの投与方法で治験薬を投与された。

表 2.7.6.1-2 被験者の各投与順序へのランダム割付け（グループ 2）

投与順序	投与期 1	投与期 2
CD	Treatment C	Treatment D
DC	Treatment D	Treatment C

- Treatment C（食後投与）：マシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として高脂肪食摂取直後に単回経口投与
- Treatment D（空腹時投与）：マシテンタン 10 mg 及びタダラフィル 40 mg を本配合剤として空腹時に単回経口投与

Treatment C では，高脂肪朝食を 30 分以内で摂取を完了し，朝食終了後 10 分以内かつ朝食開始時間から 30 分以内に治験薬を投与した。

被験者は，各投与期の Day 4（治験薬投与から約 72 時間後）の評価後に退院し，Day 4 以降は治験実施計画書で規定したスケジュールに従い，Day 6，8，10 に来院することとした。投与期 1 と投与期 2 の各投与日間には 10 日間以上の washout 期間を設けた。各投与期の投与後 216 時間まで，マシテンタン，ACT-132577，及びタダラフィルの PK プロファイルを評価することとした。試験終了時の評価は，投与期 2 の Day 10（途中脱落した場合は治験薬の最終投与から 10〜13 日後）に実施した。試験期間を通して安全性を評価し，治験薬の最終投与から 30〜33 日後に電話にて追跡調査（脱落例も含む）することとした。

(7) 被験者数（計画時及び解析時）

計画時：健康成人計 62 例（グループ 1：46 例，グループ 2：16 例）

解析時：健康成人計 62 例（グループ 1：46 例，グループ 2：16 例）を組み入れ，全例に治験薬を 1 回以上投与した。

(8) 診断及び主な組入れ基準

BMI 18.5〜30 kg/m^2，体重 50 kg 以上，18〜55 歳の健康な男女（女性は妊娠していないこと，男女共に試験期間を通じて治験実施計画書に規定された適切な避妊法を実施すること）

(9) 被験薬，用量及び投与方法

グループ 1（生物学的同等性グループ）

空腹時にマシテンタン 10 mg／タダラフィル 40 mg 配合剤を単回経口投与（Treatment A）

グループ 2（食事の影響グループ）

高脂肪食摂取後にマシテンタン 10 mg／タダラフィル 40 mg 配合剤を単回経口投与（Treatment C）

(10)対照薬，用量及び投与方法

グループ 1（生物学的同等性グループ）

空腹時にマシテンタン 10 mg 及びタダラフィル 40 mg の各単味製剤を単回経口併用投与（Treatment B）

グループ 2（食事の影響グループ）

空腹時にマシテンタン 10 mg／タダラフィル 40 mg 配合剤を単回経口投与（Treatment D）

(11)試験期間

グループ 1 及び 2 共に，washout 期間を挟んで治験薬を 2 回単回投与した。試験期間は約 6 週間であり，内訳は以下のとおりであった。

- 投与期 1：入院（Day −1），治験薬投与（Day 1），washout 期間（10 日以上）
- 投与期 2：入院（Day −1），治験薬投与（Day 1），追跡調査（治験薬の最終投与 30〜33 日後）

(12)評価基準

薬物動態

マシテンタン，ACT-132577，及びタダラフィルについて以下の血漿中 PK パラメータを投与方法（Treatment A，B，C，及び D）別に算出した。

- C_{max}，AUC_{last}，AUC_{∞}（主要 PK パラメータ）
- t_{max}，C_{last}，$AUC_{72\,h}$，$t_{1/2}$，λz，CL/F，Vdz/F（副次的 PK パラメータ）

その他の PK パラメータを探索的に推定した。

安全性

有害事象，臨床検査値，ECG，バイタルサイン，身体所見を投与方法（Treatment A，B，C，及び D）別に評価した。

有害事象の集計対象は，治験薬投与後に発現した全ての有害事象とした。

(13)統計手法

被験者数の設定

グループ 1（生物学的同等性グループ）

タダラフィルの C_{max}，AUC_{last}，及び AUC_{∞}の CV は保守的に見積もり 20%と仮定した。各 PK パラメータの被験者内 CV を 20%，片側有意水準 5%と仮定した場合，両製剤の PK パラメータの幾何平均比の真の値が 90%又は 110%であれば，37 例の完了例により，80%の検出力で生物学的同等性を結論づけることができると考えられた。脱落を考慮し，46 例をグループ 1 に組み入れた。

COVID-19 感染拡大により試験が中断されたため，グループ 1（生物学的同等性グループ）の両投与期間を完了した 33 例を対象に PK の中間解析を実施した。中間解析は，生物学的同等性試験の実施及び解析に関するカナダのガイダンス（発効日：2018 年 9 月 1 日）で推奨する C 法（Potvin 2008）で実施した。C 法では，中間解析結果に基づき試験の中止又は継続を決定する。試験を継続する場合は，中間解析で推定された CV に基づき被験者数を再推定し，試験完了後に中間解析前後の試験データを併合して最終的な生物学的同等性の検定を実施する。

中間解析の結果，グループ 1 は 33 例で中止することを決定した。その後，残りのデータ（人口統計学的データ及び安全性データ等）を解析した。

グループ 2（食事の影響グループ）

マシテンタンの C_{max}，AUC_{last}，及び AUC_{∞}の被験者内 CV を 23%と仮定すると，12 例の完了例により，絶食条件に対する食後条件のマシテンタンの相対的バイオアベイラビリティの点推定値が，90%の信頼度で真の値の 84.5%～118.3%の範囲内となると考えられた。タダラフィルの C_{max}，AUC_{last}，及び AUC_{∞}の被験者内 CV を 20%と仮定すると，12 例の完了例により，絶食条件に対する食後条件のタダラフィルの相対的バイオアベイラビリティの点推定値が，90%の信頼度で真の値の 86.4%～115.8%の範囲内となると考えられた。これらのことから，脱落を考慮し，16 例の被験者をグループ 2 に組み入れた。

薬物動態

治験薬を 1 回以上投与され，1 つ以上の評価可能な PK パラメータが得られた被験者を PK の解析対象とした。

各時点でのマシテンタン，ACT-132577，及びタダラフィルの血漿中濃度並びに血漿中 PK パラメータの記述統計量（被験者数，平均値，SD，CV，幾何平均値，中央値，最小値，及び最大値を含む）を算出した。

各グループの主要な PK 解析は以下の通り実施した。

グループ 1（生物学的同等性グループ）

主要 PK パラメータは，タダラフィルの C_{max}，AUC_{last}，及び AUC_{∞}とした。生物学的同等性の基準は，90% CI が 80%～125%の範囲内であることとした。

投与方法，投与期，及び投与順序を固定効果，被験者を変量効果とする線形混合効果モデルを用いて，試験製剤（Treatment A）及び標準製剤（Treatment B）の C_{max}，AUC_{last}及び AUC_{∞}の LS 平均値の差の 90% CI を算出した。得られた結果を逆変換して PK パラメータの幾何 LS 平均比及びその 90% CI を得た。

グループ 2（食事の影響グループ）

主要 PK パラメータは，タダラフィル及びマシテンタンの C_{max}，AUC_{last}，及び AUC_{∞}とした。

投与方法，投与期，及び投与順序を固定効果，被験者を変量効果とする線形混合効果モデルを用いて，食後投与（Treatment C）と空腹時投与（Treatment D）の C_{max}，AUC_{last}，及び AUC_{∞}の LS 平均値の差の 90% CI を算出した。得られた結果を逆変換して PK パラメータの幾何 LS 平均比及びその 90% CI を得た。

安全性

治験薬を 1 回以上投与された全ての被験者を安全性の解析対象とした。有害事象の発現割合を投与方法別に要約した。臨床検査値，バイタルサイン，及び ECG は記述統計量を用いて要約した。臨床検査値異常及び身体所見は一覧に示した。

2.7.6.1.1.2　結果

(1) 対象集団

グループ 1（生物学的同等性グループ）

46 例が投与順序 AB 又は BA にランダム化された（投与順序 AB 及び BA 各 23 例）。全例が治験薬を投与され，33 例（71.7%）が試験を完了した［投与順序 AB 16 例（69.6%），投与順序 BA 17 例（73.9%）］。13 例（28.3%）が試験を早期に中止した。中止理由は，有害事象（一過性脳虚血発作）が 1 例，治験薬の服薬不遵守が 1 例，同意撤回が 1 例，その他（COVID-19 による試験中断）が 10 例（21.7%）であった。

男性［11 例（23.9%）］と比較して女性［35 例（76.1%）］が多かった。被験者の大多数は白人［42 例（91.3%）］であった。年齢の中央値（範囲）は 40.5（21～52）歳，BMI の中央値（範囲）は 26.71（19.7～30.5）kg/m^2 であった。

グループ 2（食事の影響グループ）

16 例が投与順序 CD 又は DC にランダム化された（投与順序 CD 及び DC 各 8 例）。全例が治験薬を投与され，14 例（87.5%）が試験を完了した（投与順序 CD 及び DC 各 7 例）。2 例が同意撤回により試験を早期に中止した（投与順序 CD 及び DC 各 1 例）。

女性［5 例（31.3%）］と比較して男性［11 例（68.8%）］が多かった。被験者の大多数は白人［12 例（75.0%）］であった。年齢の中央値（範囲）は 39.5（29～53）歳，BMI の中央値（範囲）は 26.34（22.5～29.4）kg/m^2 であった。

(2) 薬物動態

グループ 1（生物学的同等性グループ）

生物学的同等性の判定のための主要 PK パラメータ（C_{max}，AUC_{last}，及び AUC_{∞}）は試験を完了した 33 例から評価可能なデータが得られた。C_{max} については，試験を早期中止した 1 例でも信頼性の高い値が得られたため，試験を完了した 33 例に 1 例を加えた 34 例を解析に含めた。

Treatment A（試験製剤：本配合剤の単回経口投与）のマシテンタン，ACT-132577，及びタダラフィルの平均血漿中濃度－時間データ及び PK パラメータは，Treatment B（標準製剤：マシテンタン及びタダラフィルの各単味製剤併用投与）と同程度であった。

評価可能な PK パラメータについて統計解析を実施した結果，タダラフィル及びマシテンタンの主要 PK パラメータの幾何 LS 平均比（試験製剤／標準製剤）の 90% CI はいずれも生物学的同等性の基準である 80%～125%の範囲内であった。（表 2.7.6.1-3 及び表 2.7.6.1-4）。事後の統計学的検出力は，タダラフィルでは 80.9%～99.9%超，マシテンタンは 99.9%超といずれも事前に規定した基準値（80.0%超）を超えていた。

表 2.7.6.1-3 空腹時に Treatment A（本配合剤）又は Treatment B（マシテンタン及びタダラフィルの各単味製剤）を経口投与したときのマシテンタンの主要 PK パラメータ解析（PK 解析対象集団）

		Geometric Means				
Analyte	PK Parameter	Treatment B (Reference)	Treatment A (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
Macitentan	C_{max} (ng/mL)	203[a]	206[a]	101.49	96.95-106.25	11.2
	AUC_{last} (h.ng/mL)	5631[b]	5685[b]	100.96	96.99-105.09	9.6
	AUC_{∞} h.ng/mL)	5736[b]	5774[b]	100.66	96.77-104.70	9.5

[a] N=34 C_{max}
[b] N=33 AUC_{last} and AUC_{∞}
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Participants who have completed both treatment periods and have PK parameter estimated are included in the analysis.
Treatment A: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (test)
Treatment B: Single oral dose of a free combination of 10 mg macitentan (Opsumit®) and 40 mg Canada-sourced tadalafil (Adcirca®) in fasted conditions (reference)
Intra-participant CV(%) = 100* (sqrt(exp(MSE)-1).

表 2.7.6.1-4 空腹時に Treatment A（本配合剤）又は Treatment B（マシテンタン及びタダラフィルの各単味製剤）を経口投与したときのタダラフィルの主要 PK パラメータ解析（PK 解析対象集団）

		Geometric Means				
Analyte	PK Parameter	Treatment B (Reference)	Treatment A (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
Tadalafil	C_{max} (ng/mL)	598[a]	528[a]	88.30	82.68-94.31	16.1
	AUC_{last} (h.ng/mL)	19579[b]	19359[b]	98.87	94.33-103.64	11.3
	AUC_{∞} (h.ng/mL)	19702[b]	19471[b]	98.82	94.27-103.60	11.3

[a] N=34 Cmax
[b] N=33 AUClast and AUC∞
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Participants who have completed both treatment periods and have PK parameter estimated are included in the analysis.
Treatment A: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (test)
Treatment B: Single oral dose of a free combination of 10 mg macitentan (Opsumit®) and 40 mg Canada-sourced tadalafil (Adcirca®) in fasted conditions (reference)
Intra-participant CV(%) = 100* (sqrt(exp(MSE)-1).

グループ 2（食事の影響グループ）

組み入れられた 16 例のうち 15 例が 1 つ以上の投与期を完了し，14 例が両投与期を完了した。食事の影響を判定するための主要 PK パラメータ（C_{max}，AUC_{last}，及び AUC_{∞}）は，Treatment C（食後投与）及び Treatment D（空腹時投与）でそれぞれ 15 例から評価可能なデータが得られた。

マシテンタン及びタダラフィルの平均血漿中濃度－時間データは，空腹時投与と比較して食後投与でいずれも投与後 24 時間まで高値傾向であり，その後は同様であった。マシテンタン及びタダラフィルの AUC の平均値は，食後投与と空腹時投与で同程度であったが，C_{max} の平均値は，空腹時投与と比較して，食後投与ではマシテンタンが約 15.9%，タダラフィルが約 42.5%高かった。

マシテンタン及びタダラフィルの食後投与と空腹時投与の AUC_{last} 及び AUC_{∞} の幾何 LS 平均比の 90% CI は生物学的同等性の基準である 80%～125%の範囲内であったが，C_{max} の幾何 LS 平均比の 90% CI は，同基準範囲を外れ（マシテンタン：107.12%～125.83%，タダラフィル：128.96%～162.97%），食後に高値を示す傾向が認められた（表 2.7.6.1-5 及び表 2.7.6.1-6）。

ACT-132577 では，食後投与と空腹時投与の主要 PK パラメータ（C_{max}，AUC_{last}，及び AUC_{∞}）の幾何 LS 平均比の 90% CI はいずれも生物学的同等性の基準である 80%～125%の範囲内であった。

表 2.7.6.1-5 本配合剤を食後（Treatment C）又は空腹時（Treatment D）に経口投与した時のマシテンタンの PK パラメータ解析（PK 解析対象集団）

Analyte	PK Parameter	Geometric Means: Treatment D (Reference)	Geometric Means: Treatment C (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
Macitentan	C_{max} (ng/mL)	207[a]	240[a]	116.10	107.12-125.83	12.4
	AUC_{last} (h.ng/mL)	6090[a]	6230[a]	102.32	97.90-106.94	6.6
	AUC_{∞} (h.ng/mL)	6200[a]	6330[a]	102.13	97.85-106.61	6.4

[a] N=15 C_{max}, AUC_{last} and AUC_{∞}

Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Participants who had PK parameter in any of the periods are included in the analysis.
Treatment C: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fed conditions (test)
Treatment D: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (reference)
Intra-participant CV(%) = 100* (sqrt(exp(MSE)-1).

表 2.7.6.1-6 本配合剤を食後（Treatment C）又は空腹時（Treatment D）に経口投与した時のタダラフィルの PK パラメータ解析（PK 解析対象集団）

Analyte	PK Parameter	Geometric Means: Treatment D (Reference)	Geometric Means: Treatment C (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
Tadalafil	C_{max} (ng/mL)	454[a]	659[a]	144.97	128.96-162.97	17.7
	AUC_{last} (h.ng/mL)	18300[a]	20400[a]	111.07	103.93-118.71	9.9
	AUC_{∞} (h.ng/mL)	18400[a]	20500[a]	111.04	103.92-118.65	9.9

[a] N=15 C_{max}, AUC_{last} and AUC_{∞}

Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Participants who had PK parameter in any of the periods are included in the analysis.
Treatment C: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fed conditions (test)
Treatment D: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (reference)
Intra-participant CV(%) = 100* (sqrt(exp(MSE)-1).

(3) 安全性

有害事象

グループ 1（生物学的同等性グループ）

全例（46 例）を安全性の解析対象とした。有害事象及び治験薬と関連ありと判断された有害事象はいずれも 45/46 例（97.8%）［Treatment A：37/41 例（90.2%），Treatment B：33/39 例

（84.6%）］に認められた。重篤な有害事象及び治験薬の投与中止に至った有害事象は 1 例（2.4%）に認められた。当該事象は同一被験者で発現した中等度の一過性脳虚血発作であり，治験薬と関連ありと判断され，治験薬投与及び試験参加を中止した。多くの有害事象は軽度であり，死亡は認められなかった。

5%以上の被験者で認められた有害事象（PT）は，頭痛［39 例（84.8%）］，筋肉痛［27 例（58.7%）］，背部痛［14 例（30.4%）］，悪心［13 例（28.3%）］，便秘［9 例（19.6%）］，潮紅及び鼻閉［各 8 例（17.4%）］，関節痛，霧視，及び不眠症［各 7 例（15.2%）］，眼痛，羞明，及び熱感［各 6 例（13%）］，浮動性めまい，腹痛，上気道感染，及び視力障害［各 5 例（10.9%）］，下腹部痛，消化不良，眼部不快感，及び眼充血［各 4 例（8.7%）］，頭部不快感，四肢痛，顎痛，胸痛，血管穿刺部位疼痛，鼻漏，そう痒症，及び動悸［各 3 例（6.5%）］であった。

本配合剤投与時（Treatment A）と各単味製剤の併用投与時（Treatment B）の安全性プロファイルに臨床的に問題となる明らかな差は認められなかった。

グループ 2（食事の影響グループ）

全例（16 例）を安全性の解析対象とした。有害事象は 15/16 例（93.8%）［Treatment C 及び D で各 13/15 例（86.7%）］に認められ，治験薬と関連ありと判断された有害事象は 15/16 例（93.8%）［Treatment C 及び D で各 12/15 例（80.0%）］に認められた。多くの有害事象は軽度であった。死亡，重篤な有害事象，及び治験薬の投与中止に至った有害事象は認められなかった。

5%以上の被験者で認められた有害事象（PT）は，頭痛［12 例（75.0%）］，筋肉痛［6 例（37.5%）］，背部痛及び便秘［各 3 例（18.8%）］，関節痛，悪寒，及び熱感［各 2 例（12.5%）］，浮動性めまい，筋骨格硬直，四肢痛，異常感，末梢腫脹，消化不良，鼓腸，口唇水疱，口唇痛，ドライアイ，羞明，勃起増強，鼻出血，鼻そう痒症，及び潮紅［各 1 例（6.3%）］であった。

有害事象の発現割合及び重症度は，食後投与（Treatment C）と空腹時投与（Treatment D）で同程度であった。

臨床検査値及びバイタルサイン

グループ 1 及び 2 を通じて，臨床的に問題となる血液学的検査，血液生化学検査又は血液凝固検査の平均値の変動は認められなかった。グループ 1 で有害事象として報告された血糖値上昇（1 例）を除き，臨床的に意味があると判断された，又は有害事象として報告された臨床検査値異常はなかった。

グループ 1 及び 2 を通じて，臨床的に問題となる収縮期血圧，拡張期血圧，脈拍数，又は呼吸数の平均値の変動は認められなかった。臨床的に意味があると判断された，又は有害事象として報告された ECG パラメータの変動はなかった。

2.7.6.1.1.3　結論

薬物動態

- グループ 1（生物学的同等性グループ）：Treatment A（試験製剤：本配合剤の空腹時単回経口投与）及び Treatment B（標準製剤：マシテンタンとタダラフィルの各単味製剤の空腹時単回経口併用投与）のマシテンタン及びタダラフィルの PK は生物学的に同等であり，C_{max}，AUC_{last}，及び AUC_{∞}の幾何 LS 平均比（試験製剤／標準製剤）の 90% CI は，生物学的同等性の基準である 80%～125%の範囲内であった。事後の統計学的検出力は，タダラフィルでは 80.9%～99.9%超，マシテンタンは 99.9%超といずれも事前に規定した基準値（80.0%超）を超えていた。ACT-132577（マシテンタンの代謝物）の PK は，試験製剤と標準製剤で同様であった。
- グループ 2（食事の影響グループ）：Treatment C（本配合剤の食後単回経口投与）と Treatment D（本配合剤の空腹時単回経口投与）のマシテンタン及びタダラフィルの AUC_{last}及び AUC_{∞}は同程度であり，AUC_{last}及び AUC_{∞}の幾何 LS 平均比（食後投与／空腹時投与）の 90% CI はいずれも生物学的同等性の基準である 80%～125%の範囲内であった。C_{max}は，食後投与と比較し空腹時投与ではマシテンタンでわずかに高く，タダラフィルで高かった。C_{max}の幾何 LS 平均比（食後投与／空腹時投与）の 90% CI は，生物学的同等性の基準である 80%～125%を超えていた。ACT-132577（マシテンタンの代謝物）では，食後投与と空腹時投与の主要 PK パラメータ（C_{max}，AUC_{last}，及び AUC_{∞}）の幾何 LS 平均比の 90% CI はいずれも生物学的同等性の基準である 80%～125%の範囲内であった。

安全性

- 健康成人被験者にマシテンタン及びタダラフィルを配合剤又は各単味製剤として投与したとき，並びに本配合剤を食後又は空腹時に投与したときの安全性は良好であった。本試験で認められた有害事象は，健康成人にマシテンタン及びタダラフィルを投与した際に報告された有害事象と同様であった。配合剤投与時と各単味製剤の併用投与時の安全性プロファイルに臨床的に問題となる明らかな差は認められなかった。有害事象の発現割合又は重症度に，空腹時投与と食後投与の間で差は認められなかった。

2.7.6.1.2　有害事象

本試験で認められた全ての有害事象及び治験薬と関連がある有害事象を表 2.7.6.1-7（グループ 1）及び表 2.7.6.1-8（グループ 2）に示す。また，重篤な有害事象（1 例）の個別症例の詳細を，5.3.1.2.1-2 CSR Section 6.1.2.3.1 に記載した。

表 2.7.6.1-7 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 1，安全性解析対象集団）

	Group 1								
	Treatment A			Treatment B			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
Analysis set: Safety	41			39			46		
Subjects with 1 or more TEAEs	37 (90.2%)			33 (84.6%)			45 (97.8%)		
System organ class Preferred term									
神経系障害	28 (68.3%)	0	28 (68.3%)	22 (56.4%)	0	22 (56.4%)	39 (84.8%)	0	39 (84.8%)
頭痛	27 (65.9%)	0	27 (65.9%)	21 (53.8%)	0	21 (53.8%)	39 (84.8%)	0	39 (84.8%)
浮動性めまい	2 (4.9%)	0	2 (4.9%)	3 (7.7%)	0	3 (7.7%)	5 (10.9%)	0	5 (10.9%)
頭部不快感	3 (7.3%)	0	3 (7.3%)	0	0	0	3 (6.5%)	0	3 (6.5%)
体位性めまい	2 (4.9%)	0	2 (4.9%)	0	0	0	2 (4.3%)	0	2 (4.3%)
感覚鈍麻	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
錯感覚	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
ジスキネジア	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
失神寸前の状態	0	0	0	1 (2.6%)	1 (2.6%)	0	1 (2.2%)	1 (2.2%)	0
傾眠	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
会話障害	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
失神	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
緊張性頭痛	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
一過性脳虚血発作	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
筋骨格系および結合組織障害	27 (65.9%)	0	27 (65.9%)	22 (56.4%)	0	22 (56.4%)	38 (82.6%)	0	38 (82.6%)
筋肉痛	15 (36.6%)	0	15 (36.6%)	18 (46.2%)	0	18 (46.2%)	27 (58.7%)	0	27 (58.7%)
背部痛	10 (24.4%)	0	10 (24.4%)	7 (17.9%)	0	7 (17.9%)	14 (30.4%)	0	14 (30.4%)
関節痛	2 (4.9%)	0	2 (4.9%)	5 (12.8%)	0	5 (12.8%)	7 (15.2%)	0	7 (15.2%)
四肢痛	2 (4.9%)	0	2 (4.9%)	1 (2.6%)	0	1 (2.6%)	3 (6.5%)	0	3 (6.5%)
顎痛	2 (4.9%)	0	2 (4.9%)	1 (2.6%)	0	1 (2.6%)	3 (6.5%)	0	3 (6.5%)
筋痙縮	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
骨痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
側腹部痛	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
筋力低下	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)

表 2.7.6.1-7 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 1，安全性解析対象集団）

	Group 1								
	Treatment A			Treatment B			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
筋骨格痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
頚部痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
脊椎痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
顎関節症候群	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
胃腸障害	14 (34.1%)	1 (2.4%)	13 (31.7%)	22 (56.4%)	1 (2.6%)	21 (53.8%)	26 (56.5%)	1 (2.2%)	25 (54.3%)
悪心	7 (17.1%)	0	7 (17.1%)	10 (25.6%)	0	10 (25.6%)	13 (28.3%)	0	13 (28.3%)
便秘	4 (9.8%)	1 (2.4%)	3 (7.3%)	6 (15.4%)	2 (5.1%)	4 (10.3%)	9 (19.6%)	3 (6.5%)	6 (13.0%)
腹痛	0	0	0	5 (12.8%)	0	5 (12.8%)	5 (10.9%)	0	5 (10.9%)
下腹部痛	1 (2.4%)	0	1 (2.4%)	3 (7.7%)	0	3 (7.7%)	4 (8.7%)	0	4 (8.7%)
消化不良	3 (7.3%)	0	3 (7.3%)	2 (5.1%)	0	2 (5.1%)	4 (8.7%)	0	4 (8.7%)
腹部膨満	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
下痢	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
嘔吐	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
口内乾燥	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
眼障害	11 (26.8%)	0	11 (26.8%)	9 (23.1%)	0	9 (23.1%)	16 (34.8%)	0	16 (34.8%)
霧視	3 (7.3%)	0	3 (7.3%)	5 (12.8%)	0	5 (12.8%)	7 (15.2%)	0	7 (15.2%)
眼痛	2 (4.9%)	0	2 (4.9%)	4 (10.3%)	0	4 (10.3%)	6 (13.0%)	0	6 (13.0%)
羞明	2 (4.9%)	0	2 (4.9%)	5 (12.8%)	0	5 (12.8%)	6 (13.0%)	0	6 (13.0%)
視力障害	2 (4.9%)	0	2 (4.9%)	3 (7.7%)	0	3 (7.7%)	5 (10.9%)	0	5 (10.9%)
眼部不快感	1 (2.4%)	0	1 (2.4%)	3 (7.7%)	0	3 (7.7%)	4 (8.7%)	0	4 (8.7%)
眼充血	2 (4.9%)	0	2 (4.9%)	2 (5.1%)	0	2 (5.1%)	4 (8.7%)	0	4 (8.7%)
複視	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
結膜充血	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
眼刺激	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
眼球浮腫	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
眼そう痒症	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
流涙増加	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
眼窩周囲痛	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
眼窩周囲腫脹	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
強膜充血	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)

表 2.7.6.1-7 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 1，安全性解析対象集団）

	Group 1								
	Treatment A			Treatment B			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
眼瞼腫脹	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
一般・全身障害および投与部位の状態	9 (22.0%)	2 (4.9%)	7 (17.1%)	11 (28.2%)	1 (2.6%)	10 (25.6%)	16 (34.8%)	2 (4.3%)	14 (30.4%)
熱感	3 (7.3%)	0	3 (7.3%)	5 (12.8%)	0	5 (12.8%)	6 (13.0%)	0	6 (13.0%)
胸痛	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	3 (6.5%)	0	3 (6.5%)
血管穿刺部位疼痛	2 (4.9%)	2 (4.9%)	0	1 (2.6%)	1 (2.6%)	0	3 (6.5%)	3 (6.5%)	0
胸部不快感	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
悪寒	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
無力症	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
顔面痛	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
疲労	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
冷感	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
末梢性浮腫	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
疼痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
腫脹	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
圧痛	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
呼吸器、胸郭および縦隔障害	11 (26.8%)	0	11 (26.8%)	8 (20.5%)	0	8 (20.5%)	16 (34.8%)	0	16 (34.8%)
鼻閉	6 (14.6%)	0	6 (14.6%)	4 (10.3%)	0	4 (10.3%)	8 (17.4%)	0	8 (17.4%)
鼻漏	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	3 (6.5%)	0	3 (6.5%)
咳嗽	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
鼻出血	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
口腔咽頭痛	2 (4.9%)	0	2 (4.9%)	0	0	0	2 (4.3%)	0	2 (4.3%)
呼吸困難	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
口腔咽頭腫脹	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
副鼻腔分泌低下	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
咽頭腫脹	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
くしゃみ	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
咽喉刺激感	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
上気道咳症候群	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
精神障害	5 (12.2%)	1 (2.4%)	4 (9.8%)	7 (17.9%)	2 (5.1%)	5 (12.8%)	12 (26.1%)	3 (6.5%)	9 (19.6%)
不眠症	3 (7.3%)	0	3 (7.3%)	4 (10.3%)	1 (2.6%)	3 (7.7%)	7 (15.2%)	1 (2.2%)	6 (13.0%)

表 2.7.6.1-7 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 1，安全性解析対象集団）

	Group 1								
	Treatment A			Treatment B			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
多幸気分	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
異常行動	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
うつ病	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
不相応な情動	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
神経過敏	0	0	0	1 (2.6%)	1 (2.6%)	0	1 (2.2%)	1 (2.2%)	0
血管障害	6 (14.6%)	0	6 (14.6%)	6 (15.4%)	0	6 (15.4%)	9 (19.6%)	0	9 (19.6%)
潮紅	5 (12.2%)	0	5 (12.2%)	6 (15.4%)	0	6 (15.4%)	8 (17.4%)	0	8 (17.4%)
ほてり	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
皮膚および皮下組織障害	1 (2.4%)	0	1 (2.4%)	6 (15.4%)	0	6 (15.4%)	7 (15.2%)	0	7 (15.2%)
そう痒症	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	3 (6.5%)	0	3 (6.5%)
多汗症	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
紅斑	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
紅斑性皮疹	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
酒さ	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
感染症および寄生虫症	3 (7.3%)	1 (2.4%)	2 (4.9%)	3 (7.7%)	0	3 (7.7%)	6 (13.0%)	1 (2.2%)	5 (10.9%)
上気道感染	3 (7.3%)	1 (2.4%)	2 (4.9%)	2 (5.1%)	0	2 (5.1%)	5 (10.9%)	1 (2.2%)	4 (8.7%)
尿路感染	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
耳および迷路障害	2 (4.9%)	0	2 (4.9%)	2 (5.1%)	0	2 (5.1%)	4 (8.7%)	0	4 (8.7%)
耳不快感	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
耳痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
耳鳴	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
生殖系および乳房障害	3 (7.3%)	0	3 (7.3%)	2 (5.1%)	0	2 (5.1%)	4 (8.7%)	0	4 (8.7%)
乳房不快感	0	0	0	2 (5.1%)	0	2 (5.1%)	2 (4.3%)	0	2 (4.3%)
月経困難症	2 (4.9%)	0	2 (4.9%)	0	0	0	2 (4.3%)	0	2 (4.3%)
月経障害	2 (4.9%)	0	2 (4.9%)	1 (2.6%)	1 (2.6%)	0	2 (4.3%)	0	2 (4.3%)
子宮付属器痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
乳房腫瘤	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
乳房圧痛	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)

表 2.7.6.1-7 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 1，安全性解析対象集団）

	Group 1								
	Treatment A			Treatment B			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
月経過多	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)
月経遅延	0	0	0	1 (2.6%)	1 (2.6%)	0	1 (2.2%)	1 (2.2%)	0
乳頭障害	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
心臓障害	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	3 (6.5%)	0	3 (6.5%)
動悸	1 (2.4%)	0	1 (2.4%)	2 (5.1%)	0	2 (5.1%)	3 (6.5%)	0	3 (6.5%)
傷害、中毒および処置合併症	1 (2.4%)	1 (2.4%)	0	1 (2.6%)	1 (2.6%)	0	2 (4.3%)	2 (4.3%)	0
転倒	1 (2.4%)	1 (2.4%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0
熱傷	0	0	0	1 (2.6%)	1 (2.6%)	0	1 (2.2%)	1 (2.2%)	0
臨床検査	0	0	0	2 (5.1%)	1 (2.6%)	1 (2.6%)	2 (4.3%)	1 (2.2%)	1 (2.2%)
血中ブドウ糖増加	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
心拍数増加	0	0	0	1 (2.6%)	1 (2.6%)	0	1 (2.2%)	1 (2.2%)	0
腎および尿路障害	1 (2.4%)	0	1 (2.4%)	1 (2.6%)	0	1 (2.6%)	2 (4.3%)	0	2 (4.3%)
排尿困難	0	0	0	1 (2.6%)	0	1 (2.6%)	1 (2.2%)	0	1 (2.2%)
頻尿	1 (2.4%)	0	1 (2.4%)	0	0	0	1 (2.2%)	0	1 (2.2%)

Key: TEAE=Treatment Emergent Adverse Event, NRel = Not Related, Rel = Related
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the strongest relationship to study drug is used.
If a subject has missing relationship to study drug for a specific adverse event, the subject is only counted in the total column for that adverse event.
Percentages are calculated with corresponding safety count in the respective treatment as denominator.
Adverse events are coded using MedDRA Version 23.0
Treatment A: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (test)
Treatment B: Single oral dose of a free combination of 10 mg macitentan (Opsumit®) and 40 mg Canada-sourced tadalafil (Adcirca®) in fasted conditions (reference)

[TSFAE04A.RTF] [\SAS\5095\67896062PAH1006\FILES\RE\CSR\PROGRAMS\TSFAE04A.SAS] 19AUG2020, 13:56

表 2.7.6.1-8 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 2，安全性解析対象集団）

	Group 2								
	Treatment C			Treatment D			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
Analysis set: Safety	15			15			16		
Subjects with 1 or more TEAEs	13 (86.7%)			13 (86.7%)			15 (93.8%)		
System organ class Preferred term									
神経系障害	10 (66.7%)	1 (6.7%)	9 (60.0%)	10 (66.7%)	0	10 (66.7%)	12 (75.0%)	0	12 (75.0%)
頭痛	10 (66.7%)	1 (6.7%)	9 (60.0%)	10 (66.7%)	0	10 (66.7%)	12 (75.0%)	0	12 (75.0%)
浮動性めまい	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
筋骨格系および結合組織障害	8 (53.3%)	0	8 (53.3%)	6 (40.0%)	0	6 (40.0%)	9 (56.3%)	0	9 (56.3%)
筋肉痛	4 (26.7%)	0	4 (26.7%)	4 (26.7%)	0	4 (26.7%)	6 (37.5%)	0	6 (37.5%)
背部痛	2 (13.3%)	0	2 (13.3%)	1 (6.7%)	0	1 (6.7%)	3 (18.8%)	0	3 (18.8%)
関節痛	1 (6.7%)	0	1 (6.7%)	1 (6.7%)	0	1 (6.7%)	2 (12.5%)	0	2 (12.5%)
筋骨格硬直	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)
四肢痛	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)
一般・全身障害および投与部位の状態	5 (33.3%)	0	5 (33.3%)	1 (6.7%)	0	1 (6.7%)	6 (37.5%)	0	6 (37.5%)
悪寒	1 (6.7%)	0	1 (6.7%)	1 (6.7%)	0	1 (6.7%)	2 (12.5%)	0	2 (12.5%)
熱感	2 (13.3%)	0	2 (13.3%)	0	0	0	2 (12.5%)	0	2 (12.5%)
異常感	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)
末梢腫脹	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)
胃腸障害	3 (20.0%)	0	3 (20.0%)	2 (13.3%)	0	2 (13.3%)	5 (31.3%)	0	5 (31.3%)
便秘	3 (20.0%)	0	3 (20.0%)	0	0	0	3 (18.8%)	0	3 (18.8%)
消化不良	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
鼓腸	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
口唇水疱	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
口唇痛	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
眼障害	2 (13.3%)	0	2 (13.3%)	0	0	0	2 (12.5%)	0	2 (12.5%)
ドライアイ	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)

表 2.7.6.1-8 全ての有害事象及び治験薬と関連がある有害事象
（PAH1006 試験，グループ 2，安全性解析対象集団）

	Group 2								
	Treatment C			Treatment D			Overall		
		Relationship			Relationship			Relationship	
	Total	NRel	Rel	Total	NRel	Rel	Total	NRel	Rel
羞明	1 (6.7%)	0	1 (6.7%)	0	0	0	1 (6.3%)	0	1 (6.3%)
生殖系および乳房障害	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
勃起増強	0	0	0	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
呼吸器、胸郭および縦隔障害	0	0	0	1 (6.7%)	1 (6.7%)	0	1 (6.3%)	1 (6.3%)	0
鼻出血	0	0	0	1 (6.7%)	1 (6.7%)	0	1 (6.3%)	1 (6.3%)	0
鼻そう痒症	0	0	0	1 (6.7%)	1 (6.7%)	0	1 (6.3%)	1 (6.3%)	0
血管障害	1 (6.7%)	0	1 (6.7%)	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)
潮紅	1 (6.7%)	0	1 (6.7%)	1 (6.7%)	0	1 (6.7%)	1 (6.3%)	0	1 (6.3%)

Key: TEAE=Treatment Emergent Adverse Event, NRel = Not Related, Rel = Related
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the strongest relationship to study drug is used.
If a subject has missing relationship to study drug for a specific adverse event, the subject is only counted in the total column for that adverse event.
Percentages are calculated with corresponding safety count in the respective treatment as denominator.
Adverse events are coded using MedDRA Version 23.0
Treatment C: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fed conditions (test)
Treatment D: Single oral dose of FDC of macitentan/tadalafil (10 mg/40 mg) in fasted conditions (reference)

[TSFAE04B.RTF] [\SAS\5095\67896062PAH1006\FILES\RE\CSR\PROGRAMS\TSFAE04B.SAS] 19AUG2020, 13:56

2.7.6.1.3 引用文献

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. Sequential design approaches for bioequivalence studies with crossover designs. Pharm Stat. 2008;7(4):245-62.

2.7.6.2　国際共同臨床第 3 相試験（AC-077A301 試験，評価資料：5.3.5.1.1-1，5.3.5.1.1-2）

2.7.6.2.1　概要

2.7.6.2.1.1　計画

(1) 治験の表題

肺動脈性肺高血圧症患者を対象に，マシテンタン又はタダラフィル単剤投与時とマシテンタン／タダラフィル配合剤投与時の有効性及び安全性を比較する，前向き，多施設共同，二重盲検，ランダム化，実薬対照，トリプルダミー，並行群間，群逐次，アダプティブ，第 3 相試験，並びにマシテンタン／タダラフィル配合剤のオープンラベル継続投与試験

(2) 治験実施医療機関

ブラジル，ブルガリア，カナダ，中国，ドイツ，イタリア，日本，マレーシア，メキシコ，ポーランド，ロシア，南アフリカ，スペイン，台湾，トルコ及び米国：76 施設（被験者が組み入れられた国又は地域，及び治験実施医療機関）

(3) 治験実施期間

2019 年 10 月 15 日（最初の被験者のスクリーニング日）～2023 年 4 月 28 日（クリニカルカットオフ日）

(4) 開発の相

第 3 相

(5) 目的

主要目的

以下の 2 つの主要目的を有する。

- PAH 治療を受けていない（以下，未治療）又は ERA 単剤が投与されている（以下，ERA 既治療）PH 臨床分類第 1 群の症候性 PAH 患者を対象に，マシテンタン 10 mg 及びタダラフィル 40 mg の配合剤（以下，本配合剤）が EDBT 時の PVR に与える効果をマシテンタン単剤と比較し，評価する。
- 未治療又は PDE5i 単剤が投与されている（以下，PDE5i 既治療）PH 臨床分類第 1 群の症候性 PAH 患者を対象に，本配合剤が EDBT 時の PVR に与える効果をタダラフィル単剤と比較し，評価する。

副次目的

以下の項目を本配合剤と各単剤とで比較する。

- 運動耐容能
- 心肺機能及び心血管機能に関する PAH 症状
- WHO FC
- 安全性及び忍容性

(6) 治験方法

本試験は，前向き，多施設共同，二重盲検，ランダム化，実薬対照，トリプルダミー，並行群間，群逐次，アダプティブ，第 3 相試験であり，PAH 患者を対象に，マシテンタン 10 mg 単剤投与又はタダラフィル 40 mg 単剤投与それぞれに対する本配合剤投与の有効性及び安全性を比較し，評価した。試験期間は，スクリーニング期，二重盲検投与期，オープンラベル投与期及び安全性フォローアップ期から構成された。同意取得後，スクリーニング期間中に被験者の適格性を評価した。適格となった被験者をベースライン時の PAH 治療（前治療；未治療，ERA 既治療及び PDE5i 既治療）を割付け因子とし，本配合剤群，マシテンタン単剤投与群又はタダラフィル単剤投与群のいずれかに以下の比でランダム化し，二重盲検下で治験薬を 16 週間投与した。

- 未治療
  本配合剤群：マシテンタン単剤投与群：タダラフィル単剤投与群＝2：1：1
- ERA 既治療
  本配合剤群：マシテンタン単剤投与群＝2：1
- PDE5i 既治療
  本配合剤群：タダラフィル単剤投与群＝2：1

16 週間の二重盲検投与期を完了した被験者は，24 カ月間のオープンラベル投与期に移行した。

(7) 被験者数（計画時及び解析時）

計画時：170 例

解析時：187 例がランダム化され，186 例が治験薬を投与された。

(8) 診断及び主な組入れ基準

主な選択基準は，右心カテーテル検査により PH 臨床分類第 1 群の PAH と確定診断され，WHO FC が class II 又は III の 18 歳以上の男女とした。また，PAH に対する治療を受けていない，又は規定の ERA 又は PDE5i の単剤治療を 3 カ月以上受けている患者を対象とした。

(9) 用量，投与方法及び治療期間

治験薬は 1 日 1 回経口投与した。二重盲検投与期及びオープンラベル投与期はいずれも治験薬投与開始後 2 週間でタダラフィルを漸増し，その後維持投与した。二重盲検投与期及びオープンラベル投与期の治験薬の用量及び投与期間をそれぞれ表 2.7.6.2-1 及び表 2.7.6.2-2 に示す。

表 2.7.6.2-1 二重盲検投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目 [1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠
維持投与	マシテンタンプラセボ 1 錠 タダラフィルプラセボ 2 錠 本配合剤 1 錠	マシテンタン 10 mg 1 錠 タダラフィルプラセボ 2 錠 本配合剤プラセボ 1 錠	マシテンタンプラセボ 1 錠 タダラフィル 20 mg 2 錠 本配合剤プラセボ 1 錠

1. ベースライン時に，事前に規定した範囲内の PDE5i（タダラフィル 40 mg/日，シルデナフィル 60～120 mg/日，又はバルデナフィル 10 mg/日）を服用している被験者には，漸増投与せず治験薬初回投与日からタダラフィル 40 mg を投与した。

表 2.7.6.2-2 オープンラベル投与期の治験薬の用量

	本配合剤群	マシテンタン単剤投与群	タダラフィル単剤投与群
漸増投与 1 週目 [1]	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 1 錠 タダラフィルプラセボ 1 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
漸増投与 2 週目	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠	マシテンタン 10 mg 1 錠 タダラフィル 20 mg 2 錠
維持投与	本配合剤 1 錠	本配合剤 1 錠	本配合剤 1 錠

1. 二重盲検投与期からの盲検性を維持するために，全被験者で単味製剤の併用投与から開始した。二重盲検投与期に本配合剤群又はタダラフィル単剤投与群にランダム化され，タダラフィル 40 mg の投与を完了した被験者は，漸増投与せずオープンラベル期の治験薬初回投与日からタダラフィル 40 mg を投与した。

(10)評価基準及び評価項目

有効性主要評価項目

・ EDBT 時の PVR のベースラインからの変化比（PVR 変化比：EDBT 時の PVR／ベースライン時の PVR）

有効性副次評価項目

・ EDBT 時の 6MWD のベースラインからの変化

・ 治験薬投与開始 16 週後の PAH-SYMPACT®の心肺症状ドメインスコアのベースラインからの変化

・ 治験薬投与開始 16 週後の PAH-SYMPACT®の心血管症状ドメインスコアのベースラインからの変化

・ ベースラインと比較し EDBT 時の WHO FC の悪化が認められない被験者の割合

安全性評価項目

・ 治験薬投与下で発現した有害事象，重篤な有害事象，死亡，治験薬投与中止に至った有害事象，注目すべき有害事象，臨床検査値，及びバイタルサイン

(11)統計手法

解析対象集団

FAS は，いずれかの投与群にランダム化され，治験薬を 1 回以上投与された全被験者とした。

安全性解析対象集団は，二重盲検投与期間に治験薬を 1 回以上投与された全被験者とした。

本配合剤群とマシテンタン単剤投与群の有効性の主な解析は，前治療が未治療又は ERA 既治療の患者層で評価した。本配合剤群とタダラフィル単剤投与群の有効性の主な解析は，前治療が未治療又は PDE5i 既治療の患者層で評価した。

CSS は，二重盲検投与期間に本配合剤群にランダム化され，治験薬を 1 回以上投与された全被験者，及びオープンラベル投与期間に治験薬を 1 回以上投与された全被験者とした。二重盲検投与期間＋オープンラベル投与期間の安全性は，CSS を用いて評価した。二重盲検投与期に本配合剤群にランダム化された被験者は，二重盲検投与期間及びオープンラベル投与期間のデータを評価した。二重盲検投与期間に各単剤投与群にランダム化された被験者は，オープンラベル投与期間のデータを評価し，二重盲検投与期間のデータは評価しなかった。ただし，二重盲検投与期のベースライン時点のデータは評価に含めた。

有効性主要評価項目

EDBT 時の PVR 変化比は，本配合剤群とマシテンタン単剤投与群及びタダラフィル単剤投与群をそれぞれ比較するため，PVR 変化比を対数変換した値に関して 2 種類の共分散分析（ANCOVA）モデルを適用し解析した。モデルの共変量には，ランダム割付けした投与群，対数変換したベースライン時の PVR 値及び層別因子（未治療，ERA 既治療，PDE5i 既治療）を含めた。中間解析時点及び最終解析時点の各ステージで ANCOVA モデルを適用し，本配合剤群と

各単剤投与群を比較した中央値不偏推定値，調整済み繰り返し CL 及びステージを併合した調整 p 値を計算した。治療効果は，前述のとおり算出した中央値不偏推定値（各単剤投与群に対する本配合剤群の EDBT 時の PVR 変化比の調整幾何平均値の比）とした。各単剤投与群と本配合剤群との比較に関する帰無仮説がいずれも棄却された場合に，本配合剤の優越性が検証されたものとした。

有効性副次評価項目

階層的検定手順を用いて有効性主要評価項目と同じ有意水準で解析した。

安全性評価項目

治験薬投与下で発現した有害事象，臨床検査値，及びバイタルサインを評価した。治験薬投与下で発現した有害事象は，治験薬の初回投与から最終投与後 30 日までに発現した有害事象と定義した。

中間解析

本試験では，有効性又は無益性が非常に大きい場合の試験の早期中止，若しくはアダプティブな症例数再推定を可能とすることを目的とした中間解析を実施した。中間解析は治験実施計画書第 6 版に基づき，100 例の被験者が二重盲検投与期間の 16 週の評価を完了した，又は 16 週の評価前に試験を中止した時点で実施した。中間解析の結果，安全性の懸念は特定されず，事前に規定した有効性の閾値を超えた。中間解析結果を踏まえた独立データモニタリング委員会からの勧告に基づき，治験依頼者は試験への更なる被験者募集を中止し，この時点までに組み入れられた被験者は試験を継続した。

2.7.6.2.1.2　結果（二重盲検投与期間）

(1) 対象集団

治験薬が 1 回以上投与された 186 例（本配合剤群 107 例，マシテンタン単剤投与群 35 例，タダラフィル単剤投与群 44 例）を FAS 及び安全性解析対象集団とした。二重盲検投与期間中に治験薬の投与を中止した被験者の割合は，本配合剤群 15.0%（16/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）であった。主な投与中止理由は，有害事象［本配合剤群 8.4%（9/107 例），マシテンタン単剤投与群 0%（0/35 例），タダラフィル単剤投与群 2.3%（1/44 例）］であった。

試験対象集団の人口統計学的特性及びベースラインの疾患特性は，対象とする疾患の患者集団の特徴と同様であった。年齢の中央値（範囲）は，本配合剤群 48.0（18～79）歳，マシテンタン単剤投与群 51.0（20～80）歳，タダラフィル単剤投与群 54.0（19～78）歳であった。いずれの群も 26～50 歳の割合が最も高かった。女性の割合は，本配合剤群 76.6%（82/107 例），マシテンタン単剤投与群 82.9%（29/35 例），タダラフィル単剤投与群 77.3%（34/44 例）であった。WHO FC は，全ての被験者が class II 又は III であった。PAH の臨床分類は，いずれの群も特発性 PAH の割合が最も高く［本配合剤群 54.2%（58/107 例），マシテンタン単剤投与群 45.7%（16/35 例），タダラフィル単剤投与群 45.5%（20/44 例），以下同順］，次に結合組織疾患に伴う PAH

の割合が高かった［33.6%（36/107 例），37.1%（13/35 例），36.4%（16/44 例）］。PAH の診断からの期間の中央値は，いずれの群も 0.5 年未満であった。

二重盲検投与期の治験薬投与期間の平均値（SD）は，本配合剤群 14.85（4.547）週，マシテンタン単剤投与群 16.87（1.307）週，及びタダラフィル単剤投与群 15.98（0.952）週であった。マシテンタン単剤投与群及びタダラフィル単剤投与群では，治験薬投与期間が 8 週間未満の被験者はおらず，本配合剤群では，4 週間未満の被験者の割合が 9.3%（10/107 例），4 週間以上 8 週間未満の被験者の割合が 1.9%（2/107 例）であった。

(2) 有効性

有効性主要評価項目

各単剤投与群に対する本配合剤群の治療効果は以下のとおりであり，各単剤投与群に対する本配合剤の統計学的に有意かつ臨床的に意味のある治療効果が認められた。また，治療効果は事前に規定した部分集団でも一貫していた。

- マシテンタン単剤投与群に対する本配合剤群の治療効果：0.71［調整済み繰り返し 95% CL：0.61～0.82，調整 p<0.0001（ANCOVA モデル）］（マシテンタン単剤投与群に比べて本配合剤群では PVR 変化比が相対的に 29%減少）
- タダラフィル単剤投与群に対する本配合剤群の治療効果：0.72［調整済み繰り返し 95% CL：0.64～0.80，調整 p<0.0001（ANCOVA モデル）］（タダラフィル単剤投与群に比べて本配合剤群では PVR 変化比が相対的に 28%減少）

有効性副次評価項目

運動耐容能の治療効果は，各単剤投与群に対する本配合剤群の EDBT 時の 6MWD のベースラインからの変化量の群間差とした。各単剤投与群に対する本配合剤群の治療効果は以下のとおりであり，各単剤投与群と比較して本配合剤群の優越性は示されなかった。

- マシテンタン単剤投与群に対する本配合剤群の治療効果：16.04 m［調整済み繰り返し 95% CL：-17.0～49.08 m，調整 p=0.3802（ANCOVA モデル）］
- タダラフィル単剤投与群に対する本配合剤群の治療効果：25.37 m，［調整済み繰り返し 95% CL：-0.93～51.59 m，調整 p=0.0591（ANCOVA モデル）］

事前規定した階層的検定手順に従い，その他の副次評価項目（PAH-SYMPACT®及び WHO FC）は検定しなかった。

(3) 安全性

- 二重盲検投与期間の有害事象の発現割合は，マシテンタン単剤投与群と比較して本配合剤群で高く，タダラフィル単剤投与群と本配合剤群で同程度であった［本配合剤群 82.2%（88/107 例），マシテンタン単剤投与群 71.4%（25/35 例），タダラフィル単剤投与群 79.5%（35/44 例），以下同順］。いずれかの群で発現割合が 10%以上の有害事象は，頭痛［16.8%（18/107 例），17.1%（6/35 例），13.6%（6/44 例）］，末梢性浮腫

［13.1%（14/107 例），11.4%（4/35 例），11.4%（5/44 例）］及び下痢［4.7%（5/107 例），0%（0/35 例），13.6%（6/44 例）］であった。

- 本配合剤群で有害事象を 1 件以上発現した被験者の割合は，ERA 既治療及び PDE5i 既治療の被験者と比較して未治療の被験者で高かった［未治療 87.8%（43/49 例），ERA 既治療 76.2%（16/21 例），PDE5i 既治療 78.4%（29/37 例）］。
- 死亡に至った有害事象は本配合剤群で 2 例に認められた。その内訳はクロストリジウム菌性胃腸炎 1 例及び心不全 1 例であり，いずれも治験薬と関連なしと判断された。マシテンタン単剤投与群及びタダラフィル単剤投与群では死亡に至った有害事象は認められなかった。
- 重篤な有害事象の発現割合は，本配合剤群 14.0%（15/107 例），マシテンタン単剤投与群 8.6%（3/35 例），及びタダラフィル単剤投与群 9.1%（4/44 例）（以下同順）であり，治験薬の投与中止に至った有害事象の発現割合は，8.4%（9/107 例），0%，及び 4.5%（2/44 例）であった。重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合はマシテンタン単剤投与群及びタダラフィル単剤投与群と比較して本配合剤群で高かったものの，PT 別の有害事象に明確な傾向は認められなかった。いずれかの群で 2 例以上に発現した重篤な有害事象は，心不全［1.9%（2/107 例），0%，2.3%（1/44 例）］及び呼吸困難［1.9%（2/107 例），0%，0%］であった。いずれかの群で 2 例以上に発現した治験薬の投与中止に至った有害事象は認められなかった。
- 複数の PT をまとめるなどして定義した注目すべき有害事象のうち，「低血圧」，「貧血」及び「浮腫」の発現割合はいずれもマシテンタン単剤投与群及びタダラフィル単剤投与群と比較して本配合剤群で高かった［「低血圧」：本配合剤群 7.5%（8/107 例），マシテンタン単剤投与群 0%，タダラフィル単剤投与群 0%（以下同順），「貧血」：18.7%（20/107 例），2.9%（1/35 例），2.3%（1/44 例），「浮腫」：20.6%（22/107 例），14.3%（5/35 例），15.9%（7/44 例）］。「肝障害」の発現割合はいずれの群でも低かった［0.9%（1/107 例），2.9%（1/35 例），9.1%（4/44 例）］。注目すべき有害事象は大部分が軽度から中等度であり，臨床的に管理可能であった。
- 16 週時点のヘモグロビンのベースラインからの平均変化量は，マシテンタン単剤投与群及びタダラフィル単剤投与群と比較して本配合剤群でより顕著に減少した（本配合剤群 -13.9 g/L，マシテンタン単剤投与群-6.8 g/L，タダラフィル単剤投与群-0.8 g/L）。

2.7.6.2.1.3　結果（二重盲検投与期間＋オープンラベル投与期間）

(1) 対象集団

CSS は 185 例であり，CCO（2023 年 4 月 28 日）までに治験薬の投与を中止した被験者の割合は，14.6%（27/185 例）であった。主な治験薬の投与中止理由は，有害事象 4.9%（9/185 例），医師判断及び同意撤回各 1.6%（各 3/185 例），並びに死亡 1.1%（2/185 例）であった。CSS 全体の投与期間の中央値（範囲）は，75.43（0.6～151.6）週であった。

(2) 安全性

- 有害事象の発現割合は 93.5%（173/185 例）であった。10%以上に発現した有害事象は，COVID-19［23.2%（43/185 例）］，頭痛［14.6%（27/185 例）］，末梢性浮腫［11.4%（21/185 例）］，及び貧血［10.8%（20/185 例）］であった。
- オープンラベル投与期に死亡に至った有害事象は 2 例に認められた。その内訳は右室不全 1 例及び呼吸不全 1 例であり，いずれも治験薬と関連なしと判断された。
- 重篤な有害事象の発現割合は 26.5%（49/185 例）であった。2 例以上に発現した重篤な有害事象は，COVID-19，及び右室不全［各 2.7%（各 5/185 例）］，肺炎［2.2%（4/185 例）］，呼吸困難［各 1.6%（各 3/185 例）］，COVID-19 肺炎，パラインフルエンザウイルス感染，ウイルス性肺炎，心房粗動，心不全，肺動脈性肺高血圧症，低酸素症，子宮ポリープ，及び前立腺癌［各 1.1%（各 2/185 例）］であった。
- 治験薬の投与中止に至った有害事象の発現割合は 9.2%（17/185 例）であった。2 例以上に発現した治験薬の投与中止に至った有害事象はヘモグロビン減少［1.1%（2/185 例）］であった。ヘモグロビン値は本配合剤の初回投与後に減少する傾向が認められた。
- 注目すべき有害事象の発現割合は，「肝障害」5.4%（10/185 例），「貧血」23.2%（43/185 例），「低血圧」6.5%（12/185 例），「浮腫及び体液貯留」18.4%（34/185 例）であった。

2.7.6.2.1.4　結論

本試験の結果，各単剤投与群と比較して本配合剤群は EDBT 時点の PVR 変化比を大きく減少させ，2 つの主要目的はいずれも統計学的に有意に達成した。また，治療効果は部分集団でも一貫していた。

本配合剤群で認められた有害事象は，PAH 患者で既に確認されている合併症，並びにマシテンタン及びタダラフィルの各単剤療法の安全性プロファイルと同様であり，臨床的に管理可能であった。各単剤投与群と比較して本配合剤群で有害事象の発現割合が高かったことは，単剤療法の安全性プロファイルが重複している可能性，及び未治療患者の割合が高かったことが影響している可能性が考えられた。また，二重盲検投与期及びオープンラベル投与期を通じて新たな安全性の懸念は認められなかった。

以上より，PAH 患者の治療に対して本配合剤は各単剤と比較して有効であることが示された。また，本配合剤の安全性プロファイルは良好であった。

2.7.6.2.2　有害事象

二重盲検投与期及びオープンラベル投与期に認められた全ての有害事象をそれぞれ表 2.7.6.2-3 及び表 2.7.6.2-4 に示す。また，死亡及びその他の重篤な有害事象の個別症例の詳細を 5.3.5.1.1-1 CSR Narratives 及び 5.3.5.1.1-2 120DSU Narratives に記載した。

表 2.7.6.2-3 全ての有害事象（A DUE 試験，二重盲検投与期，安全性解析対象集団）

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	35	70	44	86	107
Subjects with 1 or more AEs	25 (71.4%)	59 (84.3%)	35 (79.5%)	72 (83.7%)	88 (82.2%)
Related	11 (31.4%)	33 (47.1%)	11 (25.0%)	37 (43.0%)	47 (43.9%)
Not Related	14 (40.0%)	26 (37.1%)	24 (54.5%)	35 (40.7%)	41 (38.3%)
頭痛	6 (17.1%)	12 (17.1%)	6 (13.6%)	14 (16.3%)	18 (16.8%)
Related	5 (14.3%)	9 (12.9%)	2 (4.5%)	10 (11.6%)	14 (13.1%)
Not Related	1 (2.9%)	3 (4.3%)	4 (9.1%)	4 (4.7%)	4 (3.7%)
末梢性浮腫	4 (11.4%)	9 (12.9%)	5 (11.4%)	12 (14.0%)	14 (13.1%)
Related	1 (2.9%)	5 (7.1%)	3 (6.8%)	5 (5.8%)	7 (6.5%)
Not Related	3 (8.6%)	4 (5.7%)	2 (4.5%)	7 (8.1%)	7 (6.5%)
貧血	0	6 (8.6%)	0	7 (8.1%)	8 (7.5%)
Related	0	2 (2.9%)	0	2 (2.3%)	3 (2.8%)
Not Related	0	4 (5.7%)	0	5 (5.8%)	5 (4.7%)
ヘモグロビン減少	0	3 (4.3%)	0	8 (9.3%)	8 (7.5%)
Related	0	0	0	2 (2.3%)	2 (1.9%)
Not Related	0	3 (4.3%)	0	6 (7.0%)	6 (5.6%)

Key: ERA = Endothelin receptor antagonist; PDE-5i = Phosphodiesterase type-5 inhibitor; M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; EOT-DB = End of treatment in double-blind treatment period.
Note: Treatment-emergent period is defined from first intake of study treatment in the double-blind period up to and including min(EOT-DB+30 days, start date of open-label treatment).
Note: An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
Note: Subjects are counted only once in the worst relationship category for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: Treatment-naïve participants randomized to M/T FDC are counted in each M/T FDC arm and as such contribute twice in the display

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	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata		All strata
	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
低血圧	0	6 (8.6%)	0	5 (5.8%)	8 (7.5%)
Related	0	3 (4.3%)	0	2 (2.3%)	4 (3.7%)
Not Related	0	3 (4.3%)	0	3 (3.5%)	4 (3.7%)
末梢腫脹	1 (2.9%)	7 (10.0%)	0	7 (8.1%)	7 (6.5%)
Related	1 (2.9%)	6 (8.6%)	0	6 (7.0%)	6 (5.6%)
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
咳嗽	1 (2.9%)	5 (7.1%)	2 (4.5%)	6 (7.0%)	6 (5.6%)
Related	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Not Related	1 (2.9%)	4 (5.7%)	1 (2.3%)	5 (5.8%)	5 (4.7%)
筋肉痛	0	5 (7.1%)	2 (4.5%)	4 (4.7%)	6 (5.6%)
Related	0	5 (7.1%)	0	3 (3.5%)	5 (4.7%)
Not Related	0	0	2 (4.5%)	1 (1.2%)	1 (0.9%)
悪心	0	5 (7.1%)	3 (6.8%)	4 (4.7%)	6 (5.6%)
Related	0	4 (5.7%)	1 (2.3%)	4 (4.7%)	5 (4.7%)
Not Related	0	1 (1.4%)	2 (4.5%)	0	1 (0.9%)
背部痛	1 (2.9%)	5 (7.1%)	4 (9.1%)	3 (3.5%)	5 (4.7%)
Related	0	0	1 (2.3%)	0	0
Not Related	1 (2.9%)	5 (7.1%)	3 (6.8%)	3 (3.5%)	5 (4.7%)
下痢	0	4 (5.7%)	6 (13.6%)	5 (5.8%)	5 (4.7%)
Related	0	3 (4.3%)	2 (4.5%)	3 (3.5%)	3 (2.8%)
Not Related	0	1 (1.4%)	4 (9.1%)	2 (2.3%)	2 (1.9%)
関節痛	2 (5.7%)	2 (2.9%)	4 (9.1%)	4 (4.7%)	4 (3.7%)
Related	0	0	0	0	0
Not Related	2 (5.7%)	2 (2.9%)	4 (9.1%)	4 (4.7%)	4 (3.7%)
心不全	0	4 (5.7%)	1 (2.3%)	3 (3.5%)	4 (3.7%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	3 (4.3%)	1 (2.3%)	2 (2.3%)	3 (2.8%)
消化不良	0	4 (5.7%)	3 (6.8%)	4 (4.7%)	4 (3.7%)
Related	0	2 (2.9%)	2 (4.5%)	2 (2.3%)	2 (1.9%)
Not Related	0	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)

呼吸困難	0	2 (2.9%)	2 (4.5%)	4 (4.7%)	4 (3.7%)
Related	0	2 (2.9%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
Not Related	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
鼻閉	0	3 (4.3%)	0	3 (3.5%)	4 (3.7%)
Related	0	3 (4.3%)	0	3 (3.5%)	4 (3.7%)
Not Related	0	0	0	0	0
動悸	1 (2.9%)	1 (1.4%)	2 (4.5%)	3 (3.5%)	4 (3.7%)
Related	0	0	1 (2.3%)	0	0
Not Related	1 (2.9%)	1 (1.4%)	1 (2.3%)	3 (3.5%)	4 (3.7%)
発熱	0	2 (2.9%)	0	4 (4.7%)	4 (3.7%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
嘔吐	0	3 (4.3%)	2 (4.5%)	4 (4.7%)	4 (3.7%)
Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Not Related	0	2 (2.9%)	2 (4.5%)	2 (2.3%)	2 (1.9%)
狭心症	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
ＣＯＶＩＤ－１９	2 (5.7%)	2 (2.9%)	2 (4.5%)	3 (3.5%)	3 (2.8%)
Related	0	0	0	0	0
Not Related	2 (5.7%)	2 (2.9%)	2 (4.5%)	3 (3.5%)	3 (2.8%)
浮動性めまい	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
Related	1 (2.9%)	0	0	0	0
Not Related	0	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
口内乾燥	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
鼻出血	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	2 (2.3%)	2 (1.9%)
疲労	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	3 (2.8%)

Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	1 (2.9%)	1 (1.4%)	1 (2.3%)	1 (1.2%)	2 (1.9%)
潮紅	2 (5.7%)	3 (4.3%)	0	3 (3.5%)	3 (2.8%)
Related	2 (5.7%)	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
高尿酸血症	1 (2.9%)	3 (4.3%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	3 (4.3%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
上咽頭炎	1 (2.9%)	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
非心臓性胸痛	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	2 (2.9%)	3 (6.8%)	1 (1.2%)	2 (1.9%)
四肢痛	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)
Related	0	1 (1.4%)	0	0	1 (0.9%)
Not Related	0	1 (1.4%)	3 (6.8%)	2 (2.3%)	2 (1.9%)
腹部不快感	1 (2.9%)	0	2 (4.5%)	2 (2.3%)	2 (1.9%)
Related	1 (2.9%)	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Not Related	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
腹痛	0	0	2 (4.5%)	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	0	2 (4.5%)	2 (2.3%)	2 (1.9%)
労作性呼吸困難	1 (2.9%)	0	1 (2.3%)	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	1 (2.3%)	2 (2.3%)	2 (1.9%)
眼瞼浮腫	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Not Related	0	0	0	0	0
胃炎	0	0	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	0	0	2 (2.3%)	2 (1.9%)

痔出血	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
重度月経出血	0	0	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	0	0	2 (2.3%)	2 (1.9%)
感覚鈍麻	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
低カリウム血症	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
インフルエンザ	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	2 (1.9%)
鉄欠乏	1 (2.9%)	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
鉄欠乏性貧血	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
筋骨格痛	0	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
食道炎	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	2 (1.9%)
Related	0	1 (1.4%)	0	0	1 (0.9%)
Not Related	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
口腔ヘルペス	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
眼窩周囲浮腫	0	0	1 (2.3%)	2 (2.3%)	2 (1.9%)

Related	0	0	1 (2.3%)	2 (2.3%)	2 (1.9%)
Not Related	0	0	0	0	0
肺炎	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
発疹	1 (2.9%)	1 (1.4%)	2 (4.5%)	1 (1.2%)	2 (1.9%)
Related	1 (2.9%)	1 (1.4%)	1 (2.3%)	1 (1.2%)	2 (1.9%)
Not Related	0	0	1 (2.3%)	0	0
皮膚色素過剰	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
顔面腫脹	0	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Related	0	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Not Related	0	0	0	0	0
頻脈	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
尿路感染	0	2 (2.9%)	0	0	2 (1.9%)
Related	0	0	0	0	0
Not Related	0	2 (2.9%)	0	0	2 (1.9%)
霧視	1 (2.9%)	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
Related	1 (2.9%)	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
Not Related	0	0	0	0	0
体重増加	1 (2.9%)	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
腹部膨満	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	1 (2.3%)	0	0
慢性疾患の貧血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

血管浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
無力症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
喘息	1 (2.9%)	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	0	1 (0.9%)
心房粗動	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
細菌感染	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
血中クレアチニン増加	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
血中尿酸異常	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
骨髄浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
乳房腫瘤	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
ＣＯＶＩＤ－１９肺炎	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
心雑音	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
心血管障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
胸部不快感	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
胸痛	1 (2.9%)	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	1 (1.2%)	1 (0.9%)
便秘	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
冠動脈疾患	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
サイトメガロウイルス性脈絡網膜炎	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
食欲減退	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	1 (2.9%)	0	0	0	0
労作性めまい	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
体位性めまい	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
皮膚乾燥	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

斑状出血	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
子宮内膜症	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
小腸炎	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
紅斑	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
労作性頭痛	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
眼部腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
鼓腸	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
クロストリジウム菌性胃腸炎	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
胃腸障害	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
胃食道逆流性疾患	1 (2.9%)	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	1 (2.9%)	0	1 (2.3%)	0	0
全身性浮腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
歯肉炎	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
痛風	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
痔核	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
不全片麻痺	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
帯状疱疹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
ホルネル症候群	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
ほてり	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
高カリウム血症	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
遠視	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
過敏症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0

月経中間期出血	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
椎間板突出	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
左室不全	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
嗜眠	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
白血球減少症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
靭帯断裂	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
限局性感染	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
腰ヘルニア	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
片頭痛	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
卵巣粘液性嚢胞腺癌	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
筋力低下	0	1 (1.4%)	0	0	1 (0.9%)

Related	0	1 (1.4%)	0	0	1 (0.9%)
Not Related	0	0	0	0	0
筋骨格系胸痛	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	1 (2.3%)	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
好中球数減少	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
正色素性貧血	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
眼充血	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
口腔咽頭痛	0	1 (1.4%)	2 (4.5%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	2 (4.5%)	1 (1.2%)	1 (0.9%)
起坐呼吸	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
骨壊死	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
卵巣嚢胞	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
酸素飽和度低下	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
疼痛	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	1 (2.3%)	0	0

顎痛	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
汎血球減少症	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
末梢静脈疾患	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
血小板数減少	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
ヘルペス後神経痛	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
そう痒症	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
肺動脈性肺高血圧症	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
肺静脈閉塞性疾患	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
腎機能障害	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
アレルギー性鼻炎	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
肋骨骨折	0	0	0	1 (1.2%)	1 (0.9%)

Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
右室不全	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
副鼻腔炎	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
シェーグレン症候群	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
皮膚潰瘍	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
腫脹	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
失神	0	0	2 (4.5%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	2 (4.5%)	1 (1.2%)	1 (0.9%)
口渇	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	0	0	0
舌嚢胞	0	1 (1.4%)	0	0	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	0	1 (0.9%)
歯膿瘍	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
歯牙破折	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

トランスアミナーゼ上昇	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	1 (1.2%)	1 (0.9%)
Not Related	0	0	1 (2.3%)	0	0
外傷性血腫	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
上気道感染	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
腟出血	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
ビタミンＢ１２欠乏	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	1 (1.4%)	1 (2.3%)	1 (1.2%)	1 (0.9%)
体重減少	0	0	0	1 (1.2%)	1 (0.9%)
Related	0	0	0	0	0
Not Related	0	0	0	1 (1.2%)	1 (0.9%)
上腹部痛	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (2.9%)	0	1 (2.3%)	0	0
Related	1 (2.9%)	0	1 (2.3%)	0	0
Not Related	0	0	0	0	0
不安	1 (2.9%)	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	1 (2.3%)	0	0
関節炎	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
節足動物刺傷	1 (2.9%)	0	0	0	0

Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.9%)	0	2 (4.5%)	0	0
Related	1 (2.9%)	0	1 (2.3%)	0	0
Not Related	0	0	1 (2.3%)	0	0
眼瞼痙攣	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
血中アルカリホスファターゼ増加	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
血中コレステロール異常	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
血中鉄減少	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
血圧上昇	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
血中尿酸増加	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
慢性心不全	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
脳梗塞	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
結膜炎	1 (2.9%)	0	0	0	0
Related	1 (2.9%)	0	0	0	0
Not Related	0	0	0	0	0

挫傷	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
咽喉乾燥	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
発声障害	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
排尿困難	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
電解質失調	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
家族性地中海熱	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
体液貯留	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
歯肉出血	1 (2.9%)	0	0	0	0
Related	1 (2.9%)	0	0	0	0
Not Related	0	0	0	0	0
糸球体濾過率減少	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
血便排泄	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
喀血	0	0	1 (2.3%)	0	0

Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
脂肪肝	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
高コレステロール血症	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
高血糖	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
空腹時血中ブドウ糖不良	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
関節腫脹	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
口唇腫脹	0	0	1 (2.3%)	0	0
Related	0	0	1 (2.3%)	0	0
Not Related	0	0	0	0	0
倦怠感	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
閉経期症状	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
筋痙縮	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
好中球減少症	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0

食道潰瘍	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
口腔咽頭不快感	0	0	1 (2.3%)	0	0
Related	0	0	1 (2.3%)	0	0
Not Related	0	0	0	0	0
咽頭炎	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
肺高血圧症	1 (2.9%)	0	0	0	0
Related	1 (2.9%)	0	0	0	0
Not Related	0	0	0	0	0
紅斑性皮疹	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
鼻炎	1 (2.9%)	0	1 (2.3%)	0	0
Related	1 (2.9%)	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
季節性アレルギー	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
副鼻腔うっ血	0	0	1 (2.3%)	0	0
Related	0	0	1 (2.3%)	0	0
Not Related	0	0	0	0	0
皮膚裂傷	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
皮膚創傷	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
扁平上皮癌	1 (2.9%)	0	0	0	0

Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
全身性エリテマトーデス	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
耳鳴	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0
尿道出血	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
回転性めまい	0	0	1 (2.3%)	0	0
Related	0	0	0	0	0
Not Related	0	0	1 (2.3%)	0	0
頭位性回転性めまい	1 (2.9%)	0	0	0	0
Related	0	0	0	0	0
Not Related	1 (2.9%)	0	0	0	0

表 2.7.6.2-4 有害事象（A DUE 試験，二重盲検投与期+オープンラベル投与期，Combination Safety Set）

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
Analysis set: Combination Safety Set	185	185
Subjects with 1 or more AEs	170 (91.9%)	173 (93.5%)
Related	68 (36.8%)	69 (37.3%)
Not Related	102 (55.1%)	104 (56.2%)
ＣＯＶＩＤ－１９	39 (21.1%)	43 (23.2%)
Related	0	0
Not Related	39 (21.1%)	43 (23.2%)
頭痛	26 (14.1%)	27 (14.6%)
Related	19 (10.3%)	19 (10.3%)
Not Related	7 (3.8%)	8 (4.3%)
末梢性浮腫	20 (10.8%)	21 (11.4%)
Related	9 (4.9%)	10 (5.4%)
Not Related	11 (5.9%)	11 (5.9%)
貧血	19 (10.3%)	20 (10.8%)
Related	5 (2.7%)	5 (2.7%)
Not Related	14 (7.6%)	15 (8.1%)

Key: M/T FDC = Macitentan/tadalafil fixed dose combination; AE = Adverse event; DB = Double-blind; OL = Open-label; EOT = End of treatment; EOT-DB = End of treatment in double-blind treatment period; EOT-OL = End of treatment in open-label treatment period.
Note: The treatment-emergent period for the DB-M/T FDC arm is defined from first intake of DB study treatment up to EOT (EOT-DB or EOT-OL) + 30 days. The treatment-emergent period for the DB-Macitentan and DB-Tadalafil arms is defined from first intake of OL study treatment up to EOT-OL + 30 days. M/T FDC (Total) is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). DB-Macitentan, DB-Tadalafil, and DB-M/T FDC corresponds to treatment allocation in DB period.
Note: An AE is categorized as related if assessed by the investigator as related to study treatment or if relationship to study treatment is missing.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
ヘモグロビン減少	17 (9.2%)	17 (9.2%)
Related	6 (3.2%)	6 (3.2%)
Not Related	11 (5.9%)	11 (5.9%)
咳嗽	14 (7.6%)	15 (8.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	12 (6.5%)	13 (7.0%)
低血圧	12 (6.5%)	12 (6.5%)
Related	5 (2.7%)	5 (2.7%)
Not Related	7 (3.8%)	7 (3.8%)
上気道感染	12 (6.5%)	13 (7.0%)
Related	1 (0.5%)	1 (0.5%)
Not Related	11 (5.9%)	12 (6.5%)
関節痛	11 (5.9%)	11 (5.9%)
Related	0	0
Not Related	11 (5.9%)	11 (5.9%)
呼吸困難	11 (5.9%)	13 (7.0%)
Related	5 (2.7%)	5 (2.7%)
Not Related	6 (3.2%)	8 (4.3%)
筋肉痛	11 (5.9%)	12 (6.5%)
Related	6 (3.2%)	6 (3.2%)
Not Related	5 (2.7%)	6 (3.2%)
背部痛	10 (5.4%)	10 (5.4%)
Related	0	0
Not Related	10 (5.4%)	10 (5.4%)
動悸	10 (5.4%)	11 (5.9%)
Related	2 (1.1%)	2 (1.1%)
Not Related	8 (4.3%)	9 (4.9%)
発熱	10 (5.4%)	10 (5.4%)
Related	1 (0.5%)	1 (0.5%)
Not Related	9 (4.9%)	9 (4.9%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
鼻閉	9 (4.9%)	9 (4.9%)
Related	7 (3.8%)	7 (3.8%)
Not Related	2 (1.1%)	2 (1.1%)
末梢腫脹	9 (4.9%)	9 (4.9%)
Related	6 (3.2%)	6 (3.2%)
Not Related	3 (1.6%)	3 (1.6%)
尿路感染	9 (4.9%)	10 (5.4%)
Related	0	0
Not Related	9 (4.9%)	10 (5.4%)
嘔吐	9 (4.9%)	9 (4.9%)
Related	3 (1.6%)	3 (1.6%)
Not Related	6 (3.2%)	6 (3.2%)
鉄欠乏性貧血	8 (4.3%)	8 (4.3%)
Related	0	0
Not Related	8 (4.3%)	8 (4.3%)
悪心	8 (4.3%)	9 (4.9%)
Related	7 (3.8%)	7 (3.8%)
Not Related	1 (0.5%)	2 (1.1%)
肺動脈性肺高血圧症	8 (4.3%)	8 (4.3%)
Related	0	0
Not Related	8 (4.3%)	8 (4.3%)
下痢	7 (3.8%)	7 (3.8%)
Related	3 (1.6%)	3 (1.6%)
Not Related	4 (2.2%)	4 (2.2%)
胃炎	7 (3.8%)	7 (3.8%)
Related	0	0
Not Related	7 (3.8%)	7 (3.8%)
上咽頭炎	7 (3.8%)	7 (3.8%)
Related	0	0
Not Related	7 (3.8%)	7 (3.8%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
四肢痛	7 (3.8%)	8 (4.3%)
Related	2 (1.1%)	2 (1.1%)
Not Related	5 (2.7%)	6 (3.2%)
浮動性めまい	6 (3.2%)	6 (3.2%)
Related	0	0
Not Related	6 (3.2%)	6 (3.2%)
肺炎	6 (3.2%)	8 (4.3%)
Related	0	0
Not Related	6 (3.2%)	8 (4.3%)
発疹	6 (3.2%)	6 (3.2%)
Related	2 (1.1%)	2 (1.1%)
Not Related	4 (2.2%)	4 (2.2%)
右室不全	6 (3.2%)	7 (3.8%)
Related	1 (0.5%)	1 (0.5%)
Not Related	5 (2.7%)	6 (3.2%)
疲労	5 (2.7%)	5 (2.7%)
Related	1 (0.5%)	1 (0.5%)
Not Related	4 (2.2%)	4 (2.2%)
低カリウム血症	5 (2.7%)	6 (3.2%)
Related	0	0
Not Related	5 (2.7%)	6 (3.2%)
インフルエンザ	5 (2.7%)	5 (2.7%)
Related	0	0
Not Related	5 (2.7%)	5 (2.7%)
腹部不快感	4 (2.2%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	3 (1.6%)	3 (1.6%)
腹痛	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
狭心症	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
心不全	4 (2.2%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	3 (1.6%)	3 (1.6%)
白内障	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
消化不良	4 (2.2%)	4 (2.2%)
Related	2 (1.1%)	2 (1.1%)
Not Related	2 (1.1%)	2 (1.1%)
労作性呼吸困難	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
鼻出血	4 (2.2%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	3 (1.6%)	3 (1.6%)
胃食道逆流性疾患	4 (2.2%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	3 (1.6%)	3 (1.6%)
痔出血	4 (2.2%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	3 (1.6%)	3 (1.6%)
重度月経出血	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
不眠症	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
鉄欠乏	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
副鼻腔炎	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
子宮ポリープ	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
ビタミンＢ１２欠乏	4 (2.2%)	4 (2.2%)
Related	0	0
Not Related	4 (2.2%)	4 (2.2%)
心房粗動	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
ＣＯＶＩＤ－１９肺炎	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
蜂巣炎	3 (1.6%)	4 (2.2%)
Related	0	0
Not Related	3 (1.6%)	4 (2.2%)
胸部不快感	3 (1.6%)	3 (1.6%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	2 (1.1%)
便秘	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
口内乾燥	3 (1.6%)	3 (1.6%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
潮紅	3 (1.6%)	4 (2.2%)
Related	2 (1.1%)	2 (1.1%)
Not Related	1 (0.5%)	2 (1.1%)
痔核	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
高尿酸血症	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
感覚鈍麻	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
椎間板突出	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
白血球減少症	3 (1.6%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	3 (1.6%)
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	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
好中球減少症	3 (1.6%)	4 (2.2%)
Related	0	0
Not Related	3 (1.6%)	4 (2.2%)
非心臓性胸痛	3 (1.6%)	3 (1.6%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	2 (1.1%)
口腔ヘルペス	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
変形性関節症	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
腎機能障害	3 (1.6%)	3 (1.6%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	2 (1.1%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
皮膚色素過剰	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
失神	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
頻脈	3 (1.6%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	3 (1.6%)
霧視	3 (1.6%)	3 (1.6%)
Related	3 (1.6%)	3 (1.6%)
Not Related	0	0
体重減少	3 (1.6%)	3 (1.6%)
Related	0	0
Not Related	3 (1.6%)	3 (1.6%)
体重増加	3 (1.6%)	4 (2.2%)
Related	1 (0.5%)	1 (0.5%)
Not Related	2 (1.1%)	3 (1.6%)
上腹部痛	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
急性腎障害	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
腺筋症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
アラニンアミノトランスフェラーゼ増加	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
血管浮腫	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
アスパラギン酸アミノトランスフェラーゼ増加	2 (1.1%)	3 (1.6%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	2 (1.1%)
血中ブドウ糖増加	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
乳癌	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
気管支炎	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
胸痛	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)
悪寒	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
慢性腎臓病	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
結膜炎	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
冠動脈疾患	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
食欲減退	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
労作性めまい	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
体位性めまい	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
小腸炎	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
紅斑	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)
眼瞼浮腫	2 (1.1%)	2 (1.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	0	0
鼓腸	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
痛風	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
Ｂ型肝炎	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
ほてり	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
高脂血症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
低ナトリウム血症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
低酸素症	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)
月経中間期出血	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
白血球増加症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
限局性感染	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
リンパ球減少症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
筋骨格系胸痛	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
筋骨格痛	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
眼充血	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
浮腫	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
食道炎	2 (1.1%)	2 (1.1%)
Related	1 (0.5%)	1 (0.5%)
Not Related	1 (0.5%)	1 (0.5%)
口腔咽頭痛	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
卵巣嚢胞	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
疼痛	2 (1.1%)	2 (1.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	0	0
パラインフルエンザウイルス感染	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
眼窩周囲浮腫	2 (1.1%)	2 (1.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	0	0

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
処置による疼痛	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
そう痒症	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
鼻炎	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
アレルギー性鼻炎	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
鼻漏	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
ＣＯＶＩＤ－１９の疑い	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
顔面腫脹	2 (1.1%)	2 (1.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	0	0
全身性強皮症	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)
血小板減少症	2 (1.1%)	3 (1.6%)
Related	0	0
Not Related	2 (1.1%)	3 (1.6%)
歯痛	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
トランスアミナーゼ上昇	2 (1.1%)	2 (1.1%)
Related	2 (1.1%)	2 (1.1%)
Not Related	0	0
腟出血	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
食道静脈瘤	2 (1.1%)	2 (1.1%)
Related	0	0
Not Related	2 (1.1%)	2 (1.1%)
腹部膨満	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
ざ瘡	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
急性副鼻腔炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
アレルギー性副鼻腔炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
節足動物刺傷アレルギー	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
脱毛症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
慢性疾患の貧血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
真菌性肛門感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
肛門出血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
不安	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
無力症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
喘息	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心房細動	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
細菌感染	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
基底細胞癌	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血中アルカリホスファターゼ増加	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
血中ビリルビン増加	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
血中クレアチニン増加	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
失血性貧血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血圧上昇	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血中尿酸異常	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血中尿酸増加	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
体温上昇	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
体部白癬	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
骨髄浮腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
徐脈	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
脳性ナトリウム利尿ペプチド増加	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
乳房腫瘤	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
気管支反応性亢進	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
気管支分泌物貯留	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
細菌性気管支炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
滑液包炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
カンジダ感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心雑音	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心血管障害	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
子宮頚部嚢胞	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
子宮頚管炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
慢性胃炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
慢性扁桃炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
冷汗	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
大腸炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
虚血性大腸炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
挫傷	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
肺性心	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
サイトメガロウイルス性脈絡網膜炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
脱水	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
接触皮膚炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
糖尿病	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
憩室炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
薬物性肝障害	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
皮膚乾燥	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
脂質異常症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
排尿困難	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
斑状出血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
子宮頚外反	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
子宮内膜増殖症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
子宮内膜症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
子宮内膜炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
上顎炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
過剰肉芽組織	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
労作性頭痛	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
眼刺激	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
眼痛	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
眼部腫脹	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
顔面浮腫	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
顔面麻痺	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
転倒	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
線維腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
足骨折	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
排便回数増加	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
胃障害	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
胃腸炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
クロストリジウム菌性胃腸炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
胃腸障害	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
消化管感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
全身性浮腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
陰部ヘルペス	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
歯肉炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
膜性糸球体腎炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
甲状腺腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
女性化乳房	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血液学的感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血尿	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
喀血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心拍数増加	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
不全片麻痺	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
肝硬変	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
脂肪肝	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
Ｂ型肝炎抗体異常	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
Ｃ型肝炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
帯状疱疹	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
裂孔ヘルニア	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ホルネル症候群	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
聴覚過敏	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
高血糖	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
高カリウム血症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
過角化	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
遠視	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
過敏症	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
脾機能亢進	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
高血圧	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
血液量増加症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
空腹時血中ブドウ糖不良	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
左室不全	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
嗜眠	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
靭帯断裂	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
靭帯捻挫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
四肢不快感	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
腰ヘルニア	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ループス腎炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
倦怠感	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
片頭痛	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
単球減少症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
口腔内潰瘍形成	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
卵巣粘液性嚢胞腺癌	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
筋力低下	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
筋骨格不快感	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
骨髄線維症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
鼻中隔弯曲	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
好中球数減少	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
正色素性貧血	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
黄疸眼	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
食道カンジダ症	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
爪甲剥離症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
起坐呼吸	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
骨軟骨炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
骨壊死	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
骨減少症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
骨粗鬆症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
中耳炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
耳管炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
卵巣嚢胞破裂	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
過量投与	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
酸素飽和度低下	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
顎痛	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
汎血球減少症	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
丘疹	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
骨盤癒着症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心嚢液貯留	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
歯冠周囲炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
末梢静脈疾患	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
咽頭腫脹	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
咽頭炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
細菌性咽頭炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
咽頭扁桃炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
足底筋膜炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
血小板数減少	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
細菌性肺炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
シュードモナス性肺炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ブドウ球菌性肺炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ウイルス性肺炎	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
気胸	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
頻発過多月経	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ポリープ	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
門脈圧亢進症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ヘルペス後神経痛	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
ワクチン接種後症候群	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
急性ＣＯＶＩＤ－１９後症候群	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
失神寸前の状態	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
湿性咳嗽	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
前立腺癌	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
蛋白尿	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
肺塞栓症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
肺静脈閉塞性疾患	1 (0.5%)	2 (1.1%)
Related	0	0
Not Related	1 (0.5%)	2 (1.1%)
放射線肺線維症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
丘疹性皮疹	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
気道感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ウイルス性気道感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
網膜出血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
網膜静脈閉塞	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
肋骨骨折	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
仙腸骨炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
卵管卵巣炎	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
洞結節機能不全	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
シェーグレン症候群	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
皮膚色素減少	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
皮膚病変	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
皮膚潰瘍	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
睡眠時無呼吸症候群	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
傾眠	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
硬膜下血腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
亜イレウス	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
上室性頻脈	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
腫脹	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
全身性エリテマトーデス	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
熱傷	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
口渇	1 (0.5%)	1 (0.5%)
Related	1 (0.5%)	1 (0.5%)
Not Related	0	0
咽喉刺激感	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
舌嚢胞	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
歯膿瘍	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
歯牙破折	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
気管の炎症	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
外傷性血腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
２型糖尿病	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
上部消化管出血	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
尿閉	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
子宮平滑筋腫	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
腟感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
静脈瘤	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
心室性不整脈	1 (0.5%)	0
Related	0	0
Not Related	1 (0.5%)	0
心室性期外収縮	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ウイルス感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ウイルス性上気道感染	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
視力障害	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
ビタミンD欠乏	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)
創傷	1 (0.5%)	1 (0.5%)
Related	0	0
Not Related	1 (0.5%)	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
関節炎	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
慢性呼吸不全	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
結腸異形成	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
結腸直腸腺腫	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
膀胱炎	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
耳感染	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
大腿骨骨折	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
血便排泄	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
上腕骨骨折	0	2 (1.1%)
Related	0	0
Not Related	0	2 (1.1%)
陥入爪	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
腸重積症	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
リンパ節症	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
リンパ球増加症	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
黄斑変性	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
多臓器機能不全症候群	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
食道狭窄	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
外耳炎	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
肺水腫	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
呼吸不全	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
洞停止	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)

	M/T FDC (Total)	
	SCS cut-off	D120 cut-off
変形性脊椎症	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
回転性めまい	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
頭位性回転性めまい	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)
外陰腟真菌感染	0	1 (0.5%)
Related	0	0
Not Related	0	1 (0.5%)

[TSFAEOL11.RTF] [JNJ-68150420/AC-077A301/DBR_D120SU/RE_D120SU/PROD/TSFAEOL11.SAS] 08JUN2023, 11:54