25 July 2024
EMA/CHMP/332056/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

YUVANCI

International non-proprietary name: Macitentan / Tadalafil

Procedure No. EMEA/H/C/005001/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

6MWD	6-minute walk distance
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the European Pharmacopeia
CI	Confidence interval
CL	Confidence limit
Cmax	Maximum concentration
COVID-19	Coronavirus disease 2019
CYP3A4	Cytochrome P450 isoenzyme 3A4
DB	Double blind
DDI	Drug-drug interaction
EDBT	End of double-blind treatment
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
ET	Endothelin
EU	European
FC	Functional class
FDA	Food and Drug Administration
FDC	Fixed dose combination
FOIA	Freedom of Information Act
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard ratio
HCL	Hydrochloric acid
HPLC	High performance liquid chromatography
IA	Interim analysis
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IR	Infrared
LDPE	Low density polyethylene
M/M	Morbidity/mortality
MO	Major Objection
MS	Mass Spectrometry
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
M/T FDC	Macitentan/tadalafil fixed dose combination
M+T	Macitentan+tadalafil
NMR	Nuclear Magnetic Resonance
NO	Nitric oxide
NT-proBNP	N-terminal pro b-type natriuretic peptide
OL	Open label
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	PAH Symptoms and Impact
PDE-5i	Phosphodiesterase 5 inhibitor
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QTPP	Quality target product profile

RAPm	Right atrial pressure
RCT	Randomized clinical trial
RH	Relative Humidity
RHC	Right heart catheterization
rpm	Revolutions per minute
SAE	Serious adverse event
SCS	Summary of clinical safety
SmPC	Summary of Product Characteristics
SOC	Standard of care
SOR	Specific Optical Rotation
SPA	Special protocol assessment
SVI	Stroke volume index
SvO2	Mixed venous oxygen saturation
TSE	Transmissible Spongiform Encephalopathy
US	United States
UV	Ultraviolet
WHO	World Health Organization
WU	Wood unit
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen - Cilag International N.V. submitted on 22 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for YUVANCI, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2018.

The applicant applied for the following indication:

> *Long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III who are:*
>
> • *treatment-naïve to any PAH specific therapy;*
>
> • *on treatment with macitentan or tadalafil;*
>
> • *already treated with the combination of macitentan and tadalafil as separate tablets.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0243/2016 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 September 2014	EMEA/H/SA/2835/1/2014/II	Peter Mol, Angeles Alonso
28 January 2016	EMEA/H/SA/2835/1/FU/1/2015/II	Marleen Laloup, Peter Mol
28 February 2019	EMEA/H/SA/2835/1/FU/2/2018/II	Peter Mol, Mogens Westergaard
22 April 2022	EMA/SA/0000074632	Peter Mol, Clemens Mittmann, Audrey Sultana

The Scientific advice pertained to the following quality and clinical aspects:

- Adequacy of the proposed data package to demonstrate bioequivalence (BE) between the macitentan/tadalafil 10/40 mg FDC and the individual components authorised in the EU taken concomitantly in support of a substitution indication.
- Acceptability of the Phase 3 randomised clinical trial (RCT) adaptive study design with pulmonary vascular resistance (PVR) as primary endpoint (A DUE study), including suitability of patient population; acceptability of statistical analysis and safety evaluation; and adequacy of the safety database to support a substitution indication.
- Adequacy of the proposed data package (A DUE study and supportive evidence from Real-World Evidence (RWE)) to support a first line indication; adequacy of data sources, analysis and methodology to demonstrate safety and comparative effectiveness of tadalafil 40 mg o.d. and sildenafil 20 mg three times daily (t.i.d.) using Model Based Meta-Analysis (MBMA); and acceptability of Phase 3 study in terms of study design, primary endpoint and study population to support a first line indication.
- Sufficiency of the proposed data package and analysis plan to support an add-on indication for the use of M/T 10/40 mg FDC for the treatment of PAH patients already treated with either macitentan or tadalafil, including the supportive analyses 1 and 2, endpoints, and targeted population; and adequacy of the proposed data packages to support authorization of M/T 10/20 mg FDC as an uptitration dose for the treatment of PAH patients with M/T 10/40 mg FDC.
- Acceptability of the proposed macitentan and tadalafil dissolution methods for release and stability testing.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Alar Irs

The application was received by the EMA on	22 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 September 2023

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs preliminary Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 March 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs updated Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 April 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs preliminary Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 July 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to YUVANCI on	25 July 2024
The CHMP adopted a report on similarity of YUVANCI with Opsumit and Winrevair on (see Appendix on similarity)	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Although the pathogenesis of PAH is not completely understood, it likely involves an imbalance in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants that are probably consequences of pulmonary endothelial cell dysfunction and/or injury.

2.1.2. Epidemiology and risk factors, screening tools/prevention

The annual incidence of idiopathic pulmonary hypertension has been estimated within 1 or 2 cases per million individuals per year. The prevalence is well below the criteria as defined for orphan conditions. The median life expectancy from the time of the diagnosis in patients with idiopathic PAH (IPAH), before the availability of disease-specific (targeted) therapy, was 2.8 years through the mid-1980. PAH is a rare, progressive, life-threatening disease with a poor prognosis. Nowadays, PAH continues to be a progressive and fatal disease, with a life expectancy of only about 7–10 years, despite the availability of PAH-specific therapies [Benza 2012a; Fares 2016]. PAH continues to be a progressive and fatal disease, with 1-, 3- and 5-year survival rates of approximately 90%, 69% and 55%, respectively, despite the availability of PAH-specific therapies (Hoeper 2022, Zelt 2022).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

PAH is currently hemodynamically characterized by a resting mean pulmonary arterial pressure (mPAP) of at least 20 mmHg with normal pulmonary artery wedge pressure (PAWP; or left ventricular end-diastolic pressure [LVEDP]) of 15 mmHg or less, and a PVR greater than 2 Wood Units (WU). PAH is characterized by a progressive increase in pulmonary arterial pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death [Benza 2010, Kylhammar 2014, Tonelli 2013]. The complex pathogenesis of PAH involves dysfunction of 4 key pathways: the endothelin pathway, the nitric oxide pathway, the prostacyclin pathway and the activin/TGFβ pathway [Humbert 2023].

The current 2022 ESC/ERS guidelines [Humbert 2022] classify the numerous conditions that are known to lead to or be associated with the development of PAH into 6 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. Group 1, PAH, may occur in the absence of a demonstrable cause / associated etiology (idiopathic), in a familial setting (heritable), or as the result of the use of certain drugs or toxins; it can be associated with a connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis. The groups 'PAH with features of venous/capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis [PVOD/PCH]) involvement' and 'persistent PH of the newborn (PPHN)' are also included in group 1 (PAH).

Variables associated with poor survival includes, among others, a NYHA/WHO Functional Class (FC) III or IV and the presence of Raynaud's phenomenon. Patients with a NYHA/WHO Class I or II have a median survival of 59 months (approximately 5 years), while patients with a NYHA/WHO Class III have a median survival of 32 months (2.6 years), and patients with a NYHA/WHO Class IV have a median survival of 6 months. For

Primary Pulmonary Hypertension (PPH), the US National Institute of Health (NIH) registry showed survival rates for untreated patients of 68%, 48%, and 34% after 1, 3, and 5 years from diagnosis, respectively. Although advances in therapies and patient management have improved these rates, there is still no known cure for PPH or other forms of PAH.

Symptoms of PAH include dyspnoea (most commonly), fatigue, chest pain or discomfort, dizziness, syncope, near syncope, oedema, leg oedema, and palpitations. When the disease is advanced, the clinical manifestations include cyanosis, dyspnoea on exertion, haemoptysis, atypical chest pain or angina pectoris, syncope, heart failure, arrhythmias and cerebrovascular accidents.

2.1.4. Management

In the European Union (EU), multiple medicinal products have gained approval for PAH treatment. These compounds predominantly focus on pathways that either directly or indirectly enhance blood flow through the pulmonary vasculature,. The main pathways targeted by these drugs are the prostacyclin pathway, the endothelin-1 pathway, the nitric oxide pathway and the activin/TGFβ pathway. The intent behind these drugs, whether administered as monotherapy or in combination, is to ameliorate vascular tone by addressing the underlying dysregulated processes that lead to pulmonary vasoconstriction.

Endothelin-1 (ET-1), another hormone with vasoactive properties produced by endothelial cells, functions as a vasoconstrictor. In the context of PAH, dysregulated ET-1 production contributes to heightened pulmonary vascular resistance. ET-1 engages cell surface receptors known as Endothelin-A (ETA) and Endothelin-B (ETB), expressed on vascular smooth muscle cells (VSMCs) and endothelial cells respectively. Blocking these endothelin receptors has demonstrated the ability to counteract the vasoconstrictive effects of ET-1. Several approved drugs, including bosentan, ambrisentan, and macitentan, fall into the category of endothelin receptor antagonists (ERAs) and function by inhibiting one or both of these receptors. Clinical studies have attested to their capacity to decrease pulmonary vascular resistance and enhance exercise capacity. However, the use of ERAs has been associated with hepatotoxicity, even leading to the withdrawal of one such drug.

Phosphodiesterase type-5 inhibitors (PDE-5i) represent a third class of compounds extensively used in PAH treatment. Proper functioning of vascular smooth muscle cells (VSMCs) to maintain vascular tone relies on adequate levels of cyclic guanosine monophosphate (cGMP) and nitric oxide (NO). PDE5, highly expressed in the VSMCs of pulmonary vasculature and upregulated in PAH, contributes to cGMP breakdown, resulting in vasoconstriction. PDE5 inhibitors, such as sildenafil and tadalafil, intervene by preventing the degradation of cGMP, thereby maintaining its levels and promoting vasodilation.

Riociguat, distinct from PDE5 inhibitors, operates as a stimulator of soluble guanylate cyclase. This enzyme is responsible for converting guanosine triphosphate (GTP) into cGMP. Clinical trials involving riociguat and PDE5 inhibitors have evidenced improvements in disease symptoms and exercise tolerance.

Prostacyclins, potent vasodilatory hormones primarily released by endothelial cells, have played a pivotal role in the development of targeted PAH therapy. Epoprostenol, the initial therapy of this kind, is typically reserved for class III and IV patients due to its continuous intravenous infusion requirement, necessitating a permanent catheter. While newer-generation prostacyclins, such as treprostinil, offer improved physiochemical properties, they too demand continuous infusion, meticulous dose titration, and safety monitoring. Notably, inhaled and oral prostacyclins have mitigated some challenges associated with continuous infusion. Selexipag, an oral prostacyclin receptor agonist, has emerged as a recent option, exhibiting the ability to slow PAH disease progression when added to existing treatments.

Sotatercept is a human recombinant fusion protein targeting the Activin/TGF-β pathway. It acts as a ligand trap that scavenges excess Activin A, which is increased in PAH patients, to inhibit activin signalling thereby modulating vascular cell proliferation, decreasing pulmonary vascular resistance and improving haemodynamics.

Recent PAH treatment guidelines advocate a risk-adapted approach for managing most patients, highlighting the importance of combination drug therapy.

2.2. About the product

YUVANCI is a fixed dose combination of macitentan and tadalafil. Two dosage strengths were developed; a film-coated tablets containing macitentan 10 mg and tadalafil 40 mg (macitentan/tadalafil 10/40 mg film-coated tablet) and a film-coated tablets containing macitentan 10 mg and tadalafil 20 mg (macitentan/tadalafil 10/20 mg film-coated tablet).

Macitentan is an orally active, non-peptide, potent dual ETA and ETB receptor antagonist. Macitentan (OPSUMIT; macitentan 10-mg film-coated tablets, once daily) was granted a marketing authorization for the treatment of patients with PAH in the US, EEA, and other countries. Tadalafil is a selective PDE-5 inhibitor approved in the US, EEA, and other countries under the brand name ADCIRCA (20-mg film-coated tablets) for the treatment of PAH at a dosage of 40 mg once daily.

Macitentan is an orally active, potent dual ETA and ETB receptor antagonist, or ERA that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity to and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favouring penetration into lung tissue (Iglarz 2008).

Tadalafil is a potent and selective PDE-5 inhibitor, the enzyme responsible for the degradation of cGMP. PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Adherence to prescribed therapy has an impact on clinical outcomes and there is strong evidence that reducing the pill/tablet count and frequency has a major impact on patient adherence to therapies in general and to PAH therapies in particular (Thom 2013). One way to simplify treatment is to use FDC products that combine multiple treatments into a single tablet. While combination treatment is common, FDC pills or tablets that combine 2 or more PAH-specific therapies are not available, thereby requiring patients to take multiple pills/tablets daily.

2.3. Type of Application and aspects on development

The macitentan/tadalafil (M/T) 10/40 mg FDC clinical development program aligns with prior and current ESC/ERS guidelines which recommend combination therapy targeting multiple pathways, specifically initial combination therapy with macitentan and tadalafil for patients with idiopathic, heritable, or drug associated PAH without cardiopulmonary comorbidities (Galiè 2015a, Humbert 2022).

The clinical development program was discussed with the EMA as part of several CHMP scientific advices (SA). The individual components of M/T 10/40 mg FDC, macitentan (ERA, tradename OPSUMIT) and tadalafil (PDE-5i, tradename ADCIRCA), have been approved and used independently or concomitantly in the clinical setting to effectively manage PAH for nearly 10 years. Macitentan is approved for use as monotherapy or in combination for the long-term treatment of PAH in adult patients of WHO FC II to III (OPSUMIT SmPC). Both treatments are suitable for once-daily oral dosage with no PK interactions. The safety profiles of macitentan and tadalafil are well documented and acceptable in patients with PAH, including treatment-naïve patients, patients already on macitentan or tadalafil, and as a substitution for patients already on the loose combination of any ERAs and PDE-5is.

Phase 1 trials have been conducted to establish the bioequivalence of the single tablet M/T FDC (10/40 mg or 10/20 mg) with the loose combination of macitentan (10 mg) and tadalafil (40 mg [2×20mg] or 20 mg).

The primary source of efficacy and safety of the M/T 10/40 mg FDC is the pivotal Phase 3 AC-077A301 (A DUE) study. The study enrolled participants with PAH who were treatment-naïve to any PAH-specific therapy or previously treated with any ERA or PDE-5i monotherapy. Participants were randomized to either M/T 10/40 mg FDC or a monotherapy group (in a 2:1:1 fashion for naïve, and 2:1 fashion for prior ERA and prior PDE-5i therapies) whereby both naïve and previously treated participants contributed to the primary endpoint comparing M/T 10/40 mg FDC to each monotherapy. A DUE was an adaptive design, and a pre-planned IA was performed and implemented through the IDMC after 100 participants had been treated for 16 weeks. This was to allow for early termination of the study for futility, or efficacy or unblinded sample size adaptation (increase or decrease) based on the primary efficacy endpoint. For A DUE, comparing combination therapy versus each monotherapy, change from baseline to end of DB treatment (EDBT) in PVR (as measured by RHC) was chosen as the primary endpoint due to its association with disease severity and correlation with mortality (Benza 2012). In addition to its diagnostic (Hoeper 2013) and prognostic value, PVR as determined by RHC is needed to obtain an objective judgment on the hemodynamic response to treatment and to guide disease management (Tiede 2013, Galiè 2015a). The DB treatment period was planned for 16 weeks, as a study duration of 16 weeks has been demonstrated to be sufficient to observe improvement in hemodynamics as measured by RHC in studies of ERAs and PDE-5is individually (Ghofrani 2017, Galiè 2009). However, in multiple SAs it has been stated that PVR is not acceptable as a primary endpoint for registration of a FDC in add-on and first-line indications.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets in two strengths containing either 10 mg of macitentan and 20 mg of tadalafil, or 10 mg of macitentan and 40 mg of tadalafil.

Other ingredients are:

Tablet cores: hydroxypropylcellulose, low-substituted hydroxypropylcellulose (E463a), lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460i), polysorbate 80 (E433), povidone (E1201), sodium starch glycolate, sodium lauryl sulfate.

Film coating – 10 mg / 20 mg strength: hypromellose, iron oxide red (E172), iron oxide yellow (E172), lactose monohydrate, talc (E553b), titanium dioxide (E171), triacetin (E1518).

Film coating – 10 mg / 40 mg strength: hypromellose, lactose monohydrate, talc (E553b), titanium dioxide (E171), triacetin (E1518).

The product is available in aluminium perforated unit-dose blisters with integrated desiccant as described in section 6.5 of the SmPC.

2.4.2. Active Substance – tadalafil

The finished product contains two active substances; macitentan and tadalafil. For the active substance tadalafil the Certificate of Suitability of the European Pharmacopoeia (CEP) procedure is used, while for macitentan the full information was provided in the application. The information provided for macitentan is the same as approved for another centrally authorised product from the same applicant, Opsumit film-coated tablets, with the exception that in this procedure one less manufacturing site for micronisation of this active substance is proposed.

2.4.2.1. General information

The chemical name of tadalafil is (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione corresponding to the molecular formula $C_{22}H_{19}N_3O_4$. It has a relative molecular mass of 389.404 g/mol and the following structure:

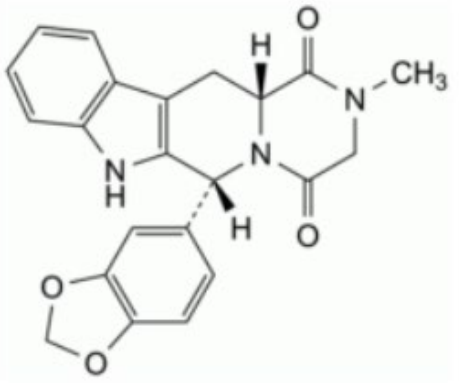


Figure 1: active substance structure - tadalafil

The active substance is a white or almost white powder, it is practically insoluble in water.

Tadalafil exhibits stereoisomerism due to the presence of 1 chiral centre. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been reported for tadalafil and various crystalline (anhydrous and solvated) forms as well as amorphous forms are reported, the applicant has justified that the polymorphic form of tadalafil produced (form A) is thermodynamically stable. In line with the manufacturing consistency and stability of the polymorphic form no specification for this is included in the active substance specification.

There is a monograph of tadalafil in the European Pharmacopoeia, the manufacturer of the active substance has been granted a CEP for the active substance which has been provided within the current Marketing Authorisation Application.

2.4.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP.

2.4.2.3. Specification

The active substance specification shown in Table 1 includes tests for: appearance, solubility, identity (IR, HPLC, SOR), impurities (HPLC), related substances (HPLC), LOD (Ph. Eur.), sulphated ash (Ph. Eur.), assay (HPLC), residual solvents (GC), particle size (laser light diffraction).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and particle size control.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for five commercial scale batches of the active substance were provided. The results are within specification and consistent from batch to batch.

2.4.2.4. Stability

The relevant information has been assessed by the EDQM before issuing the CEP. The retest period is in line with the relevant CEP.

2.4.3. Active Substance – macitentan

2.4.3.1. General information

The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide corresponding to the molecular formula $C_{19}H_{20}Br_2N_6O_4S$. It has a relative molecular mass of 588.27 g/mol and the following structure:

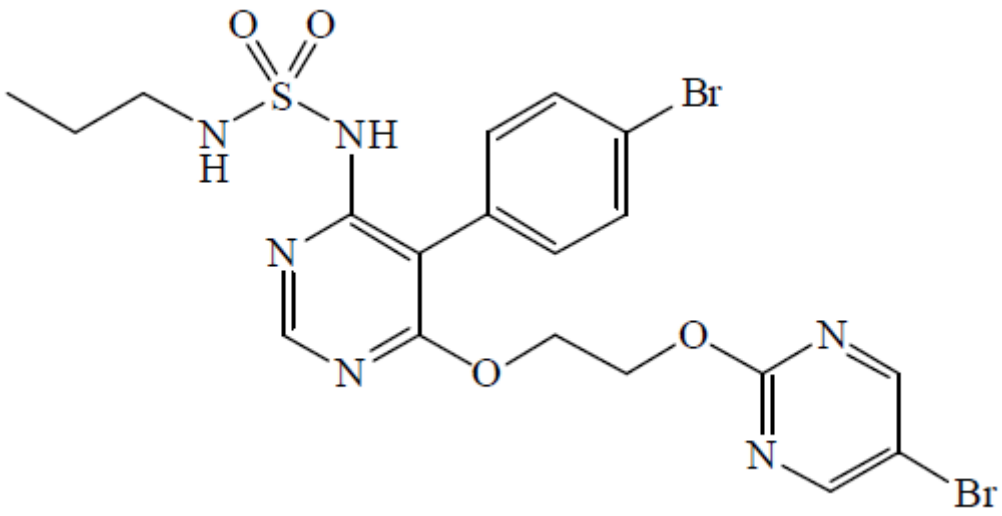


Figure 2: active substance structure - macitentan

The chemical structure of macitentan was elucidated by a combination of elemental analysis, IR ^{1}H-NMR, ^{13}C-NMR, MS, UV. The solid state properties of the active substance were measured by XRPD.

The active substance is a white to off-white solid powder, it is practically insoluble in water across the physiological pH range. Macitentan has a non-chiral molecular structure.

Polymorphism has been observed for macitentan, ten polymorphic forms have been reported and investigated, some of which only form as a result of solvent systems not relevant for the crystallisation performed in this manufacturing process. The applicant has justified that the polymorphic form manufactured (form A) is thermodynamically stable. In line with the consistency and stability of the polymorphic form no specification for this parameter is included in the active substance specification.

2.4.3.2. Manufacture, characterisation and process controls

Macitentan is manufactured at one manufacturing site, and is synthesised in three main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in two LDPE bags which comply with Commission Regulation (EU) 10/2011, as amended.

2.4.3.3. Specification

The active substance specification includes tests for: appearance (visual), colour (visual), colour & clarity of solution (Ph. Eur), identity (IR, HPLC), sulphated ash (Ph. Eur.), water content (KF), residual solvents (GC), impurities (HPLC), assay (HPLC), particle size (laser light diffraction), microbiological quality (Ph. Eur).

The limits for impurities are set in line with ICH Q3A requirements and no impurities are present at greater than the relevant qualification threshold.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from four commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

2.4.3.4. Stability

Stability data from six commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market under long term conditions (30 ºC / 65% RH) and under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions of increased heat, increased heat and moisture, light exposure in the solid phase & in solution, exposure to oxidising conditions, and in an aqueous buffer were also provided on one batch.

The following parameters were tested*:* appearance (visual), colour (visual), colour & clarity of solution (Ph. Eur), water content (KF), impurities (HPLC), assay (HPLC), particle size (laser light diffraction), microbiological quality (Ph. Eur).

All tested parameters were within the specifications, and no significant trends are observed in the long term or accelerated stability data.

In the forced degradation studies macitentan was shown to be a generally stable substance. Under the high temperature along with the high temperature and moisture conditions no significant degradation was observed. In aqueous buffers some hydrolysis can be observed at lower pH values. Degradation was observed under strong oxidizing conditions, but the active substance is stable under mild oxidative conditions. The active substance is stable to light in the solid phase, but susceptible to degradation by light when present in solution.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.4.4. Finished Medicinal Product

2.4.4.1. Description of the product and pharmaceutical development

The finished product is formulated as film-coated tablets of two strengths, each tablet contains 10 mg of macitentan and 20 mg of tadalafil, or 10 mg of macitentan and 40 mg of tadalafil.

The 10 mg/20 mg strength is pink, oblong, 13 mm × 6 mm film-coated tablets debossed with "1020" on one side and "MT" on the other side.

The 10 mg/40 mg strength is white to almost white, oblong, 15 mm × 7 mm film-coated tablets debossed with "1040" on one side and "MT" on the other side.

The aim of the proposed product development was to combine macitentan and tadalafil in an oral immediate release film-coated tablet that is bioequivalent to the administration of both single active substance formulations combined i.e. OPSUMIT: 10 mg (macitentan) and Adcirca: 20 mg (tadalafil). A quality target profile (QTTP) for the commercial tablet formulation was defined according to ICH Q8. As part of this QTTP the 10/20 mg and 10/40 mg proposed product should have an oblong shape to avoid swallowing issues and a sufficiently low level of impurities and microbial bioburden. In addition, a shelf-life minimum of 24 months when packaged in the proposed commercial packaging and stored at room temperature was proposed as part of the QTTP.

Both active substances possess low aqueous solubility and high intestinal permeability, and would therefore be considered BCS class II. The active substances are micronised to a specific particle size distribution which

is suitably defined in the specifications for the relevant active substances. Potential polymorphism has been reported for both active substances and the applicant has shown that the polymorphic form of each of the active substances is consistently produced and thermodynamically stable. Considering this aspect, and the stability data provided concerning the polymorphic forms, it was determined that it was not necessary to include the polymorphic form in the specifications of the active substances.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The development began with the higher 10/40 mg strength. This strength when produced at the proposed commercial manufacturing site was shown to be suitably bioequivalent. The knowledge gained was then also applied for the 10 mg/20 mg strength which used the same formulation and granulation approach. This formulation was also shown to be suitably bioequivalent when produced at the proposed commercial manufacturing site. For detailed information on the bioequivalence testing performed, please refer to the clinical sections of the report. Comparative dissolution results in 0.1M HCl, buffer pH 4.5 and buffer pH 6.8 showed similar dissolution profiles between the fixed dose combination product and the single agent tablets.

The manufacturing process was selected and developed in conjunction with the relevant formulation development. This process is accomplished by granulation, and relevant manufacturing process parameters were identified in line with the development performed.

The discriminatory power of the dissolution methods proposed has been demonstrated. The methods in place were shown to be discriminatory with respect to aspects such as particle size of the active substance, granulation process parameters, storage conditions, and tablet hardness.

The primary packaging is an aluminium perforated unit-dose blister with integrated desiccant. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.4.2. Manufacture of the product and process controls

The process is considered to be a standard manufacturing process, and is conducted at one manufacturing site.

As the process is standard, the applicant has presented a process validation scheme outlining the prospective validation studies to be conducted. The validation scheme is acceptable and the intended in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.4.3. Product specification

The finished product release specifications shown in Table 4 include appropriate tests for this kind of dosage form appearance (visual), dimensions (caliper), identification (UV, HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), water content (KF), nitrosamine impurity (LC-MS), microbiological purity (Ph. Eur.).

In the finished product one specified impurity exceeds the relevant qualification threshold as described by

ICH Q3B. The limit at shelf life for this impurity is however suitably qualified by the provided toxicological data. The limits for other impurities are set below the relevant ICH Q3B identification threshold.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The initial risk assessment for potential nitrosamine impurities presented by the applicant was not considered acceptable. Not all suspected and known root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) had been taken into account and a risk for the potential formation of N-nitroso-tadalafil was noted. A major objection (MO) requesting testing of this potential nitrosamine which would originate from the presence of one of the active substances was requested along with an updated risk assessment for these impurities. In response to this the applicant outlined a position that the acceptable intake for this impurity should be higher than the 18 ng/day intake described in published guidance, and provided a toxicological justification for a proposed 1500 ng/day acceptable intake. The applicant provided data showing that this 1500 ng/day limit would not be exceeded, however this proposed acceptable intake could not be sufficiently supported by the toxicological data provided. As the 1500 ng/day limit could not be accepted, and the applicant had not yet demonstrated the applicable 18 ng/day limit would not be exceeded the MO was maintained. To resolve this major objection, the applicant provided confirmatory testing data showing that the 18 ng/day limit would not be exceeded, this was conducted on nine batches of each strength which included recently manufactured batches and aged batches from stability studies. The results from this demonstrated the 18 ng/day acceptable intake for this potential nitrosamine impurity would not be exceeded and there is no indication that the levels increase on product storage. The applicant included limits for this impurity in the specifications for the finished product that ensure the acceptable intake of 18 ng/day will not be exceeded. The MO was therefore considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for nine commercial scale batches of the 10/20 mg strength and eleven commercial scale batches of the 10/40 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.4.4. Stability of the product

Stability data from three commercial scale batches of finished product for each strength and stored for up to 12 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (visual), assay (HPLC), degradation products (HPLC), dissolution (HPLC), water content (KF), and microbiological purity (Ph. Eur.). The analytical procedures used are stability indicating. No significant changes or trends were observed at long term or accelerated conditions.

In addition, one commercial scale batch of the 10/40 mg strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No instability to light is observed and the results are also considered representative for the 10/20 mg strength. The finished products should be protected from moisture exposure. .

With respect to ongoing stability studies in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 24 months and store in original package in order to protect from moisture as stated in the SmPC are acceptable.

2.4.4.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.5. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure one MO concerning quality aspects was raised, concerning the nitrosamines impurity assessment and the need to account for the potential formation of the impurity N-nitroso-tadalafil. To resolve this MO the applicant provided confirmatory testing data that demonstrated the relevant acceptable intake for this would not be exceeded, the applicant also included a limit for this impurity in the specifications of the finished product.

2.4.6. Conclusions on the chemical and pharmaceutical aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

To support the marketing authorisation application for YUVANCI according to Article 10(b) of Directive 2001/83/EC, the Applicant provided two *in vivo* pharmacology studies with co-administration of macitentan and tadalafil. Furthermore, the Applicant submitted a non-clinical overview for the M/T FDC, justifying the absence of specific data on the combination by referencing to information on the single agents. This approach is acceptable.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

To demonstrate the antihypertensive effect of co-administration of macitentan and tadalafil, several *in vivo* studies were performed in animals models of systemic and pulmonary hypertension.

In the first study (B-13.105), telemetered conscious female Dahl salt-sensitive (DSS) rats (n=6/group) received a single oral administration of either 0, 0.3, 1, 3 and 10 mg/kg macitentan or 0, 0.3, 3 and 10 mg/kg tadalafil. Systolic, mean and diastolic arterial pressures and heart rate (HR) were monitored for up to 96 hours. The blood pressure lowering effect of the treatment was expressed as the ABC (area between curves for blood pressure versus time). A dose-dependent decrease in mean arterial pressure (MAP) and ABC was observed in animals receiving ≥ 0.3 mg/kg macitentan. After 72 hours, the MAP returned to control levels. Similarly, administration of tadalafil resulted in a dose-dependent decrease in MAP and ABC in animals dosed with ≥ 1 mg/kg, although to a lesser extent compared to macitentan. After 24 hours, the MAP returned to control levels. No effect on HR was observed after treatment with either macitentan or tadalafil.

In a subsequent experiment, telemetered conscious female DSS rats (n=6/group) were given a single oral administration of the maximal effective tested dose of tadalafil (10 mg/kg), a dose of macitentan showing a similar MAP decrease (0.3 mg/kg), or the combination of 0.3 mg/kg macitentan + 10 mg/kg tadalafil and monitored for up to 72 hours. Animals receiving either macitentan or tadalafil demonstrated decreased MAP and ABC. Co-administration of macitentan and tadalafil demonstrated a slight synergistic effect on ABC and an additive effect on MAP reduction. To confirm the synergistic effects observed in female DSS rats, this experiment was repeated in telemetered conscious male spontaneously hypertensive rats (n=10-11/group), and similar results were obtained. In conclusion, synergistic hemodynamic effects of the macitentan and tadalafil combination were obtained in animal models of systemic hypertension.

To demonstrate that the synergism observed in hypertensive rats could also apply to pulmonary hypertension, a second study was performed (Study B-16.0.26). Firstly, conscious telemetered male Wistar rats (n=4-11/group) with hypoxia/Sugen-induced pulmonary hypertension (PH) received a single oral administration of either 0, 0.1, 0.3, 1, 3, 10 and 30 mg/kg macitentan or 0, 0.3, 1, 3, 10 and 30 mg/kg tadalafil. Systolic, mean and diastolic arterial pulmonary and systemic pressures and heart rate (HR) were monitored for up to 72 hours. The blood pressure lowering effect of the treatment was expressed as the ABC. A dose-dependent decrease in mean pulmonary arterial pressure (MPAP) and ABC was observed in animals receiving ≥ 0.3 mg/kg macitentan. In the highest tested dose, the MPAP returned to control levels after 48 hours. MAP did not change following macitentan treatment, but a decrease in HR was observed at the highest tested dose of 30 mg/kg macitentan. Administration of tadalafil resulted in a dose-dependent decrease in MPAP and ABC in animals dosed with ≥ 1 mg/kg and a decrease in MAP in animals dosed with ≥ 3 mg/kg. After 24 hours, the MAP/MPAP returned to control levels. HR did not change following tadalafil treatment.

In two subsequent experiments (primary and confirmatory), conscious telemetered male Wistar rats (n=5-7/group) with hypoxia/Sugen-induced PH were given a single oral administration of the maximal effective dose of tadalafil (9 mg/kg), a dose of macitentan showing a similar MPAP decrease (3 mg/kg), or the combination of 3 mg/kg macitentan + 9 mg/kg tadalafil and monitored for up to 72 hours. Co-administration of macitentan and tadalafil demonstrated an additive effect on MPAP reduction, and a slight synergistic effect on ABC. In conclusion, the combination of macitentan and tadalafil provided improved benefit on pulmonary haemodynamics in animal model of pulmonary hypertension.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted with macitentan and tadalafil in combination. To justify the absence of these data, the Applicant provided information on the single agents.

Macitentan
Only one secondary pharmacodynamics study was provided showing that macitentan did not bind to a panel of 63 receptors and enzymes. No unexpected risks have been identified in animal or clinical studies. Therefore further non-clinical studies on additional pharmacological targets are not deemed necessary.

Tadalafil
The Applicant provided literature data describing the selectivity of tadalafil. In combination with the long clinical experience of tadalafil, this is considered sufficient.

2.5.2.3. Safety pharmacology programme

No safety pharmacology studies were conducted with macitentan and tadalafil in combination. To justify the absence of these data, the Applicant provided information on the single agents.

Macitentan
Potential safety pharmacology effects were evaluated on central nervous system, respiratory function and the cardiovascular system. The only observation was a decrease in arterial blood pressure in dogs at all tested doses. This effect was not observed in healthy rats, but more importantly also not in humans.

Tadalafil
The Applicant provided literature data describing several safety pharmacology parameters. In combination with the long clinical experience of tadalafil, this is considered sufficient, and revealed no special hazard for humans.

2.5.2.4. Pharmacodynamic drug interactions

N/A

2.5.3. Pharmacokinetics

No non-clinical pharmacokinetic studies evaluating macitentan and tadalafil in combination were conducted. To justify the absence of these data, the Applicant provided information on the single agents.

Absorption

Macitentan
In vitro data showed that macitentan permeates rapidly through membranes and is not a substrate of human

P-gp. Macitentan was absorbed slowly after oral dosing in the rat, whereas peak plasma concentrations were reached 2 h post-dose in dog. Oral bioavailability was about 80% in the dog and about 30% in the rat, which increased to 89% at higher doses. After IV administration, macitentan showed a low plasma clearance in rat and dog. The volume of distribution was 1-2 L/kg in rats and about 1 L/kg in dogs, which indicates reasonable distribution into tissues. Exposure to macitentan increased dose-proportionally following IV administration in rat and dog and after oral administration in dog.

Following oral administration in rat, exposure increased more than proportionally between 1 and 30 mg/kg. This non-proportional behaviour may be caused by saturation of metabolic clearance. Non-linearity was not observed in humans and therefore this finding seems of limited relevance.

Particle size had a significant effect on macitentan exposure indicating drug dissolution in the gastrointestinal tract as a limiting factor for oral absorption. Macitentan has an active circulating metabolite, ACT-132577, which has comparable pharmacokinetic properties as macitentan. Only systemic plasma clearance was lower than macitentan, resulting in a longer half-life. Following repeated doses, the exposure to macitentan and the metabolite ACT-132577 increased less than dose-proportionally in mice, rats and dogs. There was no plasma accumulation of macitentan or ACT-132577 observed. In contrast, a decrease in the systemic exposure of macitentan and ACT-132577 was observed in rat and dog. This effect can be explained by auto-induction of macitentan metabolism in rat and dog, while auto-induction in mouse was not exhibited. Autoinduction is not expected in humans.

Tadalafil
The Applicant provided literature data describing absorption after oral administration in mice, rats and dogs, in which the extent of absorption varied with dose. These findings are similar in humans.

Distribution

Macitentan
Binding to plasma proteins is high in all species examined for macitentan (>99%), and for the metabolites ACT-132577 (98.3-99.9%) and ACT-373898 (91.0-98.5%). Partitioning of either macitentan or ACT-132577 into red blood cells was limited in any of the species investigated. Drug-related radioactivity distributed into most tissues within 2 hours after oral administration. Highest tissue concentrations were measured in liver, kidney, plasma, blood and lung. Macitentan-related radioactivity also distributed into the brain, although to a limited extent (tissue-plasma ratio: 0.02-0.06). After 7 days, drug-related radioactivity was still observed in half of the tissues examined, suggesting some accumulation in these organs when using macitentan daily.

Tadalafil
The Applicant did not provide adequate non-clinical data on the distribution of tadalafil. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

Metabolism

Macitentan
Extensive *in vitro* metabolism was observed resulting in one major metabolite ACT-132577 retaining pharmacological activity. No human specific metabolites were observed *in vitro*. In both the pre-clinical species (rat and dog) and humans macitentan is extensively metabolised before excretion. The Applicant investigated the biotransformation pattern in plasma, urine, and faeces of rat, dog and humans and in bile of rat and dog. Data from the excreta indicate that the biotransformation pattern could be different between the non-clinical species and humans. However, as macitentan and its two circulating metabolites ACT-132577 and ACT-373898 were present in rat and dog in comparable or higher absolute amounts than in humans, they are adequately covered in the animal toxicity program.

Tadalafil
The Applicant did not provide adequate non-clinical data on the metabolism of tadalafil. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

Excretion

Macitentan
The predominant route of elimination of drug-related radioactivity was via feces in rats and dogs (67-81%) independent of the route of administration. The recovery of the majority of the dose in feces suggests biliary elimination as the major route of excretion. [14C]Macitentan-derived material was excreted in milk of rats. Concentrations of radioactivity in milk were below the plasma concentrations until 48 hours post-dose. However, 96 hours post-dose the milk-plasma ratio was 2.0.

Tadalafil
The Applicant did not provide adequate non-clinical data on the excretion of tadalafil. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

Pharmacokinetic drug interactions

Macitentan
The interactions of macitentan and its major human metabolite ACT-132577 with a panel of drug transporters (P-gp, OATPB1, OATPB3, OCT1, OCT2, OAT1, OAT3, BSEP, NCTP, MATE-1 and MATE-2) have been studied in order to investigate potential drug-drug interactions. Macitentan (but not ACT-132577) could be an inhibitor of drug transporter BCRP at clinically relevant intestinal concentrations. Macitentan and its metabolites ACT-080803 (M3) and ACT-132577 (M6) are not inducers of CYP3A4 at clinically relevant concentrations.

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields the pharmacologically active metabolite ACT-132577. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99%) with minor contributions of CYP2C8, CYP2C9 and CYP2C19. Other metabolic pathways yield products without pharmacological activity. Several members of the CYP2C family, namely CYP2C8, CYP2C9 and CYP2C19, as well as CYP3A4, are involved in the formation of these metabolites.

Potentially drugs that are inhibitors of CYP3A4 could have an effect on the metabolism of macitentan and thus could lead to drug-drug interactions. Multiple clinical studies were performed regarding potential drug-drug interactions with other drugs (warfarin, sildenafil, ketoconazole, rifampicin, and cyclosporin). No clinically relevant interactions were observed for macitentan and its active metabolite M6 with drugs that are inhibitors of CYP3A4. However, concomitant treatment with rifampicin, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite. Reduced efficacy of macitentan in the presence of a potent inducer of CYP3A4 such as rifampicin should be considered.

Tadalafil
The Applicant provided limited non-clinical data on the potential pharmacokinetic drug interactions of tadalafil. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

2.5.4. Toxicology

No non-clinical toxicology studies evaluating macitentan and tadalafil in combination were conducted. To justify the absence of these data, the Applicant provided information on the single agents.

2.5.4.1. Single dose toxicity

Macitentan
Single doses of up to 2000 mg/kg by oral gavage in mouse and rat indicate that macitentan has low potential for acute toxicity. Mice showed transient overt symptoms including ptosis and/or slightly subdued behaviour during the first hour after administration, whereas rats showed no remarkable findings.

Tadalafil
The Applicant provided no non-clinical single dose toxicity data. This is acceptable, since there is sufficient clinical data and experience with tadalafil to assess acute toxicity.

2.5.4.2. Repeat dose toxicity

Macitentan

Repeat-dose toxicity studies with macitentan were performed by oral administration for time intervals up to 13 weeks in mice, 26 weeks in rats, and up to 39 weeks in dogs. The pharmacodynamic target and the major pathways of macitentan metabolism in humans were all represented in these species. Safety margins or exposure margins were calculated based on combined exposure to macitentan and the pharmacologically active metabolite ACT-132577 in males and females. Male rats wereless exposed to the drug after treatment with the same doses than females.

Macitentan was well tolerated from chronic treatment up to relatively high dose levels. Drug-related mortality was observed in the 13-week toxicity study in male Wistar rats after 2 weeks of treatment at 1500 mg/kg/day. Prolonged clotting times led to excessive bleeding and mortality. In the 4-week dog toxicity study at 500 mg/kg/day, one dog died due to drug-related anorexia. The mortality rate increased in the carcinogenicity studies at 400 mg/kg/day in female mice and at 250 mg/kg/day in female rats after approximately 1 year of treatment. A cause of death could not be established.

Overt symptoms were limited to the high doses and included occasional breathing difficulties, piloerection, coldness, unsteady gait and subdued behaviour in mice, hunched posture, prostrate position, laboured respiration, coldness of limbs; haemorrhages in rats, and decreased food consumption, reduced activity; subdued behaviour; and a rise in body temperature in dogs.

In the mouse, rat, and dog toxicity studies, the heart, liver, and testes were identified as the main organs affected by treatment with macitentan. Minor or secondary changes were observed in RBC, the haemostatic system, thyroid, kidney, uterus, ovary and nasal cavity. Arterial intimal thickening characterized by proliferation of the intimal layer was found in dogs treated with macitentan at doses ≥30 mg/kg/day, independently of the treatment duration. The right and, less often, the left coronary arteries were the preferred target. These findings were often associated with breaks of the internal elastic lamina. After subacute (4-week) treatment with doses higher than 50 mg/kg/day, atrial fibrosis with chronic inflammation, epicarditis, and neovascularization were also observed. Thus, the cardiac NOEL was established at 5 mg/kg/day in all three studies, providing an acceptable safety margin (>5.8) to maximal human exposure at 10 mg/day.

Public literature suggests that the observed coronary arteriopathy is a class effect of endothelin receptor antagonists in dogs. *In vivo* studies described in the pharmacology section show that macitentan decreases arterial blood pressure in dogs in a dose-dependent manner. As result of exaggerated pharmacology on ETA receptors (inhibition of vasoconstriction), marked hypotension, sustained vasodilatation in the coronary vascular bed and reflex tachycardia may alter flow dynamics and lead to increased shear stress and tension on the coronary wall with subsequent microscopic trauma. Although the effect of macitentan on the heart rate is limited in dogs, provided literature suggests that the dog is a species particularly sensitive to hemodynamic changes and related coronary vascular and myocardial effects. Coronary and myocardial

lesions were not observed in rats or mice. Clinically, data regarding MACE and ECG do not raise any concerns regarding the long term cardiovascular safety of macitentan.

The effects on the liver included increased weight and centrilobular hypertrophy. These findings are considered to be an adaptation to the increased metabolic demand and enzyme induction by macitentan. The increased incidence of hepatodiaphragmatic herniation observed only after 104 weeks of treatment in rats was considered to be related to the induced life-long liver hypertrophy.

In mice, focal hepatocellular necrosis and increased plasma levels of the liver enzymes (AST, ALT) were observed in dose-range finding studies of 2- and 13-weeks' duration performed for the mouse carcinogenicity study. These findings were associated with bile duct proliferation and gall bladder hyperplasia, accumulation of pigmented macrophages and granulocytic infiltration. The necrotic foci and the associated inflammatory reaction in the liver were in some cases accompanied by increased polymorphonuclear leukocyte counts in lymph nodes and increased granulopoiesis in the bone marrow. A dose-range finding study in B6C3F1-mice revealed that CD-1 are more susceptible to hepatocellular necrosis than B6C3F1 mice. The slightly decreased concentrations of albumin, cholesterol, bilirubin and/or urea and increased concentrations of triglyceride in plasma further point to a slightly decreased liver function.

In vitro cytotoxicity studies in mouse and human liver slices did not measure mitochondrial toxicity and only found cytotoxicity at concentrations far above the *in vivo* concentration at clinical therapeutic dose in humans. Thus, the liver toxicity found in the repeated dose studies can be explained by indirect mechanisms and therefore does not provide specific evidence for mitochondrial toxicity.

Bosentan but not ambrisentan inhibited human hepatic transporters, which have been discussed as a potential mechanism for the increased hepatotoxicity observed for this agent in humans. However, macitentan and metabolite M6 are not expected to interfere with hepatic and bile salt transport.

Drug-related effects on the male reproductive system were identified in rats and dogs. The alterations found included dilation of seminiferous tubules, tubular degeneration and hypospermatogenesis. The NOAELs for dilation of seminiferous tubules in rats were 50 mg/kg/day (8.2 fold the exposure in patients treated with 10 mg/day of macitentan) in the 13- week toxicity study, 250 mg/kg/day (11.6 fold the exposure in patients treated with 10 mg/day of macitentan) in 26-week rat toxicity studies and it was not determined, but it is lower than 10 mg/kg/day (4.2 fold the exposure in patients treated with 10 mg/day of macitentan) in the 104- weeks carcinogenicity study. These findings suggest that the testicular risk increases after chronic treatment. In the 39-week dog toxicity study, the NOEL was established at 5 mg/kg/day (5.8 fold the exposure in patients treated with 10 mg/day of macitentan). Seminology showed an increased percentage of morphologically abnormal sperm at 50 and 250 mg/kg/day, only in the 26-week rat study (NOEL was 10 mg/kg/day, 2.3 fold the exposure in patients). It is difficult to assess the clinical relevance of hypospermatogenesis and tubular degeneration because individual cases have been reported in different rats and dogs studies, including animals from control groups. The chronic treatment also induced an increase in the prostate weight at 250 mg/kg/day (NOEL was 50 mg/kg/day, 8.2 fold the exposure in patients treated with 10 mg/day of macitentan) in rats. Adverse effects induced by macitentan in rat male reproductive organs were reversible.

Haematological alterations as decreased haematocrit, RBC count and haemoglobin and increased WBC and platelet were observed in different mice, rat and dog toxicity studies. The changes were minimal, found at doses that indicate acceptable safety margins for humans (8.2 in rats, 5.8 in male dogs and 17 in female dogs) and reversible.

A prolonged aPTT was observed in male rats treated with 250 mg/kg/day during 13 or 26 weeks. The finding is considered to have limited relevance to humans as it was observed only at high dose levels that provide safety margins higher than 7, in only one species and only in males.

The observed increased thyroid weight, possibly a reflection of follicular cell hypertrophy, seems to be a secondary effect of drug-metabolizing enzyme induction in the liver. A similar effect has also been reported

with bosentan, which is also an inducer of P450 enzymes. A benign follicular cell adenoma was recorded for the thyroid of one male rat and a cystic follicular hyperplasia for one female rat treated with high doses of macitentan. Although both these findings can be seen as a spontaneous background change, an association with the treatment-related follicular cell hypertrophy cannot be excluded. A treatment-related altered thyroid function (mild thyroid hormone imbalance in male rats) has been reported for bosentan, but not for ambrisentan. Thus far, there is no evidence of bosentan affecting thyroid function (thyroxin, TSH) in humans.

The kidney was also affected by macitentan in Wistar rats. Treatment longer than 13 weeks at ≥50 mg/kg/day induced an increase in male kidney weights Treatment during 26 weeks increased the incidence of hyaline/pigment droplets in males at ≥ 50 mg/kg/day and in females at 250 mg/kg/day. The alterations were reversible and the NOEL for kidney damage was established at 10 mg/kg/day (2.3 fold the exposure in patients treated with 10 mg/day of macitentan).

An increased incidence of endometrial cysts in the uterus, associated with increased uterus weights, was observed in the mouse carcinogenicity study at ≥100 mg/kg/day providing a safety margin of 46, and in the rat carcinogenicity study at all doses tested. However, uterine cysts in senescent rats are considered of limited clinical relevance because the mechanism leading to this finding may be due to specific rat hormonal changes induced by macitentan.

Additionally, angiomatous change in the rat ovaries was found at the highest dose (250/50 mg/kg/day) tested. The NOAEL for the ovary effects was established at 50/25 mg/kg/day, 13.4 fold the exposure level in humans treated with 10 mg of macitentan.

Finally, proliferation of nasal mucosa and increased incidence of inflammatory infiltration were seen in nasal cavities in mouse carcinogenicity study at all dose levels. Hyaline inclusions and increased secretion were found at doses ≥ 30 mg/kg/day. Similar effects on the nasal cavity have also been observed in animals treated other ERAs. However, nonclinical data macitentan do not indicate a higher risk with macitentan than with ambrisentan, bosentan or sitaxentan, based on the number of affected species, the time of onset and severity of nasal cavity findings.

Tadalafil
The Applicant provided limited non-clinical repeat dose toxicity data of tadalafil. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

Several publications reported effects on the testis, epididymis and sperm parameters in albino rats after tadalafil treatment. Clinical data in different patient populations indicated no adverse impact of tadalafil on sperm quality or reproductive hormones, however a potential effect on human fertility cannot be excluded. This is adequately reflected in the SmPC.

2.5.4.3. Genotoxicity

Macitentan
The genotoxic potential of macitentan was evaluated using a conventional battery of tests: genetic mutation in bacteria and in L5178Y mouse lymphoma cells, chromosomal aberration in human lymphocytes and rat micronucleus in vivo. All *in vitro* and *in vivo* tests were performed according to the ICH requirements (CHMP/ICH/126642/08. Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human use (ICH S 2 (R1)) and resulted negative. Thus, it can be concluded that macitentan is not genotoxic.

The metabolite of macitentan ACT-373898 (M5) is not mutagenic.

Tadalafil
The original study reports for genotoxicity studies for the initial MAA of tadalafil (Cialis) were provided.

Tadalafil can be considered as non-mutagenic as a result of the battery of *in vivo* and *in vitro* assays carried out.

2.5.4.4. Carcinogenicity

Macitentan
No oncogenic potential was evident in mice or rats after 104 weeks of treatment with macitentan at doses that provide a safety margin for carcinogenicity ≥ 20.

Tadalafil
The original study reports for carcinogenicity studies for the initial MAA of tadalafil (Cialis) were provided. Tadalafil was tested in rats and mice when administered up to 400 mg/kg/day for 24 months, corresponding to AUCs for total (bound and unbound) tadalafil of 1.4- to 2.1-fold (female and male mice, respectively) and 5.3- to 10.3-fold (male and female rats, respectively) the AUCs in men dosed at 40 mg. Liver tumours were reported in male mice and rats in the carcinogenicity studies. While there was an apparent minor numerical increase in the number of hepatocellular neoplasms in male rats treated with the high dose of tadalafil, this difference was not statistically significant, and is likely to represent an incidental variation. Tadalafil caused hepatocellular microsomal enzyme induction in both mice and rats, and it is possible that this could lead to an increased incidence of hepatocellular neoplasms. However, even if this mechanism were operable in the mice and rats, hepatic microsomal enzyme induction is a common non-genotoxic biologic effect associated with hepatocellular tumour formation in rodents and is not considered relevant to human cancer risk.

2.5.4.5. Reproductive and developmental toxicity

Macitentan
The NOEL for male and female fertility and early embryonic development in rats was 250 mg/kg/day. However, the observed effects of macitentan on testes (tubular dilatation, tubular atrophy and hypospermatogenesis) during long-term treatment could affect the reproduction. Testes were also target organs of macitentan in the offspring (F1) of females treated during pregnancy and lactation and in juvenile treated animals. In both studies, the fertility was also affected. Additionally, testicular toxicity has not been adequately assessed in clinical trials. Thus, effects of macitentan on male human fertility cannot be excluded.

Macitentan showed clear dose-dependent teratogenic effects in rats and rabbits. In both species there were cardiovascular and mandibular arch fusion abnormalities. The observed effects are class effects of ET receptor antagonists. A NOEL for embryo-foetal development was not established. In line with other ERAs, a pregnancy contraindication is included in the SmPC.

Pharmacokinetic studies in rats have shown that macitentan is excreted into milk. Therefore, macitentan, like other ERAs, is also contraindicated during breast-feeding.

Tadalafil
No adequate non-clinical reproductive and developmental toxicity data was provided by the Applicant. However, as macitentan is teratogenic in rats and rabbits, the lack of data with tadalafil is considered covered with the contraindications which are in place for macitentan (pregnancy; breastfeeding; and women of childbearing potential who are not using reliable contraception). The absence of adequate non-clinical reproductive and developmental toxicity data on tadalafil is therefore acceptable.

2.5.4.6. Toxicokinetic data

N/A

2.5.4.7. Local Tolerance

N/A

2.5.4.8. Other toxicity studies

Macitentan
In an *in vitro* system using Balb/c 3T3 fibroblast cell cultures, macitentan exhibited weak phototoxicity at high concentrations. An *in vivo* study in hairless rats showed no phototoxic effects up to the high dose level of 60 mg/kg/day corresponding 24-fold the human exposure at 10 mg per day. It can be concluded that there is no relevant risk of phototoxicity for patients treated with macitentan at 10 mg per day.

Tadalafil
No adequate non-clinical phototoxicity data was provided by the Applicant. However, since there is sufficient clinical data and experience with tadalafil, this is acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

The doses of macitentan and tadalafil in the proposed FDC tablet are identical to the recommended doses in currently approved single agent products for the treatment of PAH. Since the FDC is not to be administered at higher dosage levels, or for different indications, significant increase in environmental exposure is not anticipated.

2.5.6. Discussion on non-clinical aspects

To support the marketing authorisation application for YUVANCI according to Article 10(b) of Directive 2001/83/EC, the Applicant provided two *in vivo* pharmacology studies with co-administration of macitentan and tadalafil. Furthermore, the Applicant submitted a non-clinical overview for the M/T FDC, justifying the absence of specific data on the combination by referencing to information on the single agents. This approach is acceptable.

Pharmacology
To demonstrate the antihypertensive effect of co-administration of macitentan and tadalafil, several *in vivo* studies were performed in animals models of systemic and pulmonary hypertension. In short, synergistic hemodynamic effects of the macitentan and tadalafil combination were obtained in animal models of systemic hypertension. Additionally, the combination of macitentan and tadalafil provided improved benefit on pulmonary haemodynamics in an animal model of pulmonary hypertension. Together with the long-term clinical experience with co-administration of macitentan and tadalafil, these primary pharmacology studies support the proposed clinical indication.

No secondary pharmacology or safety pharmacology studies were conducted with macitentan and tadalafil in combination. To justify the absence of these data, the Applicant provided information on the single agents. This is acceptable.

Pharmacokinetics
No non-clinical pharmacokinetic studies evaluating macitentan and tadalafil in combination were conducted. To justify the absence of these data, the Applicant provided information on the single agents. This is acceptable. Although limited adequate non-clinical literature data on the pharmacokinetic properties on tadalafil was provided, this can be considered covered with the sufficient clinical data and experience.

In general, it can be agreed that macitentan and tadalafil are not expected to show a pharmacokinetic interaction with one another, and the individual profiles are adequately described in the SmPC.

Toxicology

No non-clinical toxicology studies evaluating macitentan and tadalafil in combination were conducted. To justify the absence of these data, the Applicant provided information on the single agents. This is acceptable. The Applicant did not provide sufficient adequate data on potential reproductive and developmental toxicity of tadalafil. However, as macitentan is teratogenic in rats and rabbits, the lack of data with tadalafil is considered covered with the contraindications which are in place for macitentan (pregnancy; breastfeeding; and women of childbearing potential who are not using reliable contraception). The absence of adequate non-clinical reproductive and developmental toxicity data on tadalafil is therefore acceptable. A review of the animal toxicity profiles of macitentan and tadalafil revealed that testicular toxicity was observed with both drugs. Both macitentan and tadalafil can have an adverse effect on fertility in men and this is adequately reflected in the SmPC.

2.5.7. Conclusion on the non-clinical aspects

The current dossier is sufficient from a non-clinical viewpoint.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

To support the pharmacokinetics, 5 bioavailability/bioequivalence studies were carried out. In these studies, the 10/40 mg FDC (macitentan/tadalafil) was compared to the individual mono products Opsumit (macitentan 10 mg tablet) and Adcirca (tadalafil 20 mg tablet; dosed at 2 x 20 mg) obtained from the US market (study AC-077-101), the Canadian market (study 67896062PAH1006) and European market (study AC-077-103). Furthermore, the 10/20 mg FDC was compared to the individual mono products Opsumit and Adcirca obtained from the EU market (studies 67896062PAH1001 and 67896062PAH1002). Considering this is an EU application, the studies with the EU mono products are considered pivotal.

Additionally, the effect of food on the 10/40 mg FDC has been studied in study 67896062PAH1006, and on the 10/20 mg FDC in study 67896062PAH1002.

Analytical methods

For the analysis of macitentan, its metabolite ACT-132577, and tadalafil fully validated analytical methods have been applied. The methods appeared to be accurate and precise. In addition, stability data showed that the analytes were stable under sampling handling conditions. Moreover, for study samples, reproducibility was shown by the use of incurred sample reanalysis. Storage conditions were appropriate.

It is unclear whether the clinical and analytical sites responsible for the pivotal bioequivalence/ food effect studies have been inspected or audited by competent authorities. On request these data has been submitted and no concerns were identified regarding inspection.

Bioavailability/bioequivalence

In study AC-077-101, two 10/40 mg FDCs, i.e., FDC-01 and FDC-02, were compared to the individual mono product Opsumit 10 mg tablet and the US mono product Adcirca 20 mg tablet (dosed as 2 x 20 mg). The study had a randomised, 3-period, crossover study design and the formulations were administered under fasting conditions. For formulation FDC-01, bioequivalence could be shown for C_{max} and AUC_{0-t}, while for tadalafil only bioequivalence could be shown for AUC.

Based upon the results of study AC-077-101, FDC-02 was used for further development and used in all other studies, including the pivotal clinical studies. The FDC-02 formulation is similar to the commercial formulation.

In study 67896062PAH1006, the 10/40 mg FDC was compared to the individual mono product Opsumit 10 mg tablet and the Canadian mono product Adcirca 20 mg tablet (dosed as 2 x 20 mg). The study had a randomised, 2-period, crossover study design and the formulations were administered under fasting conditions. Bioequivalence could be shown for AUC_{0-t} and C_{max} for macitentan and tadalafil.

The pivotal bioequivalence study AC-077-103 was a single-dose, two-treatment, 2-way crossover bioequivalence study under fasting conditions. Thirty-eight healthy subjects, 16 males and 22 females, aged 19 - 55 years, were dosed in this study. Subjects received a single dose of the 10/40 mg FDC or a single dose of the combination of the mono product Opsumit 10 mg and the EU mono product Adcirca 20 mg (dosed as 2 x 20 mg tablets). Each dose of study drug was administered orally with approximately 240 ml of water under fasting conditions. The wash-out period was at least 7 days.

Based on the pharmacokinetic parameters of macitentan and tadalafil, the 10/40 mg Macitentan/Tadalafil FDC and the individual mono Opsumit 10 mg and Adcirca 20 mg (dosed as 2 x 20 mg tablets) are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

The bioequivalence study 67896062PAH1001 was a single-dose, two-treatment, 2-way crossover bioequivalence study under fasting conditions. Eighteen healthy subjects, 7 males and 11 females, aged 27 - 51 years, were dosed in this study. Subjects received a single dose of the 10/20 mg FDC or a single dose of the combination of the mono product Opsumit 10 mg and the EU mono product Adcirca 20 mg. Each dose of study drug was administered orally with approximately 240 ml of water under fasting conditions. The wash-out period was at least 16 days.

Based on the pharmacokinetic parameters of macitentan and tadalafil, the 10/20 mg Macitentan/Tadalafil FDC and the individual mono products Opsumit 10 mg and Adcirca 20 mg are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Comparable results were obtained in the pivotal study 67896062PAH1002, which was a single-dose, 3-treatment, 3-way crossover bioequivalence study under fasting conditions (fasting for the bioequivalence part of the study). In this study an additional arm was included to evaluate the effect of food. Forty healthy subjects, 24 males and 16 females, aged 18 - 53 years, were dosed in this study. Subjects received a single dose of the 10/20 mg FDC or a single dose of the combination of the EU mono product Opsumit 10 mg and the EU mono product Adcirca 20 mg. Each dose of study drug was administered orally with approximately 240 ml of water under fasting conditions. The wash-out period was at least 12 days.

Based on the pharmacokinetic parameters of macitentan and tadalafil, the 10/20 mg Macitentan/Tadalafil FDC and the individual mono products Opsumit 10 mg and Adcirca 20 mg are considered bioequivalent with

respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

Food effect

In study 67896062PAH1006, for the 10/40 mg FDC, intake of a high fat, high caloric meal had no impact on macitentan AUC, while C_{max} increased 16%. For the metabolite ACT-132577, no effect was observed for AUC, while C_{max} increased 7%. Furthermore, food increased tadalafil AUC and C_{max} by 11 and 45%, respectively. These differences are considered not clinically relevant. In study 67896062PAH1002, for the 10/20 mg FDC, intake of a high fat, high caloric meal had no impact of macitentan AUC, while C_{max} increased 16%. For the metabolite ACT-132577, AUC and C_{max}. increased 7 and 13%, respectively. Furthermore, food increased tadalafil AUC and C_{max} by 10 and 11%, respectively. These differences are not considered clinically relevant.

The SmPC recommends to take the tablets with or without food, which is agreed.

Special populations

Pharmacokinetic data have only been obtained in healthy volunteers. However, the data are considered extrapolatable to the target population, based on the posology of the individual compounds.

The safety and efficacy of Yuvanci in children and adolescents below 18 years have not been studied. No data are available.

Interactions

No new interaction studies have been carried out.

Both macitentan and tadalafil are cleared by hepatic metabolism, mainly catalyzed by the CYP P450 isozyme 3A4 (CYP3A4) enzyme. Neither macitentan nor tadalafil inhibit or induce CYP3A4 at clinically relevant concentrations. Furthermore, no transporter-based interaction is expected between macitentan and tadalafil. Consequently, macitentan and tadalafil are not expected to show a pharmacokinetic interaction with one another, as demonstrated by their respective clinical drug-drug interaction profiles.

2.6.2.2. Pharmacodynamics

No clinical pharmacodynamic studies were performed for the M/T 10/40 mg FDC. No transporter-based interaction is expected between macitentan and tadalafil. Consequently, macitentan and tadalafil are not expected to show an interaction with one another, as demonstrated by their respective clinical DDI profiles. No clinical drug interaction studies were conducted with M/T 10/40 mg FDC.

Mechanism of action

Macitentan is an orally active, potent dual ETA and ETB ERA that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity to and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favouring penetration into lung tissue (Iglarz 2008).

Tadalafil is a potent and selective PDE-5 inhibitor, the enzyme responsible for the degradation of cGMP. PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations

of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Primary and Secondary pharmacology

The primary and secondary pharmacology of the individual components, macitentan and tadalafil is well known and no additional primary pharmacology studies have been performed for the fixed dose combination.

The following pharmacodynamic interactions were proposed for the SmPC of M/T FDC:

Nitrates

In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, administration of Yuvanci to patients who are using any form of organic nitrate is contraindicated (see section 4.3 of the SmPC).

Riociguat

Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3 of the SmPC).

Anti-hypertensives (including Calcium channel blockers)

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4 of the SmPC). In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. In clinical pharmacology studies, the potential for tadalafil (10 and 20 mg) to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied either as monotherapy or as part of combination therapy. In patients taking multiple antihypertensive medicinal products whose hypertension was not well controlled, greater reductions in blood pressure were observed compared to patients whose blood pressure was well controlled, where the reduction was minimal and similar to that in healthy subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of doxazosin) is, in general, minor and not likely to be clinically relevant.

Alcohol

Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40% alcohol [vodka] in an 80 kg male), but in some subjects, postural dizziness and orthostatic hypotension were observed. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Theophylline

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) a small (3.5 bpm) increase in heart rate was observed.

2.6.3. Discussion on clinical pharmacology

Based on the pharmacokinetic parameters of macitentan and tadalafil, the 10/20 mg and 10/40 mg Macitentan/Tadalafil FDC and the individual mono products Opsumit 10 mg and Adcirca 20 mg (for the 10/40 mg FDC dosed as 2 x 20 mg tablets) are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

No clinically relevant food effect is observed for the Macitentan/Tadalafil FDC tablets.

No clinical pharmacodynamic studies were performed for the M/T 10/40 mg FDC. The primary and secondary pharmacology of the individual components, macitentan and tadalafil, is known and the Applicant did not perform additional pharmacology studies for the fixed drug combination, which is acceptable.

Macitentan is an orally active, potent dual ETA and ETB ERA that prevents the binding of ET-1 to its receptors. Macitentan displays high affinity to and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells and has physicochemical properties favouring penetration into lung tissue.

Tadalafil is a potent and selective PDE-5 inhibitor, the enzyme responsible for the degradation of cGMP. PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

The leading European guideline on pulmonary hypertension, the European Society of Cardiology (ESC) and European Respiratory Society (ERS) guideline for the diagnosis and treatment of pulmonary hypertension (PH), recommends combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i) in patients at low or intermediate risk of mortality at one year (mostly based on World Health Organization functional class [WHO FC]) at diagnosis. A combination of 2 effective treatments acting on the most frequently targeted pathways could provide synergistic treatment benefits to patients with PAH.

2.6.4. Conclusions on clinical pharmacology

No clinical pharmacodynamic studies were performed for the M/T 10/40 mg FDC. The primary and secondary pharmacology of the individual components, macitentan and tadalafil, is known and the Applicant did not perform additional pharmacology studies for the fixed drug combination, which is acceptable.

2.6.5. Clinical efficacy

Introduction

The primary source of efficacy and safety of the M/T 10/40 and M/T 10/20 mg FDC (for titration) mg FDC is the pivotal Phase 3 AC-077A301 (A DUE) study. Furthermore, the open label extension of this study is used as supportive data. The A DUE study is used to support the following proposed indication:

"Yuvanci is indicated as substitution therapy for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets."

Table 5: Overview of the pivotal clinical efficacy study

Study Name/ID	No of centers/ locations	Study status	Design/ Duration	Study Interventions	Objectives	Selection criteria	Main endpoints
ADUE/ AC-077A301 EudraCT 2014-004786-25 DB period	76 centers/ Asia, Africa, Europe, North America, South America	Completed Start Date: 15 October 2019 DB DBL: 10 October 2022 Participants enrolled: planned: 170 Actual: 187 FAS: 186 (M: 35; T: 44; M/T FDC: 107) 99 treatment-naïve participants randomized 2:1:1 to M/T FDC, macitentan, or tadalafil 32 participants on ERA monotherapy randomized 2:1 to M/T FDC or macitentan 56 participants on PDE-5i monotherapy randomized 2:1 to M/T FDC or tadalafil Sex Female 145 (M: 29; T: 34; M/T FDC: 82) Male 41 (M: 6; T: 10; M/T FDC: 25) Age range: 18 to 80 years	Randomized, 16-week, DB, triple-dummy Active monotherapy controls 2-week titration for participants not on a stable dose of PDE-5i	Macitentan 10 mg/ tadalafil 40 mg FDC od (For titration phase: Macitentan 10 mg/ tadalafil 20 mg loose combination Macitentan 10 mg/ tadalafil 40 mg loose combination) Macitentan 10 mg od Tadalafil 40 mg od	**Primary**: 1. To evaluate the effect of the M/T FDC vs macitentan 10 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with an ERA as monotherapy. 2. To evaluate the effect of the M/T FDC vs tadalafil 40 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with a PDE-5i as monotherapy. **Secondary**: To evaluate the effect of the M/T FDC compared to the respective monotherapies on: - Exercise capacity. - PAH symptoms in participants' cardiopulmonary and cardiovascular function - WHO FC. To evaluate the safety and tolerability of the M/T FDC in the participant population	Male or female, ≥18 y Confirmed diagnosis of symptomatic WHO Group 1 PAH, FC II or III	**Primary**: Change in PVR expressed as the ratio of geometric means of EDBT to BL. **Secondary**: Change from BL to EDBT in 6MWD. Change from BL to Week 16 in PAH-SYMPACT cardiopulmonary symptoms domain score. Change from BL to Week 16 in PAH-SYMPACT cardiovascular symptom domain score. Proportion of participants with absence of worsening in WHO FC from BL to EDBT. Other Efficacy: M/M events NT-proBNP.
ADUE/ AC-077A301 OL period	74 centers/ Asia, Africa, Europe, North America, South America	Ongoing OL cut-off: 31 December 2022 Participants enrolled in the OL period: 177 (by DB randomization: 35 DB-macitentan, 43 DB-tadalafil, 99 DB-M/T FDC). Analyzed for combined DB+OL	Median treatment duration of 59.86 (0.6, 151.6) weeks on M/T FDC (N=185) across the combined DB+OL period No active monotherapy	Macitentan 10 mg/ tadalafil 40 mg FDC od (For titration phase: Macitentan 10 mg/ tadalafil 20 mg loose combination	**Other**: To evaluate the long-term safety of the M/T FDC. To evaluate the long-term effect of the M/T FDC on: - Exercise capacity. - WHO FC. - Time to first M/M event. - Time to death due to PAH or PAH-related hospitalization.	Participants who completed the 16-week DB treatment	**Other**: Change from BL to EOLT in: - 6MWD - WHO FC . Time to first M/M event.
		M/T FDC period: 185 participants (by DB randomization: 35 DB-macitentan; 43 DB-tadalafil; 107 DB-M/T FDC) Sex Female 144 Male 41 Age range: 18 to 80 years	controls 2-week titration for participants not on a stable dose of PDE-5i	Macitentan 10 mg/ tadalafil 40 mg loose combination)	- Pharmacoeconomic measures. - Time to death (all causes).		Time to death due to PAH or hospitalization for PAH. Time to death (all causes).

2.6.5.1. Dose response study(ies)

No specific dose response studies were performed.

The proposed maintenance dose is one M/T 10/40 mg FDC tablet taken orally once daily. This proposed dose corresponds to the maintenance dose of the monotherapies, one macitentan 10mg tablet taken once daily, and two tadalafil 20 mg tablets taken once daily.

The proposed titration dose is one M/T 10/20 mg FDC tablet taken orally once daily for one week, with subsequent up-titration to the 10/40m mg FDC once daily. The proposed titration scheme depends on prior

use of tadalafil. The titration scheme is proposed for treatment naïve patients and on macitentan monotherapy. Patients with prior use tadalafil (thus for add-on or substitution indication) in the maintenance dose of 40mg per day can immediately use the maintenance dose, rather than titration dose.

The rationale for the titration step is based on improving tolerability. A strategy to improve tolerability is to initiate a therapy at a lower than recommended dose. In patients who cannot tolerate the upfront 40 mg dose of tadalafil, a starting dose of 20 mg tadalafil once daily is used for 1 to 2 weeks followed by an up-titration to the recommended 40 mg once daily dose (Adcirca SmPC, Burks 2018). An up-titration approach to combination therapy is supported by data from a number of studies. In the AMBITION trial, treatment with ambrisentan and tadalafil was initiated at 5 mg and 20 mg, respectively, followed by up-titration to 10 mg and 40 mg, respectively, over an 8-week period (Galiè 2015b). While the number of adverse events in the combination therapy arm increased, no differences were observed in the rates of discontinuations due to adverse events between the combination therapy arm (12%) and the pooled monotherapy arms (11%).

In the A DUE study, the double-blind treatment period consisted of a 2-week titration phase followed by a maintenance phase (Week 3 through Week 16). During the 2-week titration phase, depending on treatment arm, participants are treated with a loose combination of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos for Week 1, followed by a loose combination of macitentan 10 mg and/or tadalafil 40 mg and relevant placebos for Week 2. During the maintenance phase, depending on treatment arm, participants are treated with macitentan 10 mg or tadalafil 40 mg or M/T 10/40 mg FDC, and relevant placebos from Week 3 to Week 16. The open-label extension period of the ADUE study, during which all patients are receiving M/T 10/40 mg FDC, is ongoing.

2.6.5.2. Main study(ies)

Study AC-077A301 - A DUE

The main study is study AC-077A301, also known as and hereafter referred to as "A DUE". The A DUE study consists of a 16-week double-blind phase and an open-label extension phase. When referring to A DUE in this report, this refers to the 16-week double-blind phase.

A DUE is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with PAH, followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy.

The rationale of the study was to demonstrate that macitentan 10 mg and tadalafil 40 mg as a fixed dose combination (M/T FDC) is superior to 10 mg of macitentan alone, and to 40 mg of tadalafil alone, as measured by the ratio of end of double-blind treatment (EDBT) to baseline pulmonary vascular resistance (PVR). This study evaluated the efficacy at 16 weeks against each of these 2 approved PAH therapies given as monotherapy.

- ***Methods***

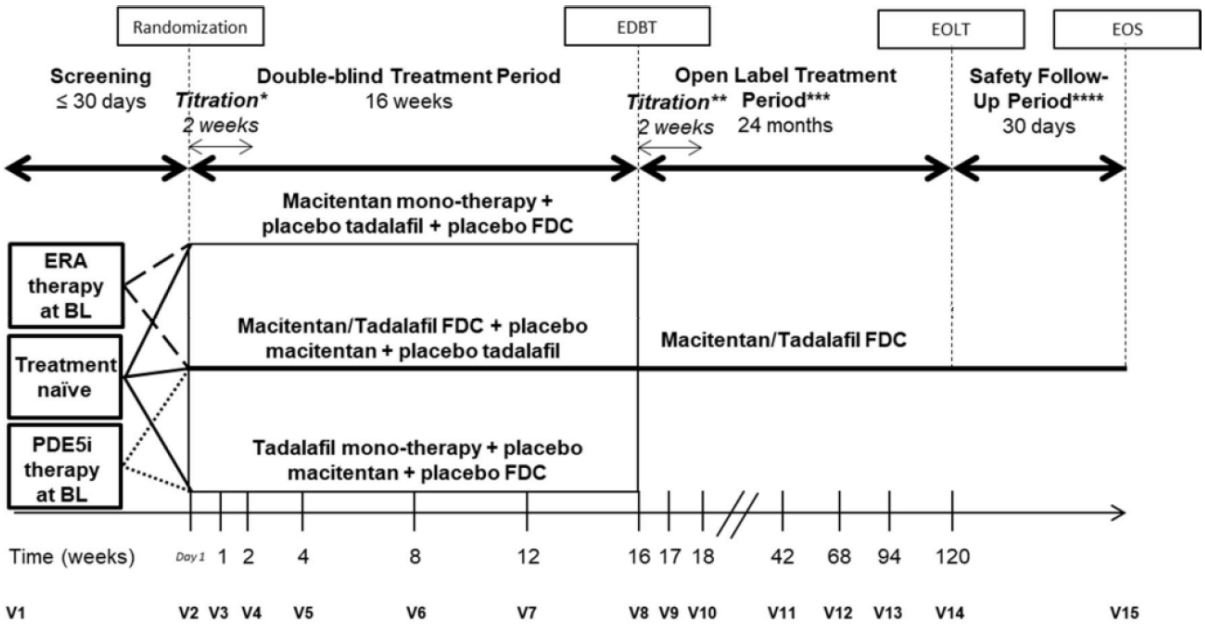
Study Participants

This study aimed to enrol male and female participants ≥18 years of age with RHC confirmed diagnosis of PAH (WHO Group 1). The study aimed to enrol approximately 50% participants who are PAH-specific treatment-naïve. Participants had to be in WHO FC II or III and be eligible for dual therapy with an ERA and a PDE-5i. Participants with concomitant significant pulmonary or cardiac conditions other than PAH were not eligible to enter the study.

This study was conducted at 76 centers that enrolled participants in Brazil, Bulgaria, Canada, China, Germany, Italy, Japan, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Taiwan, Turkey, and the United States.

An overall schematic of the study design is shown in the figure below.

Figure 3: Schematic study design



Inclusion criteria:

For inclusion in the study, all of the following inclusion criteria had to be fulfilled:

1. Signed and dated ICF.
2. Male and female participants ≥18 years old.
3. Confirmed diagnosis of symptomatic PAH in WHO FC II or III.
4. Symptomatic PAH belonging to one of the following subgroups of WHO Group 1 pulmonary hypertension [Simonneau 2013]:
    a. Idiopathic.
    b. Heritable.
    c. Drug- or toxin-induced.
    d. Associated with one of the following:
    e. Connective tissue disease.
    f. HIV infection.

g. Portal hypertension.

h. Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) with persistent pulmonary hypertension documented by an RHC ≥1 year after surgical repair.

5. PAH diagnosis confirmed by hemodynamic evaluation at rest (through central reading), evaluated within 5weeks prior to randomization.

    a. Mean pulmonary artery pressure (mPAP) ≥ 25mmHg, AND

    b. Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) 15mmHg, AND

    c. Pulmonary vascular resistance (PVR) ⩾ 3 WU (i.e., ⩾240 dyn·sec·cm−5).

6. Negative vasoreactivity test in idiopathic, heritable, and drug/toxin-induced PAH. (Patients for whom no vasoreactivity test was performed at diagnosis can be eligible if currently treated with PAH therapy for more than 3 months and PAH diagnosis confirmed by hemodynamic evaluation at least 3 months after introduction of their PAH therapy).

7. Currently receiving a stable dose of ERA or PDE-5i monotherapy for at least 3 months prior to baseline RHC, within the prespecified doses below or no history of PAH-specific treatment (defined as PAH–specific treatment is defined as prostanoids, prostacyclin-receptor agonists, guanylate cyclase stimulators, ERAs, or PDE-5is prescribed to treat PAH):

    a. Bosentan: 250 mg total daily dose

    b. Macitentan: 10 mg total daily dose

    c. Ambrisentan: 10 mg total daily dose

    d. Sildenafil: 60–120 mg total daily dose

    e. Tadalafil: 40 mg total daily dose

    f. Vardenafil: 10 mg total daily dose

8. Participant able to perform the 6MWT with a minimum distance of 100 m and maximum distance of 450 m at Screening.

9. A woman of childbearing potential is eligible only if the following applies:

    a. Negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization.

    b. Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.

    c. Agreement to follow the contraception scheme from Screening up to at least 30 days after study treatment discontinuation.

Main exclusion criteria:

Participants must not have met any of the following exclusion criteria:

1. Treatment with a soluble guanylate cyclase stimulator, L-arginine, any form of prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes) in the 3-month period prior to start of treatment.

2. Treatment with combination therapy of ERA and PDE-5i in the 3-month period prior to start of treatment or history of intolerance to ERA and PDE-5i combination therapy.

3. Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer (e.g., rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's Wort) in the 1month period prior to start of treatment.

4. Treatment with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or a moderate dual CYP3A4/CYP2C9 inhibitor (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors in the 1-month period prior to start of treatment.

5. Treatment with doxazosin.

6. Treatment with any form of organic nitrate, either regularly or intermittently.

7. Diuretic treatment initiated or dose changed within 1 week prior to the RHC or start of treatment.

8. Treatment with another investigational drug in the 3-month period prior to start of treatment.

9. Known presence of 3 or more of the following risk factors for heart failure with preserved ejection fraction at Screening:

    - BMI >30 kg/m2.

    - Diabetes mellitus of any type.

    - Essential hypertension (even if well controlled).

    - Coronary artery disease, i.e., any of the following:

        - History of stable angina, or

        - Known more than 50% stenosis in a coronary artery, or

        - History of myocardial infarction, or

        - History of or planned coronary artery bypass grafting and/or coronary artery stenting.

10. Known presence of moderate or severe obstructive lung disease (forced expiratory volume in 1 second [FEV1] / forced vital capacity [FVC] <70%; and FEV1 <65% of predicted after bronchodilator administration) any time prior to Screening.

11. Known presence of moderate or severe restrictive lung disease (total lung capacity or FVC <60% of normal predicted value) any time prior to Screening.

12. Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or congestive leftsided cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; or left ventricular outflow obstruction, in the opinion of the investigator.

13. Documented pulmonary veno-occlusive disease

14. Haemoglobin <100 g/L (<10 g/dL) at Screening.

15. Known severe hepatic impairment defined as a Model for End-Stage Liver Disease (MELD) score ≥19.7

16. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >1.5 x upper limit of normal (ULN) at Screening.

17. Severe renal impairment (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation [Levey 2009] calculated creatinine clearance <30 mL/min) at Screening.

18. Systemic hypotension (systolic blood pressure [SBP] <90 or diastolic blood pressure [DBP]<50 mmHg) at Screening or Randomization.

19. Systemic hypertension (SBP >160 or DBP >100 mmHg) at Screening.

20. Loss of vision in one or both eyes because of non-arteritic anterior ischemic optic neuropathy, regardless of whether or not this episode was in connection with previous PDE-5i treatment.

21. Hereditary degenerative retinal disorders, including retinitis pigmentosa

22. History of priapism, conditions that predispose to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia) or anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie' s disease).

23. Known concomitant life-threatening disease with a life expectancy <12 months.

24. Calcium channel blocker treatment initiated, or dose changed within 3 months prior to RHC at screening.

Treatments

Study treatments were M/T FDC, macitentan, tadalafil, and their respective matching placebos. M/T FDC was provided as film-coated tablets.

Treatment allocation was stratified by treatment status at baseline, i.e. treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy. Participants also received matching placebos for the 2 other study treatments to maintain the blind. Treatment allocation was as follows:

- treatment-naïve participants were randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil.
- participants on allowed ERA monotherapy were randomized in a 2:1 ratio to M/T FDC or macitentan.
- participants on allowed PDE-5i monotherapy were randomized in a 2:1 ratio to M/T FDC or tadalafil.

M/T FDC: The doses of macitentan (10 mg) and tadalafil (40 mg) selected for the M/T FDC are those recommended for each compound and correspond to the doses used for monotherapy. The matching placebo tablets did not contain any active substance but were otherwise identical in appearance to the active drug tablets.

Macitentan 10 mg: Macitentan 10 mg was provided as film-coated tablets debossed with '10' on both sides. The macitentan dose (10 mg) was the recommended dose and corresponds to the dose used as monotherapy and in combination with other PAH therapies, in the clinical setting. The matching placebo tablets did not contain any active substance but were otherwise identical in appearance to the trial product.

Tadalafil 20 mg: Tadalafil 20 mg was provided as over-encapsulated film-coated tablets. The dose of tadalafil (40 mg)was the recommended dose and corresponds to the dose used as monotherapy and in

combination with other PAH therapies, in the clinical setting. The matching placebo tablets did not contain any active substance but were otherwise identical in appearance to the trial product.

Study treatment administration: During the DB phase, study treatment was to be taken from the day of the Randomization visit (Day 1). Tablets were to be taken at the same time each day, preferably in the morning, including on days of study visits. The double-blind treatment period consisted of the titration phase (the first 2 weeks) and the maintenance phase (Week 3 through Week 16).

- **Titration phase:** Started on the day of randomization (Visit 2, Day 1) and lasted 2 weeks, ending on Day 14 (end of Week 2).
    - Week 1: Loose combination 10/20: Participants were treated with a loose combination of macitentan 10 mg and/or tadalafil 20 mg and corresponding placebos, depending on treatment arm, for 7 days from randomization (Visit 2, Day 1) to the end of Week 1 (Day 7).
    - Week 2: Loose combination 10/40 Up-titration: Participants were treated with a loose combination of macitentan 10 mg and/or tadalafil 40 mg and corresponding placebos depending on treatment arm from Day 8 to the end of Week 2 (Day 14).
    - Note: If a participant was already receiving a stable dose of PDE-5i within prespecified dose ranges at baseline (i.e. 40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily), no up-titration was needed and they received 40 mg tadalafil from Day 1.
- **Maintenance phase:** Participants were treated with macitentan 10 mg, tadalafil 40 mg, M/T FDC, or their respective placebos, depending on treatment arm. The period started on Day 15 and lasted until EDBT (Visit 8).
    - Note: If a participant could not tolerate 40 mg tadalafil during the titration period, the participant remained on 20 mg tadalafil. The participant was allowed to be up-titrated once again to 40 mg tadalafil during the first 2 weeks of the maintenance phase of the double-blind treatment period (i.e. between Visits 4 and 5).
    - Note: if a participant prematurely discontinued double-blind study treatment, they were asked to return for a EDBT visit (within ±2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy), a safety follow-up visit 30 days after last treatment administration, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10).

The table below summarizes the different treatment administrations during the double-blind treatment period for each study treatment group.

Table 6: Treatment administration in the double-blind treatment period

Randomization	M/T FDC[1]	Macitentan monotherapy[1]	Tadalafil monotherapy[1]
Titration phase Week 1[2]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 1 Tadalafil placebo tablet × 1	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 1 Tadalafil placebo tablet × 1
Titration phase Week 2[3]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 2
Maintenance phase[2]	Macitentan placebo tablet × 1 Tadalafil placebo tablet × 2 M/T FDC tablet × 1	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2 M/T FDC placebo tablet × 1	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 2 M/T FDC placebo tablet × 1

M/T FDC = macitentan/tadalafil fixed dose combination; PDE-5i = phosphodiesterase type-5 inhibitor.

1 Table lists tablets to be taken per day. All tablets are to be taken together daily. Tablets are to be taken at the same time of day each day, preferably in the morning, including days of study visits.

2 Participants who were on an allowable dose of PDE-5i at baseline (40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily) will not up-titrate and will receive 40 mg tadalafil starting on study Day 1.

3. If a participant cannot tolerate the higher tadalafil dose (or placebo) during the titration period, the dose will be decreased back to 20 mg daily. Within the first 2–3 weeks after decreasing the dose (up to and including Week 4 / Visit 5) and with the investigator's approval, the participant is allowed to be re-uptitrated to the tadalafil 40 mg daily dose (or its matching placebo equivalent). If the participant cannot tolerate the 40 mg dose again on the 2nd attempt to up-titrate the tadalafil dose (or its matching placebo equivalent), then they are to stay on the 20 mg tadalafil daily dose (or its placebo equivalent) for the remainder of the double-blind treatment period. These participants will receive the same treatment they received during their titration phase Week 1 throughout the entire double-blind treatment period.

During the open label period, all participants received M/T FDC. In order to maintain the blind as participants entered the open-label treatment period, all participants completed a 2-week titration phase, during which macitentan and tadalafil were administered as a loose combination. Treatment during this titration period was assigned by the Interactive Response Technology (IRT) system. Participants who completed 16 weeks of treatment with 40 mg tadalafil during the double-blind treatment period were not up-titrated but received macitentan 10 mg and tadalafil 40 mg directly from Week 1. The first dose of open-label treatment was taken after all Week 16 assessments were completed, including RHC, either in the evening after the visit or the following day, depending on the participant's normal dosing schedule. On the following days, tablets were to be taken at the same time of day each day, preferably in the morning, including on days of study visits.

Objectives and outcomes

The main objectives and associated outcomes are shown in the table below.

Table 7: Combined objectives and outcomes table.

Objectives	Outcome
Primary	
The study had two co-primary objectives: 1. To evaluate the effect of the FDC of macitentan 10 mg and tadalafil 40 mg vs macitentan 10 mg alone on pulmonary vascular resistance (PVR) at End of Double-blind Treatment (EDBT) in subjects with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with an endothelin receptor antagonist (ERA) as monotherapy. 2. To evaluate the effect of the FDC of macitentan 10 mg and tadalafil 40 mg vs tadalafil 40 mg alone on PVR at EDBT in subjects with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or currently being treated with a phosphodiesterase type-5 inhibitor (PDE-5i) as monotherapy.	Change in pulmonary vascular resistance (PVR) expressed as the ratio of geometric means of end double-blind treatment to baseline.
Secondary	
To evaluate the effect of the M/T FDC compared to the respective monotherapies on: - Exercise capacity. - PAH symptoms in participants' cardiopulmonary and cardiovascular function. - WHO FC.	- Change from baseline to end double-blind treatment in 6MWD. - Change from baseline to Week 16 in PAH-Symptoms and Impact™ (PAH-SYMPACT™) in Cardiopulmonary symptom domain score. - Change from baseline to Week 16 in PAH-SYMPACT™ in Cardiovascular symptom domain score. - Proportion of participants with absence of worsening in WHO FC from baseline to end double-blind treatment.
Other	
Evaluate the effect of the M/T FDC compared to the respective monotherapies on: - Time to first Morbidity/Mortality event. - NT-proBNP - PAH impacts on participants' physical and cognitive/emotional functions. - Other hemodynamic measures.	- Time to first morbidity or mortality event occurring between baseline and EDBT, defined as either death, non-planned PAH hospitalization, clinical worsening based on 6MWT and PAH symptoms (>15% worsening 6MTW within two weeks and increase WHO FC or signs right sided HF). - Change from baseline to EDBT in NT-proBNP - Change from baseline to EDBT in PAH-SYMPACT™ Physical impact domain score. - Change from baseline to EDBT in PAH-SYMPACT™ Cognitive/emotional impact domain score. - Change from baseline to EDBT in QoL, assessed by the Euro Quality of Life-5D-5L (EQ-5D-5L). - Change from baseline to EDBT in work productivity and activity impairment, assessed by the Work Productivity and Activity Impairment Questionnaire©: General Health (WPAI©: GH) - Changes from baseline to EDBT in right atrial pressure, right ventricular stroke work index, and other hemodynamic parameters.

For the primary outcome, the effect of FDC was assumed to be of similar extent vs each monotherapy and consistent across the treatment-naïve, prior-ERA, and prior-PDE-5i strata, i.e. a ratio of geometric means of the EDBT / baseline PVR values equal to 0.75 for FDC vs the most efficient of the two monotherapies.

Sample size

The targeted sample size of 170 participants was calculated according to the first version of the protocol and associated clinical assumptions, notably with recruitment expectations of 40% treatment-naïve, 30% prior-ERA and 30% prior-PDE-5i participants.

With protocol amendment 5, the accrual assumptions were operationally reassessed, and it was assumed that 50% treatment-naïve, 20% prior-ERA and 30% prior-PDE-5i participants would be recruited. Given the higher than expected number of treatment-naïve patients, the capping for strata distribution at interim analysis (IA) was removed and the IA was conducted at the time 100 participants had either completed their Week 16 assessment or had discontinued from the study prior to their Week 16 assessment.

The clinical assumptions remained unchanged as detailed below:

- The effect of FDC was assumed to be of similar extent versus each monotherapy and consistent across the treatment-naïve, prior-ERA, and prior-PDE-5i strata, ie, a GMR of the EDBT / baseline PVR values equal to 0.75 for FDC versus the most efficient of the two monotherapies;
- A coefficient of variation of the ratio of 0.45;
- One IA was planned using an alpha spending function from the Hwang, Shih and DeCani class with (γ) = −2; and
- Normal distribution for the loge-transformed ratio of EDBT to baseline PVR values.

Considering the initial target of 170 participants to be randomized, the updated accrual projections, the timing of the IA (Information Fraction ~59%) and the randomization scheme, it was expected that 98 participants would contribute to the FDC vs. Macitentan pairwise comparison, providing an overall power of 87% when accounting for the IA. 115 participants would contribute to the FDC vs. Tadalafil pairwise comparison, providing an overall power of 91%.

If the two comparisons between the FDC and each monotherapy were completely statistically independent, the overall power of the test for the global null hypothesis would be 79%. Those two tests are not independent and therefore the overall power will be in excess of 79% up to a maximum of 87%.

Depending on the conditional powers of each comparison at the IA, the sample size could be recalculated to between 150 and 250 participants.

Randomisation and blinding (masking)

At Screening, participants were assigned a study-specific participant number by the Interactive Response Technology (IRT) system. This number was kept throughout the study and was the main participant identifier. After having verified that the participant met all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacted the IRT system at Visit 2 to randomize the participant. The IRT assigned a randomization number to the participant. The randomization list was generated by an independent Contract Research Organization (CRO). Participants were stratified based on their prior PAH therapy, being treatment-naïve, on ERA therapy, or on PDE-5i therapy.

Participants on ERA therapy at baseline were randomized 2:1 to M/T FDC or macitentan 10 mg, respectively. Participants on PDE-5i therapy at baseline were randomized 2:1 to M/T FDC or tadalafil 40 mg, respectively. Treatment-naïve participants at baseline were randomized 2:1:1 to M/T FDC, macitentan 10 mg, or tadalafil 40 mg, respectively.

The first 16 weeks of this study were performed in a double-blind fashion. The investigator and study personnel, the participants, the Site Managers (SMs), sponsor personnel, and CRO personnel involved in the conduct of the study remained blinded to the study treatment until the final double-blind analysis.

Statistical methods

The Screened Analysis Set included all participants who were screened and had a participant identification number. The All Randomized Analysis Set included all participants who were randomized in the study. The Full Analysis Set (FAS) included all randomized participants who received at least one dose of study treatment. Participants were evaluated according to the study treatment they were assigned to. The Safety Set (SS) included all participants who received at least one dose of study treatment in the double-blind treatment period. Participants were evaluated according to the study treatment received.

The primary endpoint was tested on the FAS using 2 analysis of covariance (ANCOVA) models separately comparing the combination group to each monotherapy. Only if both tests were statistically significant and M/T FDC was shown to be superior to both monotherapies would the study be declared to show conclusive evidence of efficacy.

The alpha to be spent at the IA depended on the fraction of available information at the timing of the IA for each pairwise comparison, which depended on the recruitment process within each stratum.

If the study was not terminated early, the inverse normal combination method would be utilized to combine first- and second-stage p-values for the control of the type-1 error rate [Lehmacher 1999]. The guideline for calculating the combination weights was based on the available individual information fractions at the time of the IA. Combination weights were not adjusted based on the IA decision.

The primary PVR estimand was described according to the following 5 attributes:

A. Treatment: 2 treatment comparisons of interest: FDC of macitentan 10 mg and tadalafil 40 mg (M/T FDC) compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg; treatments as randomized.

B. Population: Participants with symptomatic World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who are PAH-specific treatment-naïve or are currently being treated with an endothelin receptor antagonist (ERA) or a phosphodiesterase type-5 inhibitor (PDE-5i) as monotherapy. FAS will be the population of interest.

C. Variable: Absolute change from baseline to EDBT visit of the log-transformed PVR values. The log-transformed change is assumed to be normally distributed.

D. Intercurrent events (events that preclude observation of the variable or affect its interpretation):

ICE		Strategy
1	Death occurring prior to the EDBT date	*Composite* The unobserved EDBT PVR value to be used will be assigned as the maximum between i) the highest observed individual ratio amongst all participants in the same stratum (without any other ICE for which a composite strategy is also applied) and ii) 1.
2	Disease progression/worsening confirmed by CEC prior to EDBT visit	*Treatment Policy* Values of PVR assessment at EDBT, if available, will be used regardless of disease progression/worsening confirmed by CEC prior to EDBT visit.
3	Prohibited PAH-specific medication prior to EDBT visit: - without death - with disease progression/worsening confirmed by CEC prior to EDBT visit	*Composite* PVR assessments obtained at EDBT visit will be disregarded and the 75th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum (without any ICE for which a composite strategy is also applied) will be used instead.
4	Prohibited PAH-specific medication prior to EDBT visit: - without death - without disease progression/worsening confirmed by CEC prior to EDBT visit	*Composite* PVR assessments obtained at EDBT visit will be disregarded and the 50th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum (without any ICE for which a composite strategy is also applied) will be used instead
5	Study treatment discontinuation/interruption >2 days immediately prior to EDBT: - without death - with disease progression/worsening confirmed by CEC prior to EDBT visit	*Composite* PVR assessments obtained at EDBT visit will be disregarded and the 75th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum (without any ICE for which a composite strategy is also applied) will be used instead
6	Study treatment discontinuation/interruption >2	*Composite*

	days immediately prior to EDBT: - without death - without disease progression/worsening confirmed by CEC prior to EDBT visit	PVR assessments obtained at EDBT visit will be disregarded and the 50th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum (without any ICE for which a composite strategy is also applied) will be used instead
7	Study treatment dose adjustments at any time prior to EDBT visit, except from planned up-titration in Weeks 1 and 2 and without ICEs 1, 3, 4, 5, 6	*Treatment Policy* Values of PVR assessment at EDBT, if available, will be used regardless of any study treatment dose adjustments at any time prior to EDBT visit

E. Population-level summary: Difference of means of log-tranformed PVR between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately and assumed to be normally distributed. The results will be presented on the absolute scale (ratio of geometric means) after exponentiation of the absolute mean changes obtained on the log-scale Ratio of the geometric means between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately.

The null hypotheses was tested by means of 2 ANCOVA models on the $\log_e$-transformed ratios of EDBT to baseline PVR values. Model covariates included randomized treatment, the $\log_e$-transformed baseline PVR value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i). The resulting least squares (LS) means and 95% CLs obtained in each treatment group, and the LS-means differences (95% CLs) for M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg were inversely transformed using the exponential function and multiplied by 100 to provide:

1. the adjusted geometric mean of the ratios of EDBT to baseline PVR values and corresponding 95% CLs, expressed in percent, in each treatment group, and

2. the adjusted geometric mean ratios (GMRs) and corresponding 95% CLs for M/T FDC vs macitentan 10 mg (GMR1) and for M/T FDC vs tadalafil 40 mg (GMR2).

The 2 p-values obtained from the tests of GMR1 and GMR2 (ie. the p-values for the LS-means differences) were to be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis was to be rejected if both tests are significant at the appropriate alpha level. Observed p-values were adjusted and can be compared to 0.05 2-sided significance level.

Sensitivity analysis 1: used a treatment policy approach, meaning this analysis was be similar as the main analysis, except for ICEs 3, 4, 5, 6 handled with treatment policy approach and RS instead of FAS as the population of interest.

Sensitivity analysis 2: To assess the sensitivity of the 75th/50th percentile single imputation approach, a delta worsening multiple imputation analysis was performed to investigate a wide range of scenarios regarding the missing data mechanism.

Sensitivity analysis 3: A multiple imputation based on jump to reference (J2R) assumption was performed.

Sensitivity analysis 4: To assess the robustness of the main results regarding the underlying normality assumption of the density distribution, the primary analysis was reproduced using rank-based analysis of covariances using the Wilcoxon rank-based pseudo-norm.

The secondary efficacy endpoints are listed here according to the hierarchical order that will be statistically tested:

- Change from baseline to EDBT in 6MWD.
- Change from baseline to EDBT in PAH-SYMPACT™ Cardiopulmonary symptom domain score.
- Change from baseline to EDBT in PAH-SYMPACT™ Cardiovascular symptom domain score.
- Absence of worsening in WHO FC from baseline to EDBT.

The corresponding estimand for each of the secondary endpoints followed the same approach as the primary endpoint estimand with the following exceptions:

- Participants with missing baseline value were excluded,
- On-treatment was defined as up to 7 days after last DB treatment intake,
- Assessments obtained in participants receiving prohibited PAH-specific medication for any reason prior to EDBT visit were not excluded from the analysis.

The rationale for handling intercurrent events differently for the secondary endpoint estimands compared to the primary endpoint was to minimize missing data. The primary endpoint estimand strategy was also applied to the secondary endpoints as a sensitivity analysis.

The change from baseline to EDBT in 6MWD and PAH-SYMPACT Symptom domain scores were analyzed for each comparison of interest by means of an ANCOVA model and included treatment group, baseline 6MWD value and the stratification factor as covariates. The proportion of participants who improved or remained stable (absence of worsening) from baseline to EDBT in WHO FC (ie, a change ≤0) was analyzed for each comparison of interest as a binary variable (no worsening vs worsening) by means of a logistic regression model, including treatment group, baseline WHO FC, and the stratification factor as covariates.

One IA was to be conducted when approximately 100 participants had completed their Week 16 assessment or had discontinued from the study prior to their Week 16 assessment.

The IA was conducted by the independent SSG on the primary endpoint to allow for early study termination due to overwhelming efficacy or futility, as well as for adaptive sample size re-estimation if the study was not terminated. The IDMC reviewed the interim results and made corresponding recommendations in line with the IDMC charter. The independent SSG made unblinded results available to the IDMC.

Hwang, Shih and DeCani alpha spending function with gamma (γ) = −2 was used to determine the required alpha levels for statistical testing which guaranteed overall Type I error control in presence of the multiplicity induced by the multiple looks at the primary endpoint.

If the study was not stopped for success, it could be stopped for futility (non-binding) if the conditional probability of reaching final study success was considered to be too low with the pre-planned sample size.

The sample size could be re-estimated at the IA based on unblinded effect estimates. If the study was not terminated early for efficacy, the total size of the study should not exceed N = 250 participants and should not be below N = 150 participants, accounting for the overrun of participants recruited during the 16 weeks of follow-up.

Results

All results presented, including study or treatment discontinuations, are based only on the 16-week DB period of this study. Unless otherwise stated, M/T FDC refers to all participants randomly assigned to M/T FDC (i.e. all strata group) in this section.

Participant flow and recruitment

The first patient was screened on 15 October 2019 and the end of the double-blind period was 23 August 2022. A total of 294 patient were screened across 16 countries/territories. A total of 187 participants were randomized (108 to M/T FDC, 35 to macitentan, and 44 to tadalafil). Twelve participants were re-screened, 5 of whom were not randomized. Most screen failures were due to not meeting eligibility criteria. The follow-up of the double-blind study was 16 weeks.

Table 8: Study Disposition in the Double-blind Period; All Randomized Analysis Set

	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: All Randomized	35	71	106	44	87	131	108
Subjects treated with study treatment	35 (100.0%)	70 (98.6%)	105 (99.1%)	44 (100.0%)	86 (98.9%)	130 (99.2%)	107 (99.1%)
Completed study participation[a]	35 (100.0%)	63 (88.7%)	98 (92.5%)	43 (97.7%)	81 (93.1%)	124 (94.7%)	99 (91.7%)
Terminated study participation prematurely[b]	0	8 (11.3%)	8 (7.5%)	1 (2.3%)	6 (6.9%)	7 (5.3%)	9 (8.3%)
Reason for termination							
Withdrawal by subject	0	4 (5.6%)	4 (3.8%)	1 (2.3%)	2 (2.3%)	3 (2.3%)	4 (3.7%)
Death	0	2 (2.8%)	2 (1.9%)	0	2 (2.3%)	2 (1.5%)	3 (2.8%)
Physician decision	0	2 (2.8%)	2 (1.9%)	0	2 (2.3%)	2 (1.5%)	2 (1.9%)

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

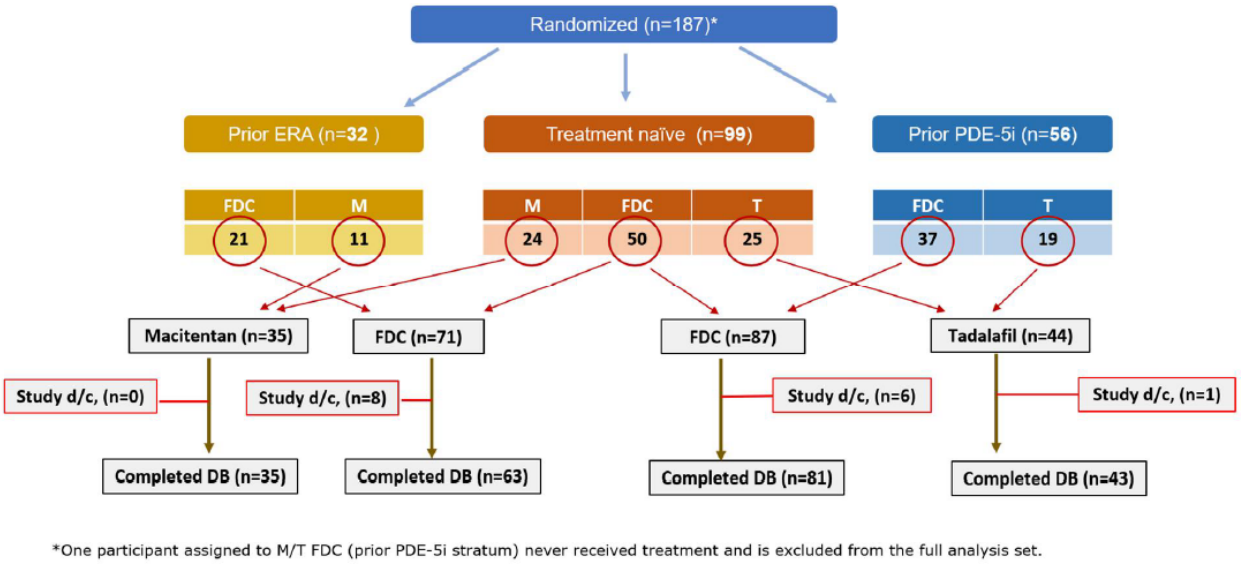
[a] Completed study participation in the DB period: the subject underwent Visit 8/Week 16.

[b] Terminated study participation prematurely in the DB period: the subject did not attend Visit 8/Week 16.

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

Participants were randomized according to 3 strata: treatment naïve (50 to M/T FDC, 24 to macitentan, and 25 to tadalafil), prior ERA (21 to M/T FDC and 11 to macitentan), and prior PDE-5i (37 to M/T FDC and 19 to tadalafil). As the co-primary objectives were comparisons of M/T FDC versus macitentan and M/T FDC versus tadalafil, treatment-naïve participants randomized to M/T FDC contributed to both comparisons and are thus counted twice.

Figure 4: Participant Disposition



*One participant assigned to M/T FDC (prior PDE-5i stratum) never received treatment and is excluded from the full analysis set.

Key: DB=double blind; d/c=discontinuation; ERA=Endothelin receptor antagonist; PDE-5i=Phosphodiesterase type-5 inhibitor; M=macitentan; M/T FDC=Macitentan/tadalafil fixed dose combination; T=tadalafil.

All randomized participants except 1 treatment-naïve participant assigned to M/T FDC received at least 1 dose of study intervention. Most participants completed study participation in the DB period. A total of 9 (8.3%) participants in the M/T FDC group and 1 (2.3%) participant in the tadalafil group prematurely discontinued the study during the DB period. Reasons for premature study participation discontinuation were death (3 participants), participant decision (5 participants) and physician decision (2 participants). Study intervention discontinuation occurred in 16 (15.0%) participants in the M/T FDC group with no treatment discontinuation in the macitentan group and 1 (2.3%) participant in the tadalafil group. Of the 16 participants in M/T FDC who discontinued treatment, 9 (18.4%) were treatment naïve, 3 (14.3%) were on prior ERA, and 4 (10.8%) were on prior PDE-5i. The 1 (4.0%) participant who discontinued tadalafil was treatment naïve. The main reasons for treatment discontinuation were AEs.

Table 9: Treatment Disposition in the Double-blind Period; Full Analysis Set (Study AC-077A301)

	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.

Conduct of the study

Changes in study conduct:

All changes in the conduct of the study were implemented by protocol amendments. Up to the data lock for the DB period, there were 5 global protocol amendments leading to 6 versions of the protocol. The main change was introduced with Amendment 5, Version 6. The protocol required a minimum number of participants in each stratum (ie, treatment naive, prior ERA; prior PDE-5i) at the interim and final analyses to ensure inclusion of a sufficient number of treatment-naive participants. With Amendment 5, Version 6, this requirement was removed because re-evaluation of external feasibility showed that the number of treatment-naive participants was projected to exceed the 40% overall randomized participants originally stipulated in the protocol. These changes were based entirely on operational aspects and not on any observed study data. The participants were allowed in the study whether they were treatment naive or not, which reflected the participant population that would be treated with M/T FDC. A standalone Coronavirus Disease 2019 (COVID-19) Appendix applicable to all concurrent protocol versions was also updated once. Additionally, a standalone appendix for Guidance on
Study Conduct During Natural Disaster/Major Disruption/Pandemic was applicable to all concurrent protocol versions.

Major protocol deviations:

Major protocol deviations (MPDs) were reported for 57%, 60% and 47.7% of patients in the M/T FDC, macitentan and tadalafil arms, respectively. The most common MPDs were categorized as "Other." Including

hemoglobin retest not done on time, Week 16 RHC done outside of time window and biomarker samples being collected without patient consent. The next most frequent MPD category related to eligibility criteria was reported for 16.8%, 20.0% and 22.7% of patients in the M/T FDC, macitentan and tadalafil arms, respectively. The observed MPD rate can be attributed to:

- a conservative approach to assigning MPDs (deviation was assessed as major if it directly or indirectly may have impacted patient's rights, safety or wellbeing, or the integrity and/or results of the study)

- Direct and indirect impact of the COVID pandemic (missed visits/assessment, impact on normal operations of site staff, limited possibility for site visits)

An impact assessment performed by the Sponsor led to the conclusion that the rate of MPDs had no impact on the conclusion of the study. The protocol deviations didn't change the robustness of the primary endpoint, or the interpretability of the results.

Baseline data

Demographics and baseline disease characteristics of the study population were representative of the target patient population (i.e. sex, age distribution, WHO FC, aetiology):

- Median age ranged from 48.0 to 54.5 years in the different treatment groups; the most represented age group was 26 to 50 years.
- 76.6% of the M/T FDC all strata group were female, 82.9% in the macitentan group, and 77.3% in the tadalafil group.
- All participants were in WHO FC II or III.
- The leading aetiology was idiopathic PAH, followed by PAH associated with connective tissue disease.
- Median time since diagnosis in all groups was <0.5 years.

The treatment groups were mostly balanced in terms of demographics and baseline disease characteristics, with a notable exception seen in WHO FC distribution. The M/T FDC group included a higher proportion of participants in WHO FC II (60.7%) compared to the macitentan (31.4%) and tadalafil (43.2%) groups. This imbalance was driven by the treatment-naïve stratum with the proportion of participants in WHO FC II in the M/T FDC (57.1%) group versus the macitentan (16.7%) and tadalafil (32.0%) groups.

Table 10: Demographics and baseline disease characteristics of the study population

	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%)
>= 65	8 (22.9%)	17 (24.3%)	25 (23.8%)	10 (22.7%)	19 (22.1%)	29 (22.3%)	20 (18.7%)
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%)
Ethnicity							
N	35	70	105	44	86	130	107
Hispanic or Latino	2 (5.7%)	4 (5.7%)	6 (5.7%)	5 (11.4%)	6 (7.0%)	11 (8.5%)	8 (7.5%)
Not Hispanic or Latino	30 (85.7%)	63 (90.0%)	93 (88.6%)	39 (88.6%)	78 (90.7%)	117 (90.0%)	95 (88.8%)
Not reported	3 (8.6%)	3 (4.3%)	6 (5.7%)	0	2 (2.3%)	2 (1.5%)	4 (3.7%)
Geographical region							
N	35	70	105	44	86	130	107
North America	4 (11.4%)	11 (15.7%)	15 (14.3%)	14 (31.8%)	14 (16.3%)	28 (21.5%)	14 (13.1%)
Latin America	7 (20.0%)	4 (5.7%)	11 (10.5%)	5 (11.4%)	8 (9.3%)	13 (10.0%)	10 (9.3%)
Asia	11 (31.4%)	31 (44.3%)	42 (40.0%)	12 (27.3%)	36 (41.9%)	48 (36.9%)	49 (45.8%)
Eastern Europe	4 (11.4%)	12 (17.1%)	16 (15.2%)	4 (9.1%)	13 (15.1%)	17 (13.1%)	19 (17.8%)
South and Western Europe	6 (17.1%)	12 (17.1%)	18 (17.1%)	7 (15.9%)	14 (16.3%)	21 (16.2%)	14 (13.1%)
Africa	3 (8.6%)	0	3 (2.9%)	2 (4.5%)	1 (1.2%)	3 (2.3%)	1 (0.9%)
Weight, kg							
N	35	70	105	44	86	130	107
Mean (SD)	66.53 (13.876)	71.68 (17.311)	69.96 (16.362)	72.16 (18.449)	69.71 (17.006)	70.54 (17.475)	69.38 (16.564)
Median	65.00	69.50	67.90	71.80	68.40	69.00	68.00
Range	(41.0; 100.0)	(34.5; 117.7)	(34.5; 117.7)	(35.0; 124.0)	(34.5; 117.7)	(34.5; 124.0)	(34.5; 117.7)
Height, cm							
N	35	70	105	44	86	130	107
Mean (SD)	160.97 (8.102)	162.84 (8.083)	162.22 (8.098)	164.34 (9.097)	162.36 (8.822)	163.03 (8.930)	162.02 (8.417)
Median	160.00	162.30	162.00	163.00	162.60	163.00	162.00
Range	(146.7; 186.0)	(143.8; 183.0)	(143.8; 186.0)	(145.0; 186.0)	(143.8; 183.0)	(143.8; 186.0)	(143.8; 183.0)
Body mass index, kg/m^2							
N	35	70	105	44	86	130	107
Mean (SD)	25.8 (5.56)	26.8 (5.25)	26.4 (5.35)	26.5 (5.53)	26.3 (5.33)	26.4 (5.38)	26.3 (5.23)
Median	25.0	26.0	26.0	27.0	25.5	26.0	26.0
Range	(17; 38)	(16; 39)	(16; 39)	(15; 40)	(16; 39)	(15; 40)	(16; 39)
Underweight <18.5	2 (5.7%)	3 (4.3%)	5 (4.8%)	5 (11.4%)	5 (5.8%)	10 (7.7%)	6 (5.6%)
Normal 18.5-<25	15 (42.9%)	22 (31.4%)	37 (35.2%)	9 (20.5%)	33 (38.4%)	42 (32.3%)	39 (36.4%)
Overweight 25-<30	11 (31.4%)	29 (41.4%)	40 (38.1%)	20 (45.5%)	27 (31.4%)	47 (36.2%)	38 (35.5%)
Obese >=30	7 (20.0%)	16 (22.9%)	23 (21.9%)	10 (22.7%)	21 (24.4%)	31 (23.8%)	24 (22.4%)
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)
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)
CO method used for PVR calculation by central reader[a]							
N	35	70	105	44	86	130	107
Fick CO	15 (42.9%)	38 (54.3%)	53 (50.5%)	21 (47.7%)	39 (45.3%)	60 (46.2%)	54 (50.5%)
Thermodilution CO	20 (57.1%)	32 (45.7%)	52 (49.5%)	23 (52.3%)	47 (54.7%)	70 (53.8%)	53 (49.5%)
mPAP calculated by central reader, mmHg							
N	35	70	105	44	86	130	107
Mean (SD)	47.0 (13.95)	46.4 (16.04)	46.6 (15.31)	46.4 (13.76)	47.8 (16.10)	47.4 (15.31)	48.0 (16.01)
Median	45.3	42.2	44.7	46.0	46.0	46.0	46.0
Range	(25; 89)	(25; 99)	(25; 99)	(27; 84)	(25; 99)	(25; 99)	(25; 99)
PAWP calculated by central reader, mmHg							
N	32	63	95	43	78	121	97
Mean (SD)	10.4 (2.42)	11.0 (3.43)	10.8 (3.13)	10.6 (5.13)	10.4 (3.61)	10.5 (4.19)	10.6 (3.50)
Median	10.0	11.0	11.0	10.0	10.0	10.0	11.0
Range	(5; 16)	(4; 23)	(4; 23)	(2; 36)	(3; 23)	(2; 36)	(3; 23)
LVEDP calculated by central reader, mmHg							
N	7	16	23	5	14	19	20
Mean (SD)	9.6 (4.43)	10.7 (3.94)	10.3 (4.03)	9.8 (2.68)	10.2 (2.52)	10.1 (2.49)	10.8 (3.55)
Median	11.0	10.0	10.0	10.0	10.0	10.0	10.0
Range	(2; 14)	(4; 22)	(2; 22)	(7; 14)	(4; 14)	(4; 14)	(4; 22)
Thermodilution CO calculated by central reader, L/min							
N	20	32	52	23	47	70	53
Mean (SD)	4.5 (1.22)	4.6 (1.17)	4.6 (1.18)	4.6 (1.35)	4.5 (1.21)	4.5 (1.25)	4.5 (1.18)
Median	4.2	4.3	4.2	4.3	4.2	4.3	4.3
Range	(3; 7)	(2; 7)	(2; 7)	(2; 7)	(2; 7)	(2; 7)	(2; 7)
Fick CO calculated by central reader, L/min							
N	15	38	53	21	39	60	54
Mean (SD)	3.2 (0.91)	3.5 (1.31)	3.4 (1.21)	3.9 (1.63)	3.5 (1.46)	3.7 (1.52)	3.5 (1.33)
Median	3.2	3.4	3.3	3.8	3.1	3.3	3.4
Range	(1; 5)	(2; 8)	(1; 8)	(1; 9)	(1; 8)	(1; 9)	(1; 8)
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; CO=Cardiac output; mPAP=Mean pulmonary artery pressure; PAWP=Pulmonary artery wedge pressure; LVEDP=Left ventricular end diastolic pressure; 6MWD=6-minute walk distance.

a. Proportion of baseline PVR assessments based on Fick CO and Thermodilution CO.

b. Note: N's for each parameter reflect non-missing values. Baseline is defined as the last observation prior to the first study treatment administration.

c. 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.

[TSIDEM01.RTF] [JNJ-68150420/AC-077A301/DBR_CSR/RE_FINAL/PROD/TSIDEM01.SAS] 13DEC2022, 16:45

Prior and concomitant medication usage:

At randomization, 53.3% of participants in the M/T FDC group, 25.7% of participants in the macitentan group, and 38.6% of participants in the tadalafil group were on a PAH-specific therapy. Prior PAH-specific medications primarily included ERAs (macitentan, ambrisentan, and bosentan) and PDE-5is (tadalafil and sildenafil).

In the treatment-naïve stratum, 2 participants in the M/T FDC group had prior use of PAH-specific medications: 1 participant received iloprost as a single inhaled dose for vasoreactivity testing during baseline RHC as per local practice, and 1 participant who was stratified incorrectly received tadalafil until 2 days prior to randomization.

After medications for PAH, the most frequent prior medications used to treat PAH symptoms or comorbidities included glucocorticoids (7.5%, 2.9%, 2.3% in the M/T FDC, macitentan, and tadalafil groups, respectively) and loop diuretics (5.6%, 14.3% and 2.3% in the M/T FDC, macitentan, and tadalafil groups, respectively). Medications used during the RHC procedures (local anaesthetics, anticoagulants from the heparin group) were reported as prior medications for up to 20% of participants. COVID-19 vaccines were received by 26.2%, 40.0%, and 31.8% in the M/T FDC, macitentan, and tadalafil groups, respectively. There were 4 participants who received a red blood cell transfusion. In 3 participants, the transfusion was given in the context of an anaemia AE and 1 participant required a transfusion due to gastrointestinal bleeding.

At baseline (i.e. on the day of first dose of study intervention), a total of 7 participants were reported as being on a forbidden PAH medication: 3 (2.8%) participants in the M/T FDC group, 2 (5.7%) participants in the macitentan group, and 1 (2.3%) participant in the tadalafil group; and 1 additional participant who received tadalafil at baseline is not displayed in the summary table since the start date of administration is missing. An MPD was assigned in 4 of these 7 participants. For 3 participants, the end date of the PAH medication (2 participants) or the study intervention start date (1 participant) were wrongly reported in the eCRF. None of these 3 participants received a forbidden PAH medication concomitantly with study intervention. Hence, only 4 participants were on a forbidden PAH medication at baseline.

The most common study intervention concomitant medications (i.e. medication ongoing at start of study intervention or initiated during the DB treatment period) were loop diuretics (i.e. sulfonamides; 60.7%, 57.1%, and 47.7% in the M/T FDC, macitentan, and tadalafil groups, respectively), aldosterone antagonists (41.1%, 51.4%, and 34.1% in the M/T FDC, macitentan, and tadalafil groups, respectively), and proton pump inhibitors (36.4%, 28.6%, and 45.5% in the M/T FDC, macitentan, and tadalafil groups, respectively).

Table 11: Prior PAH-specific Medications by Stratum; Full Analysis Set

	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%)	20 (95.2%)	17 (89.5%)	35 (94.6%)
Special interest category Standardized medication name							
PDE-5i	0	0	1 (2.0%)	0	1 (4.8%)	17 (89.5%)	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%)	20 (95.2%)	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.

Dose modifications:

During the maintenance phase, the tadalafil dose was only adjusted for participants in the M/T FDC group. The tadalafil dose decreased from 40 mg to 20 mg once in 3 participants (2 due to an AE, and 1 for an unspecified reason) and increased from 20 mg to 40 mg once in 2 participants. There was also 1 participant who underwent >3 dose adjustments as a bridging measure while COVID-19 related lockdown measures precluded delivery of the M/T FDC 10/40 mg tablets to the participant.

Table 12: Tadalafil Dose Adjustment in the Double-blind Study Treatment Period; Safety Set

	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 receiving tadalafil 40 mg at least once	NA	67 (95.7%)	44 (100.0%)	85 (98.8%)	104 (97.2%)
Total duration of tadalafil 20 mg administration (weeks)[a]					
N	-	69	25	48	69
Mean (SD)	-	1.40 (2.369)	1.00 (0.000)	1.01 (0.093)	1.40 (2.369)
Median	-	1.00	1.00	1.00	1.00
Range	-	(0.6; 16.9)	(1.0; 1.0)	(0.7; 1.6)	(0.6; 16.9)
Total duration of tadalafil 40 mg administration (weeks)[a]					
N	-	67	44	85	104
Mean (SD)	-	13.39 (4.831)	15.31 (1.382)	14.40 (4.245)	14.21 (4.350)
Median	-	15.14	15.36	15.71	15.71
Range	-	(0.6; 19.0)	(7.9; 18.0)	(0.6; 20.3)	(0.6; 20.3)
Adjustment of tadalafil dose					
Increase from 20 mg to 40 mg	-	2 (2.9%)	0	1 (1.2%)	2 (1.9%)
Decrease from 40 mg to 20 mg	-	3 (4.3%)	0	1 (1.2%)	3 (2.8%)
Number of tadalafil dose adjustments per subject					
0	-	66 (94.3%)	44 (100.0%)	84 (97.7%)	103 (96.3%)
1	-	3 (4.3%)	0	2 (2.3%)	3 (2.8%)
2	-	0	0	0	0
3	-	0	0	0	0
>3	-	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; SD=Standard deviation.

[a] Total duration of tadalafil 20 mg/40 mg is a sum of all intervals where tadalafil 20 mg/40 mg was taken. Interval duration is defined as (date of last tadalafil 20 mg/40 mg in the interval - date of first tadalafil 20 mg/40 mg in the interval + 1)/7.

Note: Titration phase is excluded from the summary of tadalafil adjustments.

Compliance with Intervention:

Mean compliance was comparable across groups is shown in the table below. Study intervention compliance was based on study intervention accountability. There were 12 participants reported to have a compliance >120% as the information relating to the number of returned tablets was not entered prior to these participants' EDBT date. The participants' compliance has been checked post-DB cutoff date and confirmed to be <120% based on the full return of information entered.

Table 13: Summary of Double-blind Study Treatment Compliance; Full Analysis Set

	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: Full	35	70	44	86	107
Compliance (%)[a]					
N	35	70	44	86	107
Mean (SD)	102.93 (9.687)	99.46 (15.656)	105.90 (10.770)	100.24 (13.392)	100.64 (13.449)
Median	100.00	100.00	100.00	100.00	100.00
Range	(76.0; 140.0)	(32.6; 158.6)	(79.3; 132.3)	(32.6; 158.6)	(32.6; 158.6)
Compliance category[a]					
<80%	1 (2.9%)	5 (7.1%)	1 (2.3%)	3 (3.5%)	5 (4.7%)
80 - <=100%	17 (48.6%)	44 (62.9%)	23 (52.3%)	61 (70.9%)	69 (64.5%)
>100 - <=120%	16 (45.7%)	18 (25.7%)	14 (31.8%)	17 (19.8%)	28 (26.2%)
>120%	1 (2.9%)	3 (4.3%)	6 (13.6%)	5 (5.8%)	5 (4.7%)

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; LC=Loose combination.

[a] Compliance is calculated as [(number of tablets dispensed at all visits − number of tablets returned at all visits) / Total number of tablets that should have been taken from the first dose of study treatment to EOT-DB]× 100.

Note: Only compliance to active study treatment is derived, compliance to placebo is not calculated.

Note: In case a subject from the M/T FDC treatment group takes LC of tadalafil and macitentan, such intervals are not used for the derivation of compliance.

Note: Subjects (&pt_ids.) were on the lower dose of tadalafil (20 mg) and took only 1 orange tablet. It cannot be discerned whether tadalafil or placebo was taken, therefore it is assumed that the subjects took the tadalafil tablet in the computation of compliance.

Numbers analysed

The number of participants included in each analysis set is provided in the table below. The full analysis set and safety analysis set were identical. The participant randomized to M/T FDC who did not take study intervention was excluded from all analysis sets (except the all-randomized analysis set). No other participants were excluded from the full analysis set or the safety analysis set. "No baseline value" was the most common reason participants were excluded from an analysis set.

Table 14: Number of Subjects in Each Analysis Set; All Randomized Analysis Set

	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
All randomized	35	71	106	44	87	131	108
Full analysis set	35 (100.0%)	70 (98.6%)	105 (99.1%)	44 (100.0%)	86 (98.9%)	130 (99.2%)	107 (99.1%)
Safety set	35 (100.0%)	70 (98.6%)	105 (99.1%)	44 (100.0%)	86 (98.9%)	130 (99.2%)	107 (99.1%)
PAH-SYMPACT symptoms analysis set	33 (94.3%)	66 (93.0%)	99 (93.4%)	42 (95.5%)	81 (93.1%)	123 (93.9%)	100 (92.6%)
PAH-SYMPACT impacts analysis set	30 (85.7%)	60 (84.5%)	90 (84.9%)	43 (97.7%)	77 (88.5%)	120 (91.6%)	94 (87.0%)
EQ-5D-5L analysis set	33 (94.3%)	67 (94.4%)	100 (94.3%)	43 (97.7%)	83 (95.4%)	126 (96.2%)	103 (95.4%)
WPAI analysis set	33 (94.3%)	65 (91.5%)	98 (92.5%)	43 (97.7%)	80 (92.0%)	123 (93.9%)	100 (92.6%)

Key: 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; EQ-5D-5L=Euro Quality of Life-5D-5L; WPAI=Work Productivity and Activity Impairment.

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

Primary outcome

The primary efficacy endpoint (change in PVR expressed as the ratio of geometric means of EDBT to baseline) was met: a highly statistically significant and clinically meaningful treatment effect was observed for both the M/T FDC versus macitentan and the M/T FDC versus tadalafil comparisons, and the treatment effect was consistent across all subgroups. Due to the adaptive nature of the study and as planned in the protocol, the main analysis of the primary efficacy endpoint was conducted on the full analysis set using the inverse normal combination method with prespecified weights to combine first and second-stage p-values. The prespecified weights are proportional to the pre-planned sample size of 170 participants. The ANCOVA model on the loge transformed ratio of EDBT to baseline PVR was applied to derive the first-stage (i.e. at the interim analysis timepoint) and second-stage p-values (i.e. after interim analysis) to be used for the final inference. Predefined model covariates include randomized treatment group, stratification factor and loge transformed baseline PVR. Final inference was based on the final adjusted and combined 2-sided p-value, and the median unbiased estimator for the overall treatment effect with corresponding adjusted repeated confidence limits (RCLs).

Based on the ANCOVA model run at each stage with treatment group, stratum, and baseline value as covariates, the median unbiased estimates of the geometric means ratios (95% adjusted RCL) were:

- 0.71 (0.61, 0.82) between M/T FDC and macitentan (29% reduction in PVR with M/T FDC compared to macitentan);
- 0.72 (0.64, 0.80) between M/T FDC and tadalafil (28% reduction in PVR with M/T FDC compared to tadalafil).

The treatment effect was highly statistically significant for both comparisons (2-sided adjusted p-values both <0.0001, see table below).

The intercurrent events of Death, prohibited PAH-specific medication, and treatment discontinuation/interruption for more than 2 days prior to EDBT were used as a composite strategy and led to imputations if they occurred. Disease progression and treatment dose adjustments were used with a treatment policy strategy, i.e. did not lead to exclusion of on-treatment PVR values. In addition, disease progression was used to determine how to impute in case of other intercurrent events or missing data (imputation was worse if disease progression had occurred).

The most frequent intercurrent event was treatment discontinuation prior to EDBT without death or disease progression. Consistent with the higher number of treatment discontinuations in M/T FDC group, there were higher numbers of Intercurrent event "Treatment discontinuation / interruption for more than 2 days prior to EDBT" and missing data in the M/T FDC group than in the macitentan and tadalafil groups. This was mainly driven by Stage 1 results.

Despite these differences, Stage 1 (interim analysis) and Stage 2 results showed consistent results. Pre-planned sensitivity and supportive analyses (e.g. impact of missing values, intercurrent events, and imputation; deviations from the normality assumption) were consistent with the primary estimand.

A planned tipping point analysis was also run to assess the robustness of the analysis, focusing on the participants with missing data after accounting for the intercurrent events (i.e. 3 and 2 participants in the M/T FDC groups for the macitentan and tadalafil comparisons, respectively). After a first step of multiple imputation for these participants, ratios of imputed participants in the M/T FDC groups were shifted by steps of 0.15. After shifting the ratios of these participants by 3, results were still significant, indicating a high robustness of the main analysis results.

The treatment effect (ANCOVA [95% CL], analyses not taking into account the adaptive design) between M/T FDC and the monotherapies was consistent across strata:

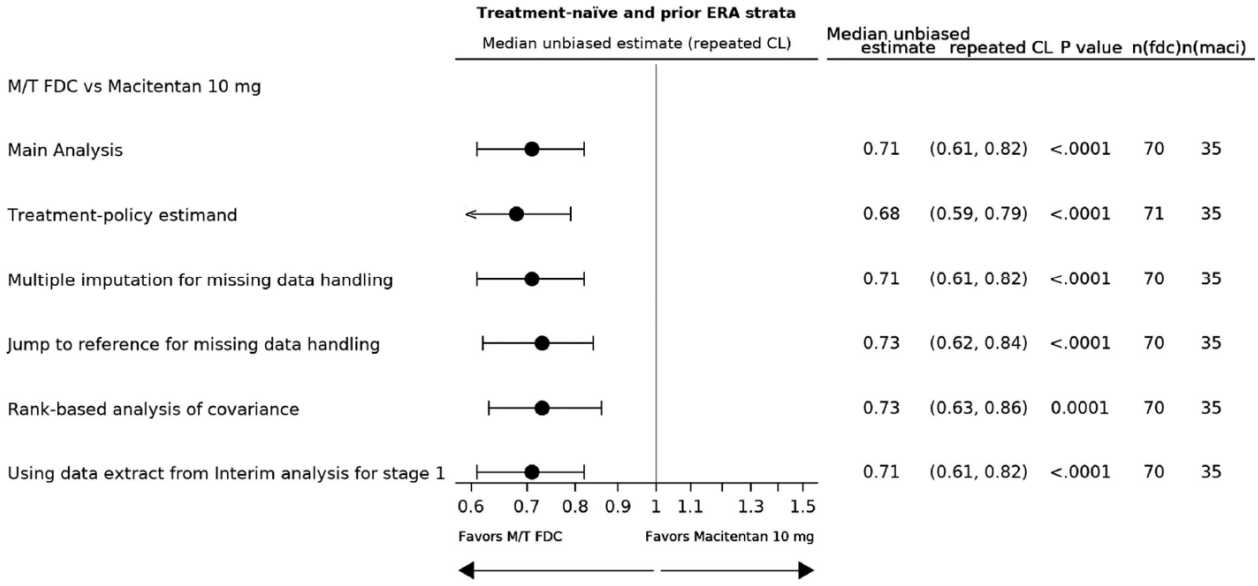
- M/T FDC vs macitentan:
    - treatment naïve: 0.70 (0.58, 0.84; p=0.0002)
    - prior ERA: 0.68 (0.53, 0.86; p=0.0025)
- M/T FDC vs tadalafil:
    - treatment naïve: 0.66 (0.56, 0.78; p<0.0001)
    - prior PDE-5i: 0.81 (0.70, 0.94; p=0.0066)

The treatment effect was also consistent across predefined subgroups and stages, see figures below. Upon request of the CHMP, as an additional subgroup analyses according to therapy prior to baseline was provided in the table below.

Table 15: Primary Endpoint (Primary Estimand): Ratio of EDBT to Baseline PVR; Full Analysis Set

	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] (n, %)				
N	4	15	3	14
Death occurring prior to EDBT date	0	1 (1.4%)	0	1 (1.2%)
Disease progression/worsening confirmed by CEC prior to EDBT visit	0	2 (2.9%)	0	2 (2.3%)
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 (5.7%)	1 (1.4%)	2 (4.5%)	2 (2.3%)
Treatment discontinuation/interruption for more than 2 days prior to EDBT without death and with disease progression	0	1 (1.4%)	0	1 (1.2%)
Treatment discontinuation/interruption for more than 2 days prior to EDBT without death and without disease progression	0	8 (11.4%)	2 (4.5%)	8 (9.3%)
Treatment dose adjustments prior to EDBT	2 (5.7%)	4 (5.7%)	0	2 (2.3%)
Number of subjects with imputation of missing values[a] (n, %)				
N	1	3	2	2
Disease progression (confirmed) prior to Week 16	0	0	0	0
No disease progression (confirmed) prior to Week 16	1 (2.9%)	3 (4.3%)	2 (4.5%)	2 (2.3%)
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

Figure 5: Forest Plot of primary outcome main & sensitivity analysis and main analysis by subgroup for the treatment naive and prior ERA strata



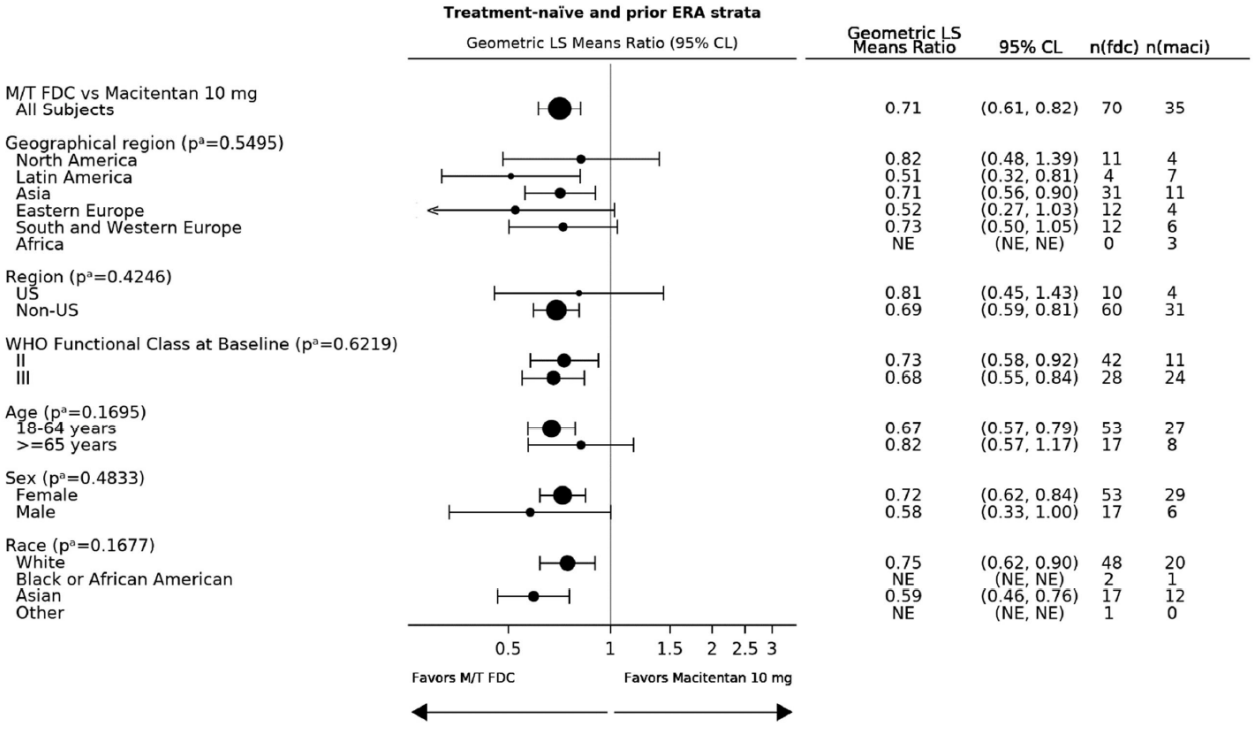
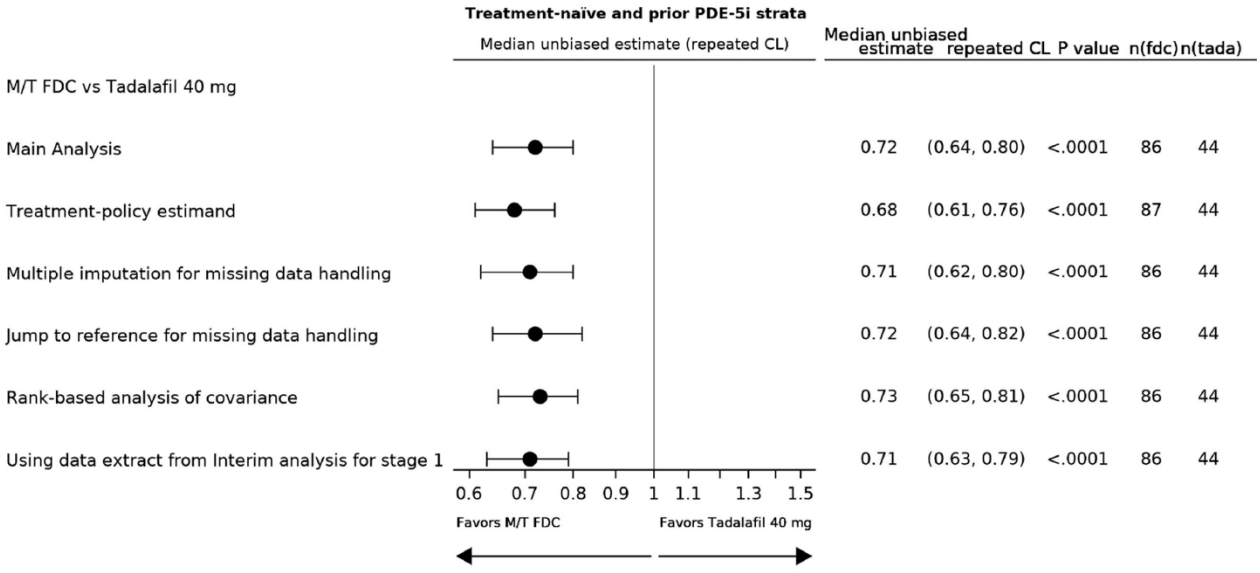


Figure 6: Forest Plot of primary outcome main & sensitivity analysis and main analysis by subgroup for the treatment naive and prior PDE-5i strata



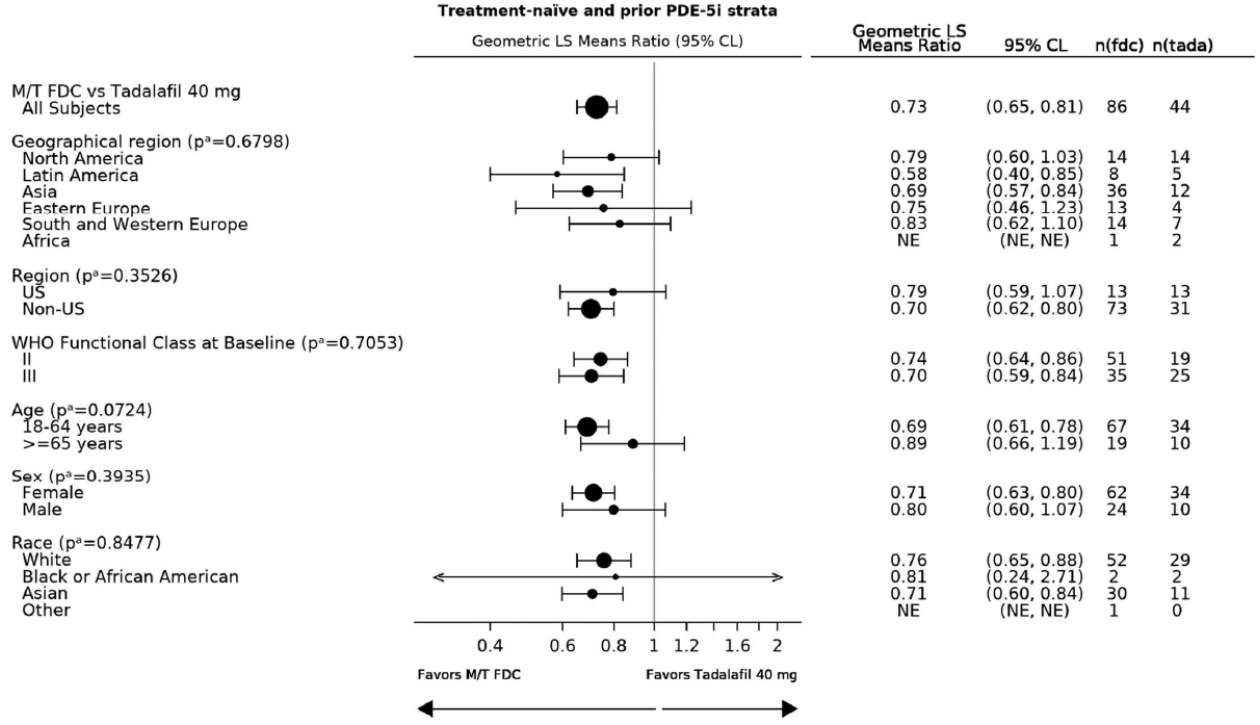


Table 16: Ratio of EDBT to Baseline PVR (ANCOVA) by Stratum and by previous treatment; Full Analysis Set

	Treatment-naïve			Prior ERA strata				Prior PDE-5i strata			
				Macitentan		M/T FDC		Tadalafil		M/T FDC	
	Macitentan	Tadalafil	M/T FDC	Ambri. or Bosentan	Macitentan	Ambri. or Bosentan	Macitentan	Sildenafil	Tadalafil	Sildenafil	Tadalafil
Analysis set: Full	24	25	49	6	5	11	10	14	4	33	4
Number of subjects included in the analysis	24	25	49	6	5	11	10	14	4	33	4
Baseline											
N	24	25	49	6	5	11	10	14	4	33	4
Mean (SD)	897.3 (350.86)	923.2 (659.85)	830.6 (655.36)	839.4 (560.51)	396.5 (85.38)	852.1 (590.06)	832.4 (611.49)	648.1 (317.52)	714.8 (335.96)	998.3 (641.85)	610.1 (247.15)
Median	856.9	746.9	604.1	755.3	389.0	673.1	634.0	527.8	819.4	816.0	600.8
Range	(263; 1464)	(244; 3322)	(192; 3802)	(261; 1525)	(313; 503)	(317; 2381)	(263; 2037)	(332; 1236)	(249; 971)	(322; 2779)	(391; 848)
EDBT											
N	23	23	42	6	5	7	9	14	3	29	4
Mean (SD)	667.2 (328.37)	705.3 (450.21)	421.6 (321.19)	836.8 (627.36)	453.9 (134.48)	534.9 (222.25)	563.7 (426.79)	521.4 (229.88)	789.4 (269.47)	665.9 (386.60)	369.0 (89.57)
Median	657.7	662.9	342.7	667.2	489.5	496.4	388.4	461.4	810.0	574.4	383.7
Range	(142; 1329)	(189; 2171)	(50; 1838)	(241; 1613)	(244; 589)	(286; 852)	(104; 1441)	(253; 908)	(510; 1048)	(197; 1591)	(249; 459)
Ratio of EDBT to baseline											
N	24	25	49	6	5	11	10	14	4	33	4
Geometric mean	0.70	0.75	0.51	0.94	1.00	0.74	0.58	0.81	0.89	0.64	0.63
Geometric CV	0.354	0.268	0.394	0.122	0.235	0.379	0.311	0.256	0.159	0.274	0.272
95% CL of geometric mean	(0.60, 0.81)	(0.67, 0.83)	(0.45, 0.56)	(0.83, 1.06)	(0.75, 1.33)	(0.58, 0.95)	(0.47, 0.73)	(0.70, 0.93)	(0.69, 1.15)	(0.59, 0.71)	(0.41, 0.96)

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.
Source: Extracted from Attachment TEFPVR15C

Secondary outcomes

6-minute walking distance

The difference in 6MWD change from baseline to EDBT was not statistically significant between M/T FDC and macitentan or between M/T FDC and tadalafil. Based on the ANCOVA model run at each stage with treatment group, stratum, and baseline value as covariates, the median unbiased estimates of change from baseline to EDBT (adjusted RCL) and combined p-values were:

- M/T FDC versus macitentan: 16.04 m (-17.0,49.08), p=0.380
- M/T FDC versus tadalafil: 25.37 m (-0.93,51.59), p=0.059

Figure 7: Secondary Endpoint (Main Estimand): Change from Baseline to EDBT in 6MWD; Full Analysis Set

	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] (n, %)				
N	4	13	3	12
Death occurring prior to EDBT date	0	1 (1.4%)	0	1 (1.2%)
Disease progression/worsening confirmed by CEC prior to EDBT visit	0	2 (2.9%)	0	2 (2.3%)
Prohibited PAH-specific medication prior to EDBT visit	2 (5.7%)	1 (1.4%)	2 (4.5%)	2 (2.3%)
Treatment discontinuation/interruption for more than 7 days prior to EDBT without death and with disease progression	0	1 (1.4%)	0	1 (1.2%)
Treatment discontinuation/interruption for more than 7 days prior to EDBT without death and without disease progression	0	6 (8.6%)	1 (2.3%)	6 (7.0%)
Treatment dose adjustments prior to EDBT	2 (5.7%)	3 (4.3%)	0	1 (1.2%)
Number of subjects with imputation of missing values[a] (n,%)				
N	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

There was a numerical trend for a greater improvement in favour of M/T FDC in 6MWD versus both monotherapies. The numerical trend was more pronounced in the M/T FDC versus tadalafil comparison, especially in the treatment-naïve subgroup. The treatment effect of M/T vs macitentan was 20.4m (95% CI: -20.3; 61.1; P=0.32) in the treatment-naïve strata and 8.5m (95% CI: -41.0; 58.0; P=0.73) in the prior ERA strata. The treatment effect of M/T vs tadalafil was 33.0m (95% CI: -5.3; 71.4; P=0.09) in the treatment naïve strata and 25.9m (95% CI: 0.9; 50.9; P=0.04) in the prior PDE-5i strata.

Figure 8: Change from Baseline to EDBT in 6MWD (ANCOVA) by Stratum; Full Analysis Set. Treatment effect for treatment-naive stratum highlighted in blue

	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
Number of subjects included in the analysis	24	25	49	11	21	19	37
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 M/T FDC vs Macitentan							
N	24	-	49	11	21	-	-
Mean (SD)	44.1 (77.18)	-	54.1 (94.41)	26.3 (54.06)	50.2 (73.84)	-	-
Median	31.5	-	43.0	27.0	21.6	-	-
Range	(-100; 233)	-	(-135; 454)	(-71; 103)	(-25; 273)	-	-
Change from baseline to EDBT M/T FDC vs Tadalafil							
N	-	25	49	-	-	19	37
Mean (SD)	-	18.4 (39.95)	50.5 (97.22)	-	-	12.6 (51.94)	33.9 (40.14)
Median	-	19.0	40.0	-	-	12.0	36.0
Range	-	(-59; 96)	(-141; 454)	-	-	(-78; 102)	(-75; 119)
Adjusted change from baseline (contributing to M/T FDC vs. Macitentan 10 mg comparisons)							
LS mean	37.15		57.53	36.37	44.86		
SE	16.68		11.64	19.36	13.86		
95% CL	(3.89,70.40)		(34.32,80.74)	(-3.23,75.97)	(16.51,73.22)		
Treatment effect: Adjusted change from baseline difference vs. Macitentan 10 mg							
LS mean			20.38		8.49		
SE			20.41		24.18		
95% CL			(-20.3,61.08)		(-41.0,57.95)		
p-value			0.3214		0.7279		
Adjusted change from baseline (contributing to M/T FDC vs. Tadalafil 40 mg comparisons)							
LS mean		17.79	50.83			9.59	35.48
SE		15.65	11.18			10.07	7.18
95% CL		(-13.4,48.99)	(28.54,73.11)			(-10.6,29.80)	(21.09,49.88)
Treatment effect: Adjusted change from baseline difference vs. Tadalafil 40 mg							
LS mean			33.04				25.89
SE			19.23				12.47
95% CL			(-5.31,71.39)				(0.88,50.90)
p-value			0.0902				0.0427

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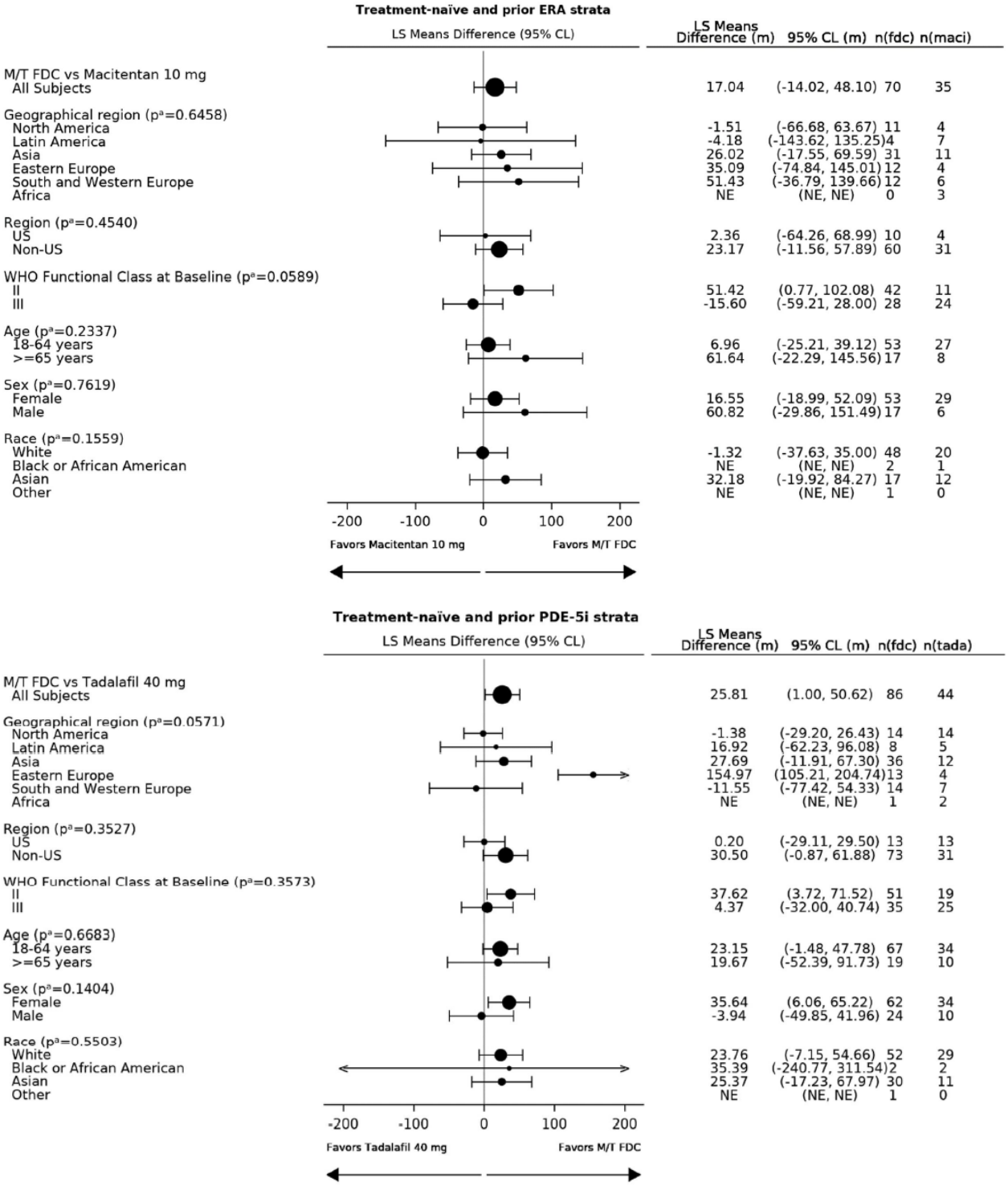
Predefined sensitivity and supportive analyses (treatment policy, rank-based, multiple imputation) were largely consistent with the main analysis of the secondary outcome 6MWT, with the following exceptions. The effect of M/T over tadalafil was lower in the rank-based linear model, the treatment effect of M/T over macitentan was 9.86m (95% CI: -19.2; 38.84; P=0.58), whereas the treatment effect of M/T over tadalafil was 23.6m (95% CI: 2.86; 44.17; P=0.0251). On the contrary, in the supportive analyse using mixed model repeated measures, the treatment effect of M/T over macitentan was 24.9 (95% CL: -4.4; 54.3; P=0.095), whereas the treatment effect of M/T over tadalafil was 21.6 (95% CL: -1.2; 44.4; P=0.063).

In general, p-values of the interaction were >0.10 across subgroups, except for WHO FC III in the M/T FDC versus macitentan comparison. In the treatment strata "treatment naïve and prior ERA", the treatment effect on 6MWT was in favour of M/T/ FDC for WHO FC II (51.42 (95% CL: 0.77; 102.08)), whereas it was in favour of macitentan for WHO FC III (-15.60 (-59.21; 28.00)).

Figure 9: Forest Plot of Change from Baseline to EDBT in 6MWD by Subgroups; Full Analysis Set



Given these 6MWD results, and in accordance with the predefined hierarchical testing procedure, subsequent secondary endpoints could not be formally tested. Therefore, results presented in the subsequent subsections are exploratory in nature.

PAH-SYMPACT

The PAH-SYMPACT cardiopulmonary and cardiovascular symptom domain scores range from 0 to 4, with higher scores indicating greater symptom severity. A negative treatment effect indicates an increase in symptoms or no change in symptoms. A positive treatment effect indicates a reduction in symptoms. Across all treatment groups, participants reported a change in both cardiopulmonary and cardiovascular symptom domain scores from baseline to EDBT. However, the reductions in symptoms between treatment groups were not statistically significant.

Participants that were treatment naïve had a greater reduction in their cardiopulmonary and cardiovascular symptom domain scores when on treatment, compared to participants that were on prior ERA or PDE-5i. However, this reduction was not statistically significant.

Cardiopulmonary Domain

There were no differences in change from baseline to EDBT (treatment effect, 95% CI) between groups in the PAH-SYMPACT cardiopulmonary domain score:

- -0.03 (-0.21,0.15) for M/T FDC versus macitentan
- -0.04 (-0.21,0.13) for M/T FDC versus tadalafil

Cardiovascular Domain

There were no differences in change from baseline to EDBT (treatment effect, 95% CI) between groups in the PAH-SYMPACT cardiovascular domain score:

- 0.01 (-0.17,0.19) for M/T FDC versus macitentan
- 0.02 (-0.15,0.19) for M/T FDC versus tadalafil

Absence of or worsening of WHO FC

The main analysis of WHO FC is presented by stages only. The first-stage set of participants constitutes all participants who have contributed to the IA. The remaining participants required to reach the total sample size based on the IA decision constitute the second-stage set of participants. In Stage 2 of the M/T FDC versus macitentan comparison, worsening of WHO FC was only observed in 2 participants within the same treatment group, stratum, and baseline WHO FC. The ANCOVA analysis on Stage 2 was thus performed without adjusting for stratum and baseline WHO FC category, and upper bound of CI could not be estimated. Consequently, stage results were not combined to provide the median unbiased estimate and repeated CI.

There were numerically more worsenings reported in the M/T FDC group due to having a higher number of participants with intercurrent events and missing data that were imputed as worsening. This is more apparent in Stage 1. The treatment effect (adjusted odds ratio of M/T vs monotherapy) for Absence of Worsening in WHO FC from Baseline to EDBT was 0.20 (0.01; 1.73) and 0.98 (0.01; 7.74) for stage 1 in the treatment-naïve and prior ERA and treatment-naïve and prior PDE-5i strata, respectively. The treatment effect (adjusted odds ratio of M/T vs monotherapy) for Absence of Worsening in WHO FC from Baseline to EDBT was 0.77 (not estimatable; 6.56) and 0.44 (0.01; 4.94) for stage 2 in the treatment-naïve and prior ERA and treatment-naïve and prior PDE-5i strata, respectively.

Based on observed (i.e., non-imputed) WHO FC data, the proportion of participants who experienced a worsening in WHO FC for the M/T FDC vs macitentan comparison was 3.2% vs 2.9% and for the M/T FDC vs tadalafil comparison it was 2.5% vs 4.5%.

Other efficacy outcomes

Morbidity and Mortality Events

During the 16-week DB period, all events occurred in the M/T FDC group: 2 deaths (all cause) and 3 nonplanned hospitalizations due to PAH.

NT-proBNP

In the main analysis of NT-proBNP (only on observed values), a greater decrease (approximately 40% reduction) in the ratio of EDBT to baseline was observed for M/T FDC versus each monotherapy.

Table 17: Change from Baseline to EDBT in NT-proBNP (ng/L) (ANCOVA); Full Analysis Set

	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	33	69	43	86
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	30	50	41	68
Mean (SD)	750.0 (948.65)	317.0 (325.05)	776.8 (980.76)	489.3 (964.75)
Median	422.3	220.5	459.9	215.7
Range	(51; 3704)	(51; 1415)	(53; 5112)	(51; 7202)
Change from baseline to EDBT				
N	27	48	40	66
Mean (SD)	-540.6 (1109.37)	-950.6 (1516.54)	-105.3 (459.41)	-817.6 (1481.35)
Median	-126.9	-284.9	-13.1	-156.3
Range	(-4466; 279)	(-8031; 256)	(-1321; 1125)	(-8031; 608)
Ratio of EDBT to baseline				
Geometric mean	0.66	0.38	0.86	0.48
Geometric CV	0.788	1.503	0.820	1.456
95% CL of geometric mean	(0.50, 0.87)	(0.28, 0.52)	(0.68, 1.08)	(0.37, 0.62)
Adjusted geometric LS means of ratios of EDBT to Baseline values (%)	0.71	0.40	0.86	0.49
95% CL	(0.54, 0.93)	(0.32, 0.50)	(0.68, 1.10)	(0.41, 0.59)
Treatment effect: Adjusted geometric mean ratio vs monotherapy		0.57		0.57
95% CL		(0.41, 0.80)		(0.42, 0.77)
p-value		0.0015		0.0003

Key: ERA=Endothelin receptor antagonist; PDE-5i=Phosphodiesterase type-5 inhibitor; M/T FDC=Macitentan/tadalafil fixed dose combination; NT-proBNP=N-terminal pro B-type natriuretic peptide; EDBT=End of Double-blind Treatment; CV=Coefficient of variation; CL=Confidence limit; SD=Standard deviation.

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.

Ratio of EDBT to baseline NT-proBNP is log-transformed (base e) and analyzed using one analysis of covariance (ANCOVA) for each pairwise comparison, 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.

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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Patient reported outcomes

Participants reported a small reduction in their Physical Function and Cognitive/Emotional Function domain scores from baseline to EDBT. However, differences in domain scores between groups were not statistically significant.

Table 18: Change from Baseline to EDBT in PAH-SYMPACT Physical Impact Domain Scores (ANCOVA)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Change from baseline to EDBT				
N	30	60	43	77
Mean (SD)	-0.46 (0.796)	-0.23 (0.597)	-0.23 (0.756)	-0.30 (0.543)
Median	-0.21	-0.14	0.00	-0.14
Range	(-2.9; 0.7)	(-2.0; 2.1)	(-1.7; 2.0)	(-2.3; 1.3)
Adjusted change from baseline				
LS mean	-0.4	-0.2	-0.2	-0.3
SE	0.11	0.08	0.09	0.06
95% CL	(-0.6, -0.2)	(-0.4, -0.1)	(-0.4, -0.1)	(-0.4, -0.2)
Treatment effect: Adjusted change from baseline difference vs. monotherapy				
LS mean		0.2		-0.1
SE		0.13		0.11
95% CL		(-0.1, 0.4)		(-0.3, 0.1)
p-value		0.176		0.433
Change from baseline to EDBT				
N	30	60	43	77
Mean (SD)	-0.46 (0.796)	-0.23 (0.597)	-0.23 (0.756)	-0.30 (0.543)
Median	-0.21	-0.14	0.00	-0.14
Range	(-2.9; 0.7)	(-2.0; 2.1)	(-1.7; 2.0)	(-2.3; 1.3)
Adjusted change from baseline				
LS mean	-0.4	-0.2	-0.2	-0.3
SE	0.11	0.08	0.09	0.06
95% CL	(-0.6, -0.2)	(-0.4, -0.1)	(-0.4, -0.1)	(-0.4, -0.2)
Treatment effect: Adjusted change from baseline difference vs. monotherapy				
LS mean		0.2		-0.1
SE		0.13		0.11
95% CL		(-0.1, 0.4)		(-0.3, 0.1)
p-value		0.176		0.433

Table 19: Change from Baseline to EDBT in PAH-SYMPACT Cognitive/Emotional Impact Domain Scores (ANCOVA)

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: PAH-SYMPACT Impacts	30	60	43	77
Number of subjects included in the analysis	30	60	43	77
Baseline				
N	30	60	43	77
Mean (SD)	1.03 (0.801)	1.13 (0.897)	1.06 (0.835)	1.24 (0.977)
Median	0.75	0.88	0.75	1.00
Range	(0.0; 3.3)	(0.0; 4.0)	(0.0; 3.0)	(0.0; 4.0)
EDBT visit				
N	30	60	43	77
Mean (SD)	0.88 (0.733)	1.03 (0.903)	0.97 (0.803)	1.06 (0.934)
Median	0.75	0.75	0.75	0.75
Range	(0.0; 3.0)	(0.0; 3.3)	(0.0; 3.0)	(0.0; 3.5)
Number of subjects with imputation of missing values (n, %)				
N	3	16	11	17
Missing EDBT PAH-SYMPACT score for any reason[a]	3 (10.0%)	16 (26.7%)	11 (25.6%)	17 (22.1%)
Change from baseline to EDBT				
N	30	60	43	77
Mean (SD)	-0.16 (0.850)	-0.10 (0.547)	-0.10 (0.655)	-0.18 (0.532)
Median	-0.13	0.00	0.00	0.00
Range	(-3.0; 1.0)	(-1.8; 1.3)	(-1.8; 1.8)	(-2.3; 1.3)
Adjusted change from baseline				
LS mean	-0.2	-0.1	-0.1	-0.2
SE	0.11	0.09	0.08	0.06
95% CL	(-0.4, 0.1)	(-0.2, 0.1)	(-0.3, 0.0)	(-0.3, 0.0)
Treatment effect: Adjusted change from baseline difference vs. monotherapy				
LS mean		0.1		0.0
SE		0.14		0.10
95% CL		(-0.2, 0.4)		(-0.2, 0.2)
p-value		0.515		0.711

Health status was assessed using EQ-5D-5L and EQ-VAS. The EQ-5D-5L is composed of 5 single-item domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, where higher scores reflect greater impairment/more severe symptoms. The single index score (a derived summary score), ranges from 0 to 1.00, where 1.00 indicates the best possible health The EQ-VAS is a single-item health status assessment that uses a visual analogue scale that ranges from 0 to 100, higher scores indicate a better health state. There were no differences between treatment groups for change from baseline to EDBT for EQ-5D-5L index score or EQ-VAS score.

The WPAI assess the impact of a person's physical and emotional health problems on their ability to work and perform other normal activities. The WPAI yields scores on a percentage scale: higher scores represent greater productivity impairment. There were no meaningful differences between treatment groups for change from baseline to EDBT for WPAI score.

Table 20: Differences between treatment groups for change from baseline to EDBT forEQ-5D-5L index score or EQ-VAS score

	Treatment-naive and prior ERA strata		Treatment-naive and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
EQ-5D-5L index score[a]				
Baseline				
N	33	67	43	83
Mean (SD)	0.71 (0.199)	0.70 (0.201)	0.71 (0.195)	0.73 (0.188)
Median	0.73	0.74	0.75	0.74
Range	(0.2; 1.0)	(0.1; 1.0)	(0.2; 1.0)	(0.1; 1.0)
EDBT visit				
N	30	54	40	73
Mean (SD)	0.77 (0.154)	0.79 (0.172)	0.77 (0.153)	0.81 (0.171)
Median	0.79	0.77	0.80	0.83
Range	(0.3; 1.0)	(0.3; 1.0)	(0.2; 1.0)	(0.3; 1.0)
Change from baseline				
N	30	54	40	73
Mean (SD)	0.07 (0.199)	0.05 (0.190)	0.06 (0.205)	0.06 (0.174)
Median	0.01	0.03	0.04	0.02
Range	(-0.3; 0.6)	(-0.5; 0.5)	(-0.7; 0.5)	(-0.5; 0.5)
EQ-5D-5L VAS score				
Baseline				
N	33	67	43	83
Mean (SD)	60.7 (23.35)	63.4 (19.86)	65.7 (17.44)	66.9 (19.59)
Median	60.0	64.0	68.0	70.0
Range	(9; 92)	(27; 100)	(30; 96)	(11; 99)
EDBT visit				
N	30	54	40	73
Mean (SD)	68.9 (21.02)	74.3 (17.09)	70.7 (15.88)	75.3 (17.67)
Median	70.5	80.0	70.5	80.0
Range	(20; 100)	(30; 98)	(42; 100)	(10; 100)
Change from baseline				
N	30	54	40	73
Mean (SD)	9.3 (29.58)	7.7 (18.20)	4.4 (18.09)	5.2 (18.52)
Median	11.0	5.5	5.0	3.0
Range	(-60; 85)	(-48; 60)	(-45; 31)	(-71; 60)

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Hemodynamic Measures

In general, a decrease in mPAP was noted between baseline and Week 16/EDBT. On average, this decrease was more pronounced in participants in the M/T FDC groups (approximately -9 to -10 mm Hg) than in participants in the monotherapy groups (approximately -3 to -4 mm Hg). Concurrently, there was a general increase in cardiac index, which, similarly, was more pronounced in participants in the M/T FDC groups (approximately +0.5 to +0.6 L/min/m2) than in participants in the monotherapy groups (approximately +0.2 L/min/m2). In keeping with this, there was a substantially greater increase in stroke volume index (SVI, approximately +10 mL/m2) as well as in mixed venous oxygen saturation (SvO2; approximately +4%) in the M/T FDC groups than in the monotherapy groups (approximately +2 to +4 mL/m2 and +2%, respectively). On average, there were no significant changes in markers of postcapillary pulmonary pressure.

Mean right atrial pressure (mRAP) decreased in the M/T FDC and macitentan groups (-1.4mm Hg and -0.3 mm Hg respectively) and increased in the tadalafil group (+0.4 mm Hg). There was no difference in the proportion of participants with right atrial pressure ≤8 mm Hg at EDBT between M/T FDC and macitentan or between M/T FDC and tadalafil.

Table 21: Proportion of Subjects Achieving a Right Atrial Pressure of ≤8 mmHg at EDBT; Full Analysis Set

	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
Number of subjects achieving right atrial pressure of <= 8 mmHg at EDBT	22(62.9%)	34(48.6%)	24(54.5%)	40(46.5%)
95% CL[a]	(44.9, 78.5)	(36.4, 60.8)	(38.8, 69.6)	(35.7, 57.6)
Risk ratio				
vs monotherapy		0.8		0.9
95% CL[a]		(0.5, 1.2)		(0.6, 1.3)
p-value[b]		0.214		0.459

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.

[a] Confidence limits based on the exact binomial distribution.

[b] p-value obtained from Fisher's exact test.

Note: Right atrial pressure is based on RHC results assessed by the central reader. If a subject does not have right atrial pressure measurement or it was done after EDBT visit date such subject will be considered as not achieving the right atrial pressure of ≤ 8 mmHg.

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

Ancillary analyses

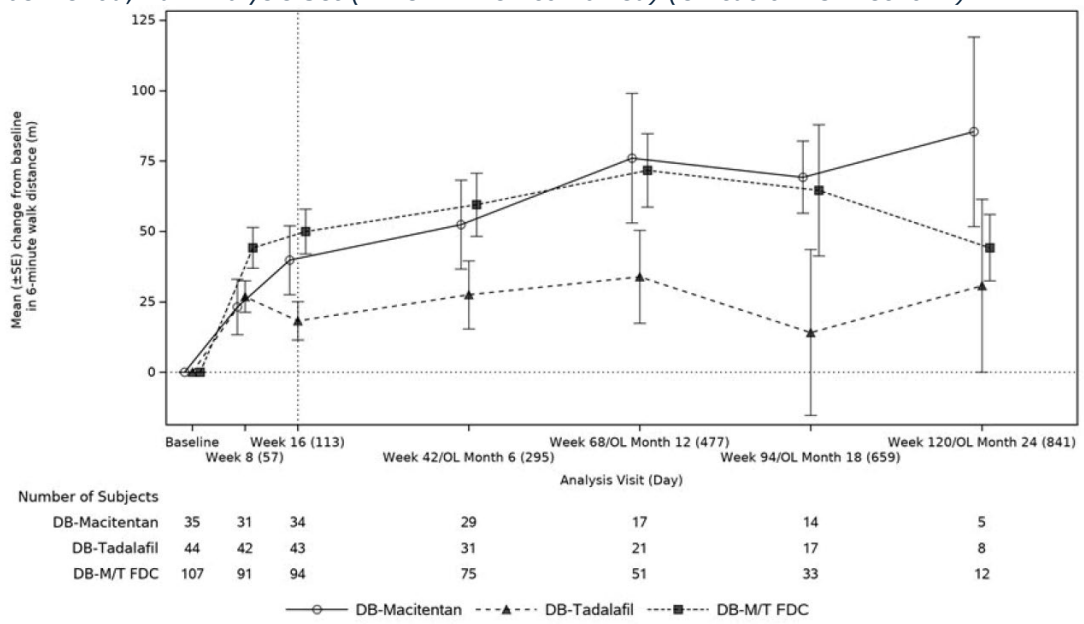
Post-hoc combined double-blind and open label analyses of 6MWD:

The study also includes a 24-month OL single-arm treatment period to evaluate long-term safety and efficacy. As the OL period is ongoing, a cut-off date of 31 December 2022 was applied to allow evaluation of longer-term data. A Month 12 analysis was performed, as the maximum change in 6MWD was expected to be achieved by this time and data were not available for most participants beyond 12 months at the time of cut-off.

Over the combined DB+OL period, 6MWD was analyzed on the FAS including all randomized participants who received at least one dose of study treatment (for participants on FDC at least one dose of either macitentan or tadalafil). Up to Week 16 (DB period) participants received macitentan 10 mg (DB-macitentan), tadalafil 40 mg (DB-tadalafil) or M/T 10/40 mg FDC (DB M/T FDC). Subsequently, all participants received M/T FDC in the OL period. The results should be considered in the context that the A DUE OL period of the study is ongoing, and the duration of follow-up is variable.

Over the combined 12-month DB+OL period, 6MWD data showed a trend towards improvement compared with DB baseline following transition of participants from monotherapy treatment groups in the DB period to treatment with M/T 10/40 mg FDC over 12 months in the OL period. Participants who had received DB-tadalafil treatment had smaller improvements in 6MWD. The mean (SD) change from DB baseline to OL Month 12 was 76.1 (95.2) m in the DB macitentan group (n=17), 33.9 (75.6) m in the DB-tadalafil group (n=21), and 71.8 (93.1) m in the DB-M/T FDC group (n=51).

Figure 10: Mean (±SE) Change from Baseline in 6MWD Over Time in the Combined Double-blind and Open-label Period; Full Analysis Set (A DUE DB-OL combined) (OL cut-off: 31Dec2022)



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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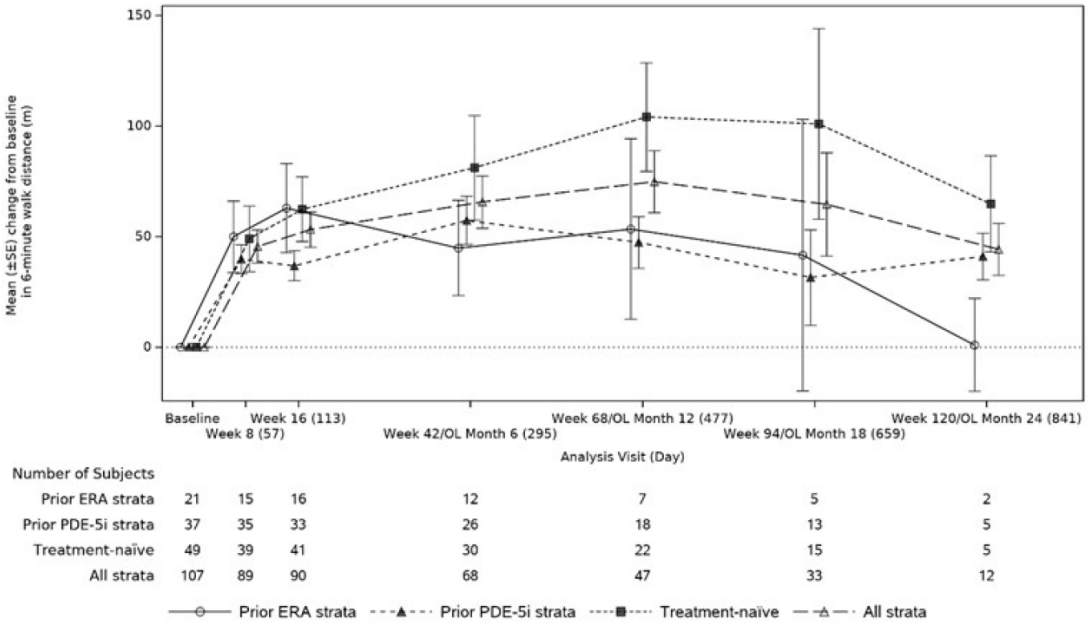
Figure 11: Mean (±SE) Change from Baseline in 6MWD Over Time in the Combined Double-blind and Open-label Period; Long-term M/T FDC Set (A DUE DB-OL combined) (OL cut-off: 31Dec2022)



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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Summary of main efficacy results

Design

Table 22: Summary of main efficacy results

Title: A DUE, 16-Week Double-Blind Period			
Study identifier	AC-77A301, 2014-004786-25, NCT03904693		
Design	Prospective, multi-center, double-blind (DB), randomized, active-controlled, triple dummy, parallel group, group-sequential, adaptive Phase 3 study. Treatment allocation was stratified by treatment status at baseline: • Treatment-naïve participants were randomized in a 2:1:1 ratio to macitentan 10 mg/tadalafil 40 mg fixed dose combination (M/T FDC), macitentan or tadalafil • Participants on prior ERA monotherapy were randomized in a 2:1 ratio to M/T FDC or macitentan • Participants on prior PDE-5i monotherapy were randomized in a 2:1 ratio to M/T FDC or tadalafil The study consisted of 2 periods: a DB treatment period of 16 weeks, followed by a 24-month single-arm open-label extension period. The open-label extension period is ongoing.		
	Duration of main (double-blind) phase: Duration of Run-in phase: Duration of Extension (Open-label) phase:		16 Weeks Not applicable 24 Months
Hypothesis	Superiority		
Treatment groups	M/T FDC for macitentan comparison		M/T 10/40 mg FDC (treatment-naïve and prior ERA strata), 16 weeks, n=71
	M/T FDC for tadalafil comparison		M/T 10/40 mg FDC (treatment-naïve and prior PDE-5i strata), 16 weeks, n=87
	Macitentan		Macitentan 10 mg monotherapy, 16 weeks, n=35
	Tadalafil		Tadalafil 40 mg monotherapy, 16 weeks n=44
Endpoints and definitions	Primary endpoint	PVR	Change in pulmonary vascular resistance (PVR) expressed as the ratio of geometric means of EDBT (end of double-blind treatment) to baseline
	First Secondary endpoint	6MWD	Change from baseline to EDBT in 6-minute walk distance (6MWD)
Database lock	10 October 2022		

Primary & secondary Analysis

Analysis population and time point description				
Full Analysis Set (FAS) consisted of all randomized participants who received at least one dose of study treatment. One participant in the M/T FDC group was randomized but did not receive any study treatment and was thus excluded from FAS. Baseline was the last observation prior to the first study treatment administration. EDBT was planned at the end of DB period (Week 16). For participants who discontinued treatment prematurely, an EDBT was planned within 2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy.				
Descriptive statistics and estimate variability				
Treatment group	Macitentan	M/T FDC for macitentan comparison	Tadalafil	M/T FDC for tadalafil comparison
Number of subjects	35	70	44	86
Primary endpoint: PVR (geometric mean of ratio of EDBT to baseline)	0.77	0.55	0.78	0.56
Coefficient of Variation of geometric mean#	0.34	0.41	0.26	0.37
First Secondary endpoint: 6MWD (Mean Change from baseline) (m)	38.5	52.9	15.9	43.4
SD	70.42	88.23	45.04	78.03
Effect estimate per comparison				
Comparison groups			M/T FDC vs macitentan	M/T FDC vs tadalafil
Primary endpoint – PVR	Adjusted geometric means ratio (median unbiased estimate)		0.71	0.72
	95% repeated CI#		0.61, 0.82	0.64, 0.80
	P-value		<0.0001	<0.0001
Secondary endpoint – 6MWD	Adj. change from baseline difference (median unbiased estimate)		16.04	25.37
	95% repeated CI		-17.00, 49.08	-0.93, 51.59
	P-value		0.3802	0.0591

Notes: Due to the adaptive nature of the study and the Interim Analysis (IA) allowing for premature stop or sample size re-estimation, overall results are the combination of results from each stage (before and after IA

Clinical studies in special populations

Upon CHMP request, the Applicant provided analyses in elderly.

Table 23: PVR (ANCOVA) & 6MWD by age in elderly in DB period; Full Analysis Set (Study AC-077A301)

	Treatment-naïve and prior ERA strata		Treatment-naïve and prior PDE-5i strata	
	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Full	35	70	44	86
PVR				
Age in elderly: 65-74 years	7	11	7	12
Ratio of EDBT to baseline				
N	7	11	7	12
Geometric mean	0.76	0.60	0.68	0.60
Geometric CV	0.410	0.373	0.253	0.355
95% CL of geometric mean	(0.53, 1.10)	(0.47, 0.76)	(0.54, 0.86)	(0.48, 0.75)
Age in elderly: 75-84 years	1	6	3	7
Ratio of EDBT to baseline				
N	1	6	3	7
Geometric mean	0.48	0.55	0.80	0.67
Geometric CV	NE	0.416	0.315	0.546
95% CL of geometric mean	(NE, NE)	(0.36, 0.84)	(0.37, 1.73)	(0.42, 1.08)
6MWD				
Age in elderly: 65-74 years	7	11	7	12
Change from baseline to EDBT				
N	7	11	7	12
Mean (SD)	11.8 (85.32)	84.6 (133.54)	3.9 (52.67)	90.8 (124.25)
Median	12.0	80.0	20.0	82.5
Range	(-100; 132)	(-44; 454)	(-78; 68)	(-30; 454)
Age in elderly: 75-84 years	1	6	3	7
Change from baseline to EDBT				
N	1	6	3	7
Mean (SD)	-1.0 (-)	1.9 (97.82)	22.0 (44.91)	-17.3 (60.07)
Median	-1.0	-1.4	15.0	-9.0
Range	(-1; -1)	(-135; 158)	(-19; 70)	(-135; 43)

In vitro biomarker test for patient selection for efficacy

N/A

Analysis performed across trials (pooled analyses and meta-analysis)

Supportive A

To support the efficacy of the pivotal Phase 3 study AC-077-A301 (A DUE) and in the absence of head-to-head trials comparing macitentan + tadalafil versus macitentan monotherapy from various trials, an indirect

treatment comparison is a useful approach of evaluating the effectiveness of the different therapies. Due to the lack of a common comparator, an unanchored indirect treatment comparison (ITC) was performed to evaluate the effectiveness of the loose combination of macitentan and tadalafil (M + T) versus macitentan (M) monotherapy in treatment-naïve, newly diagnosed patients with pulmonary arterial hypertension (PAH). This analysis was carried out using pooled individual patient-level data (PLD) from five internally completed trials conducted by clinical global development; AC-065A308 (TRITON), AC-055-403 (REPAIR), AC-055-302 (SERAPHIN), AC-055-310 (ORCHESTRA) and AC-055-401 (SYMPHONY). Due to lack of randomization, as well as the lack of an anchor and the limited assessment time points across studies/arms, supportive analysis A is to be considered supportive in nature.

Objective:

The primary objective was to compare the efficacy of initial (first line) treatment with the loose combination of macitentan + tadalafil (M + T) versus M monotherapy on the change from baseline to Week 16, and Week 26 in 6-minute walking distance (6MWD).

An overview of the used studies is shown in the table below.

Table 24: Overview of used studies for Supp A

Study	Study Design	Objective	Treatment Period
AC-065A308 TRITON	Prospective, multi-center, double-blind, randomized, placebo-controlled, parallel group, Phase 3b study Macitentan 10 mg + tadalafil 40 mg once daily + placebo twice daily OR Macitentan 10 mg + tadalafil 40 mg once daily + selexipag 200-1600 µg twice daily	Efficacy and safety in treatment-naïve participants with PAH	Start of open-label M + T (Day 1) until end of treatment (Approximately 4 months after end of main observation period (26 ± 1 weeks after enrollment of the last participant))
AC-055-403 REPAIR	Prospective, multicenter, single-arm, open-label Phase 4 study Macitentan 10 mg once daily	Evaluate the effect of macitentan on right ventricle and haemodynamic properties and safety in participants with PAH	First dose of study treatment (Day 1) until the premature discontinuation of study drug or end of treatment on the day of the last dose of study drug at Week 52 ±7 days.
AC-055-302 SERAPHIN	Multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven phase 3 study (morbidity/mortality events) Macitenan 10mg or placebo once daily	Efficacy and safety in participants with PAH	Randomization to end of treatment or premature treatment discontinuation
AC-055-310 ORCHESTRA	Prospective, multi-center, open-label, single-arm, phase 3b psychometric validation study Macitentan 10 mg once daily	Validation of the French, Italian, and Spanish version of the PAH-SYMPACT in participants with PAH	Baseline (Day 1) to end of treatment (Week 16) or premature treatment discontinuation
AC-055-401 SYMPHONY	Prospective, multi-center, open-label, single-arm, phase 3b psychometric validation study Macitentan 10 mg once daily	PAH-SYMPACT validation and safety in participants with PAH	Baseline (Day 1) to end of treatment (Week 16 ± 3 days) or premature treatment discontinuation

Pooling

For the analyses. two treatment groups are identified as follows:

- Macitentan 10 mg + Tadalafil 40 mg combination therapy (M + T),
- Macitentan 10 mg monotherapy (M).

The analyses of the pooled data focussed on the comparison of M + T versus M monotherapy.

The following individual participant-data were pooled:

- TRITON AC-065A308 - data used only up to the end of the main observation period from the double treatment arm (macitentan 10 mg + tadalafil 40 mg once daily + placebo twice daily). All the participants will contribute to the M + T combination therapy group.
- REPAIR AC-055-403 - data from the final analysis set. Participants who at baseline did not take tadalafil as a standard of care therapy AND are not initiating tadalafil up to week 26 will contribute to the M monotherapy group. Participants who at baseline received tadalafil will contribute to the M + T combination therapy group.
- SERAPHIN AC-055-302 - data only from the double-blind (DB) phase, participants from the macitentan 10mg arm will contribute to the M monotherapy group - there were no participants in this group who used tadalafil. Participants who initiated Sildenafil before week 26 will not be pooled.
- ORCHESTRA AC-055-310 and SYMPHONY AC-055-401 - data only from the prospective phase of the study will be used (open-label extension study will not be used). Participants will contribute to the M monotherapy group.

Statistical hypotheses:

No formal hypothesis is planned. The statistical comparisons (point estimates with confidence intervals) are exploratory in nature.

Sample sizes

The sample sizes per outcome are shown in the tables below.

Table 25: Sample Size for 6MWD

Study	Treatment	Visit				
		Baseline	Week 8	Week 12	Week 16	Week 26
TRITON	M+T combination	124		116		110
REPAIR	M+T combination	27				27
	M monotherapy	21				19
SERAPHIN	M monotherapy	34		29		27
ORCHESTRA	M monotherapy	40	37		37	
SYMPHONY	M monotherapy	115	100		97	

Inclusion criteria

Participants must meet all the following inclusion criteria for eligibility in the pooled analyses:

1. Aged ⩾18 years at screening
2. Initial PAH diagnosis <6 months prior to first dose. For the REPAIR study where the date of PAH diagnosis was not collected, this is defined as participants where age at diagnosis is equal to the age at enrolment.
3. PAH diagnosis confirmed by right heart catheterization (RHC) meeting the following criteria:
    a. mean right atrial pressure (mPAP) ⩾25 mmHg;

b. pulmonary arterial wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) ⩽15 mmHg;

c. pulmonary vascular resistance (PVR) ⩾240 dyn.s/cm5).

4. PAH treatment-naïve, whose first PAH treatment was macitentan 10 mg as monotherapy or in combination with tadalafil.

5. Having WHO FC II to III and 6MWD between 50 and 450 m.

Statistical analyses

Three random, longitudinal mixed models for a normally distributed dependent variable will be used to estimate of the treatment effect of M + T versus M monotherapy at Week 16 and 26 in 6MWD.

The common features for these models include that participants are considered as a random factor (random intercept), the difference between treatment group will be adjusted for baseline categorical and continuous variables (i.e. 6MWD (in meters), PVR (logarithmically transformed (natural log) of assessment in dyn·sec/cm5), Age (years), BMI (kg/m2), SBP (mmHg), DBP (mmHg), WHO FC (II or III), Sex (male/female), Arterial hypertension (yes/no), Connective tissue disease (yes/no), Diabetes mellitus (yes/no)).

The selection of baseline covariates is based on clinical judgment and availability of data. Derivation of the point estimates and their 95% CIs for treatment specific means and between treatment mean differences will be obtained from the LSMEANS statement. This statement allows for estimating predicted population margins that is, the procedures will estimate the marginal means over a balanced population.

Model Assumptions are made that all models assume interaction between time since first dosing and treatment, and all models will use data on the actual study day of the measurement (not the nominal time for the planned visit). The models differ regarding the assumed effect of time from the time since first dosing on the dependent variable:

- Model 1: assumes that the effect is linear,
- Model 2: assumes that the effect is quadratic (both parameters for time would be treatment specific for M + T this would be a1*time+b1*time2, for M this would be a2*time+b2*time2),
- Model 3: does not assume any parametric effect of time, this effect would be modelled using splines.

Results

The pooled analysis set contained a total of 287 participants; 109 assigned to the M+T arm and 178 assigned to macitentan monotherapy. Before any covariate adjustment, baseline characteristics were generally evenly distributed between the two treatment groups. However, notable differences were observed in the following baseline characteristics:

- Gender: in the study population, the overall proportion of females was higher to the proportion of males (79.4% vs 20.6%);
- Race: in the pooled analysis set, most participants were white (78%);
- Age: the proportion of participants aged ⩾65 years in the macitentan monotherapy arm was slightly higher in comparison to the M+T arm (38.8% vs 25.7%);

- WHO FC: participants in the macitentan monotherapy arm had more severe baseline symptoms when compared to the M+T arm (36% vs 12.8% WHO FC II);

- PVR: mean baseline PVR (SD) was higher in M+T arm compared to the M monotherapy arm (1023.9 (361.82) dyn·s/cm5 vs 697.5 (418.05) dyn·s/cm5).

Results for changes from baseline to week 16, and week 26 in 6MWD (imputed) in the pooled analysis set are presented in the table below.

A conservative approach to interpretation was taken for the time effect in the random-effects model. Hence, results were based on the model with the lowest point estimate and that assumed a linear time effect. The adjusted least squares mean difference (95% CIs) of macitentan + tadalafil versus macitentan monotherapy was 34.3m (13.7m, 55.0m) at week 16, whilst the adjusted least squares mean difference (95% CIs) of macitentan + tadalafil versus macitentan monotherapy was 41.6m (20.8m, 62.3m) at week 26.

Table 28: Adjusted Least Squares Means for Change from Baseline to Week 16, and Week 26 in 6MWD (Imputed)

	Adjusted Means (95% CI)		
Timepoint	Macitentan + Tadalafil (N=109)	Macitentan (N=178)	Least Squares Mean Difference (95% CI)
Week 16	37.7 (16.2, 59.2)	3.4 (-14.4, 21.3)	34.3 (13.7, 55.0)
Week 26	44.6 (23.4, 65.8)	3.0 (-15.5, 21.5)	41.6 (20.8, 62.3)

Supportive B

To further support efficacy of the pivotal Phase 3 A DUE study and in the absence of other randomized clinical studies comparing M/T 10/40 mg FDC vs either monotherapy, indirect treatment comparison (ITC) was considered a useful approach for evaluating the effectiveness of the different therapies.

Clinical studies which constitute all the applicable and relevant data available to the Applicant on macitentan + tadalafil combination, macitentan monotherapy, and tadalafil monotherapy, were used for ITC for naive participants, as described below:

Applicant-sponsored completed clinical studies in treatment-naïve patients in WHO Group 1 PAH were included as treatment arms:

- Co-administration of the loose combination of M+T 10+40 mg

- Macitentan monotherapy (M10 mg)

Tadalafil monotherapy T40 mg arm was taken from an external study, AMBITION, in treatment-naïve patients in WHO Group 1 PAH (Galiè 2015b).

<u>Objectives</u>

To compare the effectiveness of loose combination of macitentan and tadalafil versus tadalafil monotherapy in treatment-naïve, newly diagnosed participants with PAH were followed regarding changes from baseline to Week 24/26 in 6MWD.

Design

An unanchored matching-adjusted indirect treatment comparison (MAIC) was implemented, making use of the IPD of the TRITON double-combination regimen arm and the patients from REPAIR that are on double-combination and the aggregated data from the literature for AMBITION.

The comparison is unanchored as there is no within-study common comparator that can be used, so that TRITON and REPAIR double-combination patients will be compared directly to the AMBITION monotherapy arm.

A) Study treatments in TRITON dual oral regimen arm are:

- Macitentan oral tablet, 10 mg once daily starting from Day 1.
- Tadalafil oral tablet, 20mg once daily at start of treatment (Day 1), increased to 40 mg once daily from day 8 ± 3 (up-titration to 40 mg once daily should be based on individual tolerability in subjects with mild or moderate renal impairment)

B) Study treatment in REPAIR was:

- Macitentan oral tablet, 10 mg once daily starting from Day 1. Participants with a treatment strategy of initial combination of macitentan and PDE-5i (as ticked in CRF for treatment strategy), who received at least one dose of both macitentan and tadalafil and started any dose of tadalafil 2 weeks before or after the first dose of macitentan will be included as dual-combination patients, following the intent-to-treat principle.

C) Study treatments in AMBITION tadalafil therapy arm are:

- Tadalafil oral tablet, 20mg once daily at start of treatment, increased to 40 mg once daily from Week 4 visit onward (Subjects with mild to moderate renal impairment should be carefully assessed for tolerability at the week 4 visit and a risk-benefit decision made by the investigator whether the subject remain on the 20mg once daily dose or up-titrate to 40mg once daily.)

The matching-adjusted indirect comparison (MAIC) approach proposed by Signorovitch, et al (2010) will be used to estimate weights for TRITON/REPAIR subjects such that the weighted average of the baseline characteristics chosen match those from AMBITION. The indirect comparisons are then conducted based on the balanced populations. The matching is accomplished by re-weighting TRITON and REPAIR patients by their inverse odds of enrollment in the TRITON/REPAIR trial vs. AMBITION trial i.e., the matching will be based on the combined TRITON / REPAIR vs the AMBITION population. TRITON and REPAIR are considered one trial for the purpose of this analysis.

Statistical Hypotheses

No formal hypothesis testing will be performed. The significance level (Type I error rate) is not controlled in this exploratory post hoc analysis and therefore no statistical significance testing will be applied.

Inclusion criteria:

For the AMBITION trial: Confirmed diagnosis of PAH (Based on right heart catheterization before screening) with:

- - mPAP ⩾25 mm Hg
- - PVR ⩾300 dyne·sec/cm5

- - PCWP or LVEDP ⩽12 mm Hg if PVR ⩾300 to <500 dyne·sec/cm5
- - or PCWP or LVEDP ⩽15 mm Hg if PVR ⩾500 dyne·sec/cm5

Exclusion criteria:

For the AMBITION trial: Participants must not have ⩾3 of the following HFpEF risk factors:

- BMI ⩾30 kg/m2
- History of essential hypertension
- Diabetes mellitus (any type)
- Historical evidence of significant CAD established by any of the following:
    - History of MI
    - History of PCI
    - Angiographic evidence of CAD
    - (>50% stenosis in ⩾1 vessel)
    - Positive ST
    - Previous CABG
    - Stable angina

For the purpose of this analysis only results from subjects receiving Tadalafil monotherapy will be used for the comparison with TRITON/REPAIR. The PAS analysis set will be used for all comparative effectiveness analyses.

Relevant inclusion/exclusion criteria of TRITON/REPAIR were aligned with the AMBITION trial by excluding participants in TRITON/REPAIR that were not able to be enrolled in AMBITION. To increase the potential effective sample size of the macitentan and tadalafil arm, PLD from TRITON and REPAIR was pooled. Aggregate level data from the tadalafil arm AMBITION was used as comparator.

The MAIC approach proposed by (Signorovitch 2010) was used carry out an unanchored indirect treatment comparison. In this method, participants in TRITON/REPAIR were weighted by the inverse of their propensity score to balance the covariate distribution with that of participants in AMBITION. Potential covariates (gender, world health organization functional class (WHO FC), age, hypertension, etiology, prior diuretics, right arterial pressure, cardiac index, pulmonary vascular resistance, 6MWD and log(NT-proBNP)) were selected following clinical judgement of the variables used in REVEAL risk score calculator for PAH. A logistic model was used to estimate the weights as described by Signorovitch (2010).

Statistical analyses

Analyses of change from baseline to week 24 in 6MWD were conducted using a weighted analysis of covariance (ANCOVA) model from TRITON/REPAIR and aggregate results reported in AMBITION. The ITC based on (Bucher 1997) method was also performed to obtain the ITC mean difference and its 95% confidence interval (CI). Change from baseline to week 24 in NT-proBNP was considered as an exploratory

endpoint in the SAP. Aggregate results in the primary manuscript for AMBITION (Galiè 2015) were summarized as a percentage difference but no standard error or confidence limits were reported.

The analyses were performed on 2 analysis sets the; AMBITION-like analysis set and modified full analysis set (mFAS). The AMBITION-like analysis set was the primary analysis set of interest.

The full analysis set (FAS) includes all Full Analysis Set subjects as per CSR definition, that are dual combination participants and received at least one dose of study drug. The FAS will be used to describe the number of subjects excluded from the mFAS due to missing baseline covariates used for weighting.

The modified full analysis set (mFAS) includes all subjects included in the FAS with no missing baseline covariates used for weighting.

The AMBITION-like analysis set includes all subjects in the FAS who received a study drug and who meet at baseline the following criteria (originally from AMBITION study inclusion/exclusion criteria. Inclusion criteria: WHO FC II or III, 125m $\leqslant$ 6MWD $\leqslant$ 500m; Exclusion criteria: Body weight < 40 kg, SBP $\geqslant$ 180 mmHg, serum ALT or AST > 2xULN).

- Post-Hoc Analysis

The MAIC was repeated on the AMBITION-like analysis set using a subset of the original covariates; WHO FC, 6MWD and log(NT-proBNP) to assess the contribution of different variables when calculating the weights required for the indirect treatment comparison. The choice of covariates was based on the European Respiratory Society/European Society of Cardiology (ESC/ERS) 2022 risk stratification assessment.

Results

The AMBITION-like analysis set contained 111 participants assigned to the M+T arm whilst the mFAS contained 134 participants assigned to the M+T arm. Before matching, baseline characteristics were generally evenly distributed between the two populations. However, a notable difference in the proportions for WHO FC was observed in the AMBITION-like analysis set; TRITON/REPAIR had a lower proportion of patients with WHO FC I-II (16.2% vs 34%) and WHO FC III-IV (83.8% vs 66%). This suggests that WHO FC was a contributory factor for the M+T and T treatment arms being smaller (39.2) than the sample size before matching (111). A 65% reduction from the original sample size was observed, suggesting a low degree of similarity between the patient populations compared prior to matching, and resulting in insufficient power to detect the difference of the magnitude observed in the pivotal Phase 3 study AC-077-A301 (A DUE).

Main Analysis for Changes from Baseline to Week 24 in 6MWD (Imputed)

Results for changes from baseline to week 24 in 6MWD (imputed) in the AMBITION-like analysis set and mFAS are presented in the table below. The estimated mean difference of macitentan + tadalafil versus tadalafil after matching was 3.9m, whilst the result prior to matching was 32.5m in the AMBITION-like analysis set. Conversely, in the mFAS the estimated mean difference of macitentan + tadalafil versus tadalafil after matching was -2.1m, whilst the result prior to matching was 29.9m.

Table 30: Changes From Baseline to Week 24 in 6MWD – Main Analysis

	ITC Mean Difference (SE) (95% CI) p-value
AMBITION-like Analysis Set	
Bucher's Method - Unweighted	32.5 (9.81) (13.3, 51.8) 0.0009
Matched-Adjusted Indirect Comparison - Weighted	3.9 (20.50) (-36.3, 44.1) 0.8492
mFAS	
Bucher's Method - Unweighted	29.9 (9.62) (11.1, 48.7) 0.0019
Matched-Adjusted Indirect Comparison - Weighted	-2.1 (17.45) (-36.3, 32.1) 0.9042

Post-hoc Analysis for Changes from Baseline to Week 24 in 6MWD (Imputed)

Results for changes from baseline to week 24 in 6MWD (imputed) in the AMBITION-like analysis set and mFAS are presented in the table below. The estimated mean difference of macitentan + tadalafil versus tadalafil after matching was 31.6m, whilst the result prior to matching was 32.5m in the AMBITION-like analysis set. Similarly, in the mFAS the estimated mean difference of macitentan + tadalafil versus tadalafil after matching was 29.4m, whilst the result prior to matching was 29.9m.

Table 31: Changes From Baseline to Week 24 in 6MWD – Post-hoc Analysis

	ITC Mean Difference (SE) (95% CI) p-value
AMBITION-like Analysis Set	
Bucher's Method - Unweighted	32.5 (9.81) (13.3, 51.8) 0.0009
Matched-Adjusted Indirect Comparison - Weighted	31.6 (10.59) (10.9, 52.4) 0.0028
mFAS	
Bucher's Method - Unweighted	29.9 (9.62) (11.1, 48.7) 0.0019
Matched-Adjusted Indirect Comparison - Weighted	29.4 (10.68) (8.5, 50.4) 0.0058

2.6.5.3. Supportive study(ies)

Disease specific program data on PDE5 inhibitor and ERA therapy prescribing in a real-world setting in Europe

The disease specific programs (DSPs) are real-world surveys that reflect current clinical practice, regardless of what guidelines or recommendations are advocated. DSPs are large, quantitative, point-in-time surveys allowing multiple research questions to be objectively explored, currently covering over 80 disease areas. DSP™ provides a unique insight into the World Health Organisation (WHO) Group one PAH patient population through the collection of real world evidence. In particular, the DSP dataset was designed to provide unbiased evidence regarding treatment patterns and market understanding across disease areas due to its hypotheses-free methodology.

The objectives were to investigate the proportion of patients initiated on ERA and PDE5i for the treatment of PAH in 2020 and 2022, across EU5 (France, Germany, Italy, Spain, and UK) and to categorize the proportion of patients in the EU5 receiving combination treatment of both ERA and PDE5i as initial line of treatment and the number then prescribed this at six months and a year following initiation.

Physician inclusion criteria were 1) personally responsible for the treatment decisions of WHO group 1 PAH patients and 2) must see a minimum of 2 PAH patients per month. Patient inclusion criteria were adult patients (not currently in a clinical trial) with a physician-confirmed diagnosis of WHO group 1 PAH, that were prescribed PAH-specific treatments. A quarter of patients were initiated on PAH treatment with a PDE5i & ERA combination, most commonly also in combination with supportive therapies. The proportion of patients prescribed combination therapy at initiation in the 2022 dataset was consistent with that in 2020. The proportion of patients prescribed a PDE5i + ERA increased over time, from 22.3% at initiation to 29.1% at 12 months after initiation.

In both the 2020 and 2022 populations of patients treated with PAH specific therapy, a similar female to male split was seen; patients were on average reported to be in their late 50s, with a diagnosis of APAH or IPAH. At the time of the survey, most patients were prescribed monotherapy with over a third receiving PAH-specific combination therapy.

Just under a third of those treated with PAH specific therapies in the 2020 and 2022 populations were initially prescribed combination therapy. Prescribing of PAH-specific combination therapy at treatment initiation was more frequently reported for patients consulting with a physician based in an affiliated center at the time of the survey.

Pulmonary Arterial Hypertension (PAH) Therapy Monitor

A online physician survey including demographic form, perceptual questionnaire and patient charts was performed in Germany, Italy, Spain, and UK, collected annually from 2017 – 2022.

The survey included cardiologists, pulmonologists and rheumatologists who have been managing PAH patients for at least 2 years.

The survey demonstrated that initial dual therapy was started in 41% of the patients. ERA + PDEP-5i represented 75% of drug class in dual dual-therapy received as initial treatment, of which 29% was macitentan + tadalafil, compared to 33% ambrisentan + tadalafil.

Targeted literature search on PDE5i+ERA prescribing

The aim of this literature review was to assess whether the ESC/ERS guideline recommendation to start with initial treatment of ERA + PDE5i has been translated into clinical practice by looking at real-world evidence,

specifically focusing on combination therapy prescription practices in newly diagnosed patients with PAH in Europe. This literature review described real-world prescribing practices of initial double oral combination therapy in PAH in Europe. To do so, 17 full text articles and 3 abstracts were retrieved, and relevant data were extracted and summarized.

The available data have been collected mainly through three large registries (The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension registry [COMPERA], the French PH Registry and the Swedish Pulmonary Arterial Hypertension Registry [SPAHR]). Overall, PAH patients with a variety of aetiologies are included in the publications reviewed, covering the range of group 1 PAH subclassifications (with some publications focusing on specific aetiologies). According to the 2022 ESC/ERS Guidelines, all patients without cardiopulmonary comorbidities should be started on combination therapy, whereas in patients with cardiopulmonary comorbidities monotherapy is recommended at initiation. Only three publications (Rosenkranz 2023, Hoeper 2022 and Escribano 2022) provided an analysis specific to this recommendation. While a higher proportion of patients with a low comorbidity burden were initiated on combination therapy compared to those with a high comorbidity burden, approximately half were still prescribed initial monotherapy.

Two publications analyzed the change in initial treatment strategy over time, with an increase observed in the proportion of patients started on initial double oral combination therapy between 2010 and 2019 (from 10% to 25%) in COMPERA and from 2016 to 2018 in the IPSOS Healthcare PAH Therapy Monitor research (reported as a decrease in monotherapy from 67% to 59%). The authors of the first publication proposed that this increase was related to the publication and subsequent dissemination of the 2015 ESC/ERS Guidelines. However, these analyses suggest that less than half the patients were initiated on combination therapy, even up to 2019. Where initial combination therapy was used, the classes of drugs most commonly prescribed together were ERA and PDE-5i.

In summary, this literature review has identified discrepancies between the evidence-based recommendations for initial double oral combination therapy in patients with PAH and clinical practice in Europe, suggesting double combination therapy is underutilized as an initial treatment strategy. The real-world data included in this review suggest that even after the ESC/ERS Guidelines made the recommendation for double combination therapy in 2015, a greater proportion of patients were initiated on monotherapy than on double combination therapy in Europe. In some older papers, with data collection periods mainly before 2015, the proportion of patients prescribed initial double combination therapy was approximately 10 – 20%. In more recent publications that included the largest number of patients, approximately 20 – 40% of patients were initiated on double combination therapy. There appears to be a gap between the recommendation in the ESC/ERS Guidelines for double combination therapy in most newly diagnosed patients and what is observed in clinical practice.

DARWIN EU® - Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH).

Rationale and Background

Pulmonary Arterial Hypertension (PAH) is a rare type of pulmonary hypertension characterized by increased mean pulmonary arterial pressure. PAH can be idiopathic, heritable, drug-induced, or secondary to other chronic diseases such as HIV infection, congenital heart diseases, portal hypertension. Median survival is about 7 years from the time of diagnostic catheterisation. The therapeutic management differs based on type and severity and usually involves a mono or combination therapy from the following agents: Endothelin receptor antagonists (ERAs), and Phosphodiesterase-5 inhibitors (PDE5-is). There is interest in understanding how these therapies are used in clinical practice to contextualise assessments of potential future development programs in this indication.

Research question and Objectives

Research question:

To understand how PAH is treated in clinical practice. Specific objectives of this study are listed below.

Study objectives:

(1) To estimate proportions of patients with newly diagnosed pulmonary arterial hypertension (PAH) who initiate treatment with endothelin receptor antagonists (ERAs) or phosphodiesterase-5 inhibitors (PDE-5is), either as monotherapy or in combination, during the period from January 1, 2012, to December 31, 2022.

(2) To estimate the duration of prescription for ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(3) To describe the prescription patterns and sequences of ERAs and PDE-5is in patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022.

(4) To estimate the proportion of patients with newly diagnosed PAH who experience specific events of interest, namely cardiovascular hospitalization, all-cause hospitalization, and death, after initiating treatment with ERAs and PDE-5is between January 1, 2012, and December 31, 2022.

Research Methods

Study design

Retrospective cohort study in patients with newly diagnosed PAH.

Population

Patient-level characterization – Disease epidemiology study: The patient-level characterization included patients with newly diagnosed PAH between January 1, 2012, and December 31, 2022 (or the latest available date if earlier), with at least 1 year of data availability prior to their diagnosis, and no record of being diagnosed with PAH in the previous year. To investigate treatment patterns, a minimum follow-up time of 30 days were applied to capture PAH treatment (objective 1), and treatment sequences (objective 3).

Patient-level drug utilization: New users of ERAs/PDE-5is in patients newly diagnosed with PAH in the period between January 1, 2012, and December 31, 2022 (or latest date available), with at least 1 year of data

visibility prior to index date, and no use of the respective ERAs/PDE-5is in the previous 1 year, were included for patient-level drug utilisation analyses. Therefore, children aged <1 year were excluded.

Variables

Drug of interest: Drugs of interest were identified through RxNorm drug codes.

1. Endothelin receptor antagonists: Ambrisentan, Bosentan, Macitentan, and Sitaxentan.

2. Phosphodiesterate-5 inhibitors: Sildenafil and Tadalafil.

Condition of interest: PAH was identified through SNOMED disease codes.

Outcomes of interest: Study outcomes were identified based on the presence of events of cardiovascular hospitalisation, all-cause hospitalisation, and death.

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France

2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

3. Estonian Biobank (EBB), Estonia

4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

Sample size was not calculated, as our primary focus was to examine the characteristics and treatment patterns of all incident PAH patients, irrespective of the sample size.

Data analyses

The number and % of patients receiving each of a pre-specified list of PAH treatments (objective 1) and treatment combinations (objectives 1 and 3) were described at index date, 1 to 30, 1 to 90, and 1 to 365 days post index date. A treatment pattern analysis was conducted to describe the sequence of prescribing of the specific ERAs/PDE-5is following diagnosis. Index date was the date of diagnosis of PAH. Sunburst plots and Sankey diagrams were used to describe treatment patterns and sequences over time (objective 3).

Large-scale patient-level characterisation was conducted to describe age and sex at time of PAH diagnosis and for 365 to index date. The medical history included clinical symptoms and signs (chest pain, dyspnea, fatigue, syncope), comorbidities (obesity, congenital heart disease, heart failure, pulmonary embolism, chronic obstructive pulmonary disease, pulmonary fibrosis, obstructive sleep apnea and chronic kidney disease), and important factors possibly related to PAH diagnosis (idiopathic, heritable, connective tissue disease, corrected congenital shunts, drug or toxin induced PAH, and others). We also reported the proportion of patients with outcomes of interest for 1-, 3-, and 5-years post index date (objective 4).

Patient-level ERAs/PDE-5is use: Patient-level features were characterized, and the treatment duration of prescriptions of the respective drugs of interest was estimated. Index date was the date of the first prescription of the specific ERAs/ PDE-5is for each person. Treatment duration was estimated for the first treatment era and the minimum, p25, median, p75, and maximum was provided.

For all analyses a minimum cell count of 5 was used when reporting results, with any smaller counts obscured.

Results

During the study period, 9,474 patients newly diagnosed with PAH were identified namely 75 (0.8%) in EBB, 2,061 (21.8%) in CHUBX, 3,378 (35.7%) in CPRD and 3,960 (41.8%) in IQVIA DA Germany. In all databases, patients with PAH were mainly diagnosed at the age of 65 years or above (49-81%) and the proportion of females (51-65%) was slightly higher than the proportion of males. Comorbidity was high in all databases and consisted of heart failure (19.3 - 66.7%), COPD (17.6 - 22.7%), connective tissue disorder (14.0 - 64.0%), diabetes mellitus (17.3-24.4%), systemic hypertension (28.0 - 64.9%), and ischemic heart disease (14.8 - 45.3%). Use of drugs known to be associated with PAH was low or non-existing except for selective serotonin reuptake inhibitors (SSRIs) (1.4-14.7% in the year prior to the index date (i.e. date of diagnosis of PAH)) and tramadol (1.1-10.5%). Use of concomitant drugs was the lowest for IQVIA DA Germany.

Amongst patients with newly diagnosed PAH and with at least 30 days of follow-up post-PAH diagnosis, there were less than 10% of individuals being treated in IQVIA DA Germany (n=117, 3.3%) and CPRD GOLD (n=210, 6.4%) whereas this proportion was around 19.1% in CHUBX (n=335, 19.1%), and 20.8% in EBB (n=15).

The use of PAH-targeted drugs varied across different databases during the observation period. The predominant therapeutic category of PAH-targeted drugs used as index treatment was PDE-5is (mainly sildenafil), with prescription rates of 1.3% in both CPRD GOLD and IQVIA DA Germany, 2.1% in CHUBX, and relatively higher rate in EBB (6.9%). Unlike other databases, ERAs were the most common therapeutic category of PAH-targeted drugs used as index treatment in CHUBX (2.5%), predominately bosentan (2.3%). Conversely, ERAs were not used as index treatment in CPRD GOLD and EBB. In IQVIA DA Germany, ERAs were sparingly prescribed (0.4%).

The post-index treatment with PDE-5is demonstrated increasing prescription rates within the year following PAH diagnosis across all databases namely 13.1% for CHUBX, 4.7% for CPRD Gold, 20.8% EBB and 2.2% for IQVIA DA Germany at 365 days post-index. A similar trend was observed for ERAs, although the increase in their utilization demonstrated a more moderate pattern, notably in CHUBX. In general, the use of combination therapy, which entails the prescription of both ERAs and PDE-5is, remained minimal, with rates remaining below 1% in all databases and throughout various time intervals.

The median duration of ERAs was one day in CHUBX and CPRD GOLD but 30 days in EBB and IQVIA DA Germany. The specific ERA, ambrisentan, was usually prescribed for one day in all databases, except for IQVIA DA Germany, where it extended to 30 days. Bosentan was prescribed for much longer duration, with median duration of 28 days in both CPRD GOLD and IQVIA DA Germany, 30 days in EBB, and typically one day in CHUBX. The median duration of the first prescription of PDE-5is was 30 days in both EBB and IQVIA DA Germany, 28 days in CPRD GOLD, and notably shorter in CHUBX, where it averaged just one day.

Treatment patterns varied between databases where in CHUBX, 47.5% of PAH patients received monotherapy and 52.5% received combination therapy. Most patients in CPRD GOLD received monotherapy (89%), with PDE-5is being the dominant choice (83.3%), and sildenafil was the preferred drug within this class (73.8%). Only a small fraction of patients (7.1%) received combination therapy, with sildenafil-bosentan emerging as the most prescribed combination (2.9%). In IQVIA DA Germany, the majority of patients received monotherapy (81.2%), with PDE-5is being the most common choice (72.6%), particularly sildenafil (49.6%). Combination therapy was less common, with only 6.8% of patients receiving such treatment, primarily macitentan-sildenafil (4.3%) combination. In EBB, PDE-5is (53.3%), particularly sildenafil (46.7%), was the primary choice for monotherapy treatment, with 46.7% of patients receiving combination therapy. Overall, the predominant treatment approach for PAH across all databases was monotherapy with PDE-5is, specifically sildenafil. ERAs were less frequently used as monotherapy, with

bosentan being the most prescribed drug in this class and often initiated in combination therapy with other PAH-targeted drugs. The use of combination therapy was generally less common but was more frequent in CHUBX and EBB than in CPRD GOLD and IQVIA DA Germany.

With regard to hospitalisation as outcome, percentages were 100% for CHUBX which is a hospital database and thus all patients were inherently hospitalized. Estonian Biobank database (EBB) had a high hospitalization rate of 86.7% at index, and notably, within one year following PAH diagnosis, all patients in EBB had experienced hospitalization. A parallel pattern was discerned in cardiovascular hospitalization, with both CHUBX and EBB starting at high rates at index (99.7% and 93.3%, respectively) and reaching 100% in both databases within one-year post-index. No hospitalisation rates could be provided for IQVIA DA Germany and CPRD Gold.

The trajectory of mortality rates over the years showed distinct patterns among the databases. EBB had a relatively stable mortality rate of less than 1%. In contrast, CHUBX and CPRD GOLD demonstrated a progressively increasing mortality rate (14.3% mortality at three years post-index for CHUBX and 31.9% for CPRD Gold).

Discussion

This study provides a comprehensive analysis of 9,474 patients diagnosed with incident pulmonary arterial hypertension (PAH) between 2012 and 2022 in four European countries, offering valuable insights into real-world settings. The patient population was predominantly comprised of older adults with a slight female preponderance, and common symptoms preceding PAH diagnosis included dyspnea and chest pain. Furthermore, over 75% of the participants had pre-existing cardiovascular disease. Pre-index exposure to certain medications was notable, with selective serotonin reuptake inhibitors and tramadol showing high usage. Importantly, the utilization of PAH-specific therapies varied across databases, with CHUBX having the highest prescription rate before the index date.

In terms of PAH treatments, PDE-5 inhibitors, particularly sildenafil, were the primary choice as index treatment for newly diagnosed PAH patients. The study revealed an increasing trend in the prescription of PDE-5 inhibitors and ERAs in the year leading up to the PAH diagnosis. Monotherapy with PDE-5 inhibitors was the predominant treatment strategy for PAH, with less frequent use of combination therapy, usually involving bosentan. Notably, sildenafil was frequently used as a standalone treatment, while tadalafil was preferred in combination therapy, often in conjunction with bosentan or ambrisentan for dual therapy. The duration of the first prescriptions for these therapies varied, with combination therapy lasting the longest in IQVIA DA Germany and other PAH-specific therapies having extended durations in the Estonian Biobank database.

The findings on PAH treatment outcomes and prognosis are remarkable. Hospitalization was universal within a year of PAH diagnosis, with high cardiovascular hospitalization rates observed at the index date across the databases. Importantly, a concerning pattern of progressively increasing mortality rates, doubling between one and three years post-index, was observed in CHUBX and CPRD GOLD, indicating the importance of further research and intervention to improve the outcomes and prognosis for PAH patients.

PVR report

The aim of this PVR report is to determine whether PVR can be considered as a surrogate endpoint for clinical outcomes such as 6MWD and time to clinical worsening.

For PVR to be accepted as a surrogate it must fulfil 3 conditions defined in the ICH Guidelines on Statistical Principles for Clinical Trials (ICH 1998). In practice the strength of the evidence for the surrogacy depends on biological plausibility of the relationship, demonstration in epidemiological studies of the prognostic value of

the surrogate for the clinical outcome, evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome.

Biological Plausibility of the Association of PVR with Clinical Outcomes

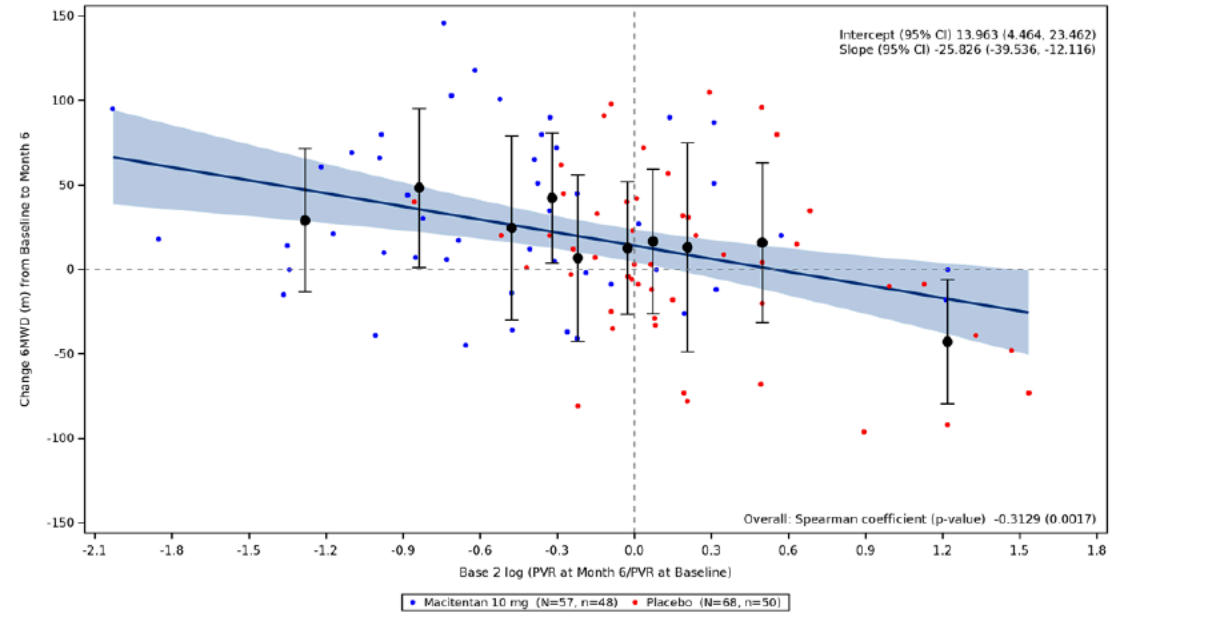
The increase in PVR is closely related to the occurrence and development of PAH (Deng 2021). From a pathophysiological point of view, PAH is a type of cardiopulmonary disease that can affect the arterial and venous circulation of the lung and right ventricle (RV) of the heart. Continuous vasoconstriction, excessive pulmonary vascular remodeling, and in situ thrombosis lead to an increase in PVR, which eventually can lead to right heart failure and even death (Tuder 2013, Humbert 2019). However, the influencing factors that lead to the acceleration or deterioration of PAH are still unclear and may be related to genetics and the combined effects of multiple influencing factors. The influencing factors mainly include the process of vasoconstriction and promotion of remodeling, inflammation, vasoactive molecules, anti-apoptosis, and autoimmune mediators, as well as the interaction of cells and cells, cells and substrates, etc. (Archer 2010). From a pathological point of view, PAH is a progressive pulmonary vasculature disease, which is mainly characterized by the proliferation of various types of vascular wall cells (including endothelial cells, smooth muscle cells and fibroblasts) and then develops into a wide range of pulmonary vascular remodeling, which ultimately leads to an increase in PVR (Nickel 2015, Tian 2019, Calvier 2019, Ventetuolo 2020). The increase in PVR is mainly caused by pulmonary artery constriction and complex arterial damage, to include medial hypertrophy and intimal and adventitial thickening, which may be related to the imbalance of different types of cell proliferation and apoptosis in the blood vessel wall. However, complex arterial damage is manifested as plexiform lesions, dilated lesions and arteritis. These changes are considered to be signs of the rapid progress of PAH (Pietra 2004, Stewart 2009).

Association between ΔPVR and Δ6MWD

SERAPHIN / AC-055-302:

Only subjects included in the hemodynamic sub-study and with available values for PVR and 6MWD were included in the analyses evaluating the association between ΔPVR and Δ6MWD at month 6 in the SERAPHIN trial (n = 48/242 participants randomized to macitentan 10 mg and 50/250 randomized to placebo, respectively). Participants treated with the non-approved dose (macitentan 3 mg) were excluded. The selection of the approved dose was considered to perform the surrogacy analysis (statistical significance of treatment effect on the clinical outcome is part of Prentice criteria). The relationship between ΔPVR (logarithm of the ratio between PVR values at month 6 and at baseline), and Δ6MWD (absolute change from baseline to month 6 in 6MWD) was assessed graphically using a scatter plot and regression analysis for the pooled treatment groups (placebo and macitentan 10 mg). A statistically significant correlation (ρ = -0.3129, p-value = 0.0017) was observed providing evidence of a correlation between ΔPVR and Δ6MWD.

Figure 16: Correlation between Log-transformed Changes in PVR vs Absolute Change in 6MWD from baseline to 6 months.



Key: 6MWD = 6-minute walk distance; CI = Confidence interval; PVR = Pulmonary vascular disease. Shown overall regression line and 95% confidence interval.

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An assessment of the treatment effect of PVR (logarithm of the ratio of month 6 PVR to baseline PVR) as a candidate surrogate endpoint on absolute change from baseline to month 6 in 6MWD was evaluated using Prentice's criteria (Prentice 1989) and the proportion of the treatment effect explained by PVR was estimated using Freedman proportion explained (Freedman 1992). ΔPVR was found to explain Δ6MWD, with approximately 66% of the treatment effect being explained by PVR.

Table 33: Criteria to establish Log(M6/BSL) in PVR as a Mediator of the Treatment Effect (macitentan 10 mg vs. placebo) for Absolute Change from Baseline in 6MWD at Month 6

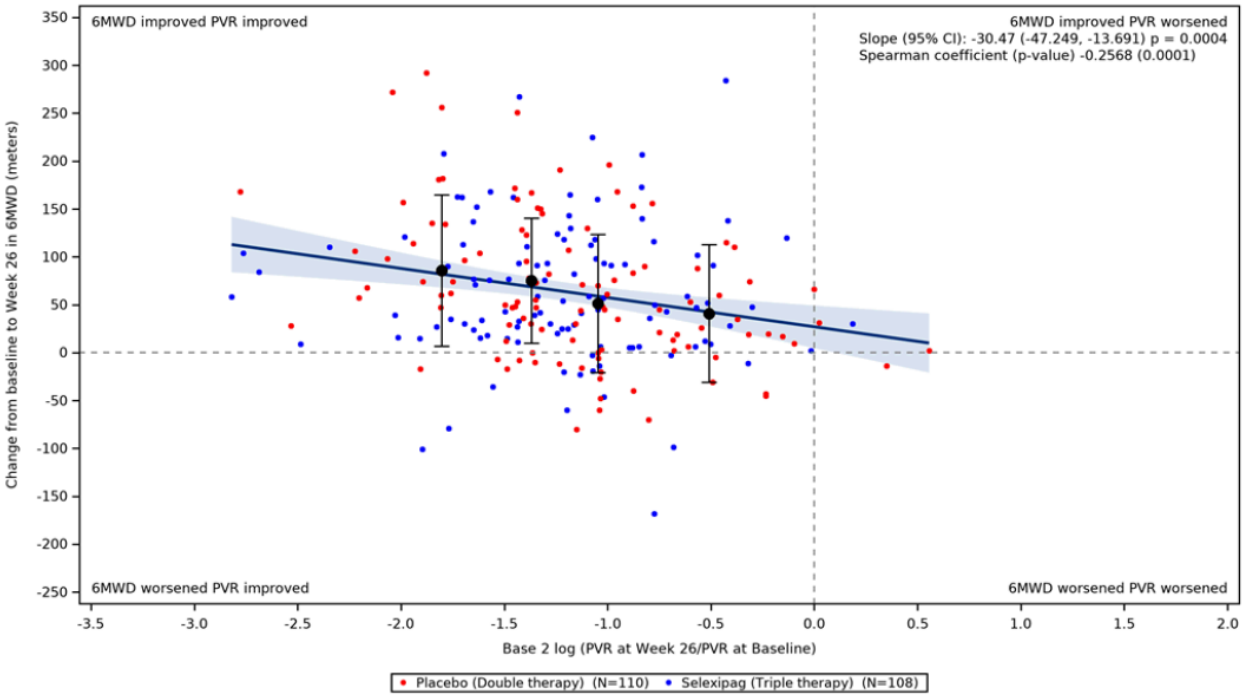
Prentice Criteria*		Results (N=98)
1st	Treatment has a significant effect on the log_2(Month 6/Baseline) in PVR	Geometric mean ratio: 0.62 (p<0.0001)
2nd	Treatment has a significant effect on the change from baseline in 6MWD	Mean difference vs Placebo: 24.63 m (p=0.0144)
3rd	PVR log_2(Month 6/Baseline) has a significant effect on the change from baseline to Month 6 in 6MWD	-25.93m (p=0.0003)
4th	Treatment effect on the change in 6MWD is captured by the log_2(Month 6/Baseline) in PVR	8.474 m (p=0.45)
	Freedman's Proportion Explained (%)	**65.5**

*Only subjects with non-missing changes from baseline to Month 6 for both PVR and 6MWD
Note: criteria 1-3 are met if p<0.05, the 4th criterion is met if p>0.05 (Prentice 1989)

TRITON / AC-065A308:

The correlation between ΔPVR and Δ6MWD at week 26 was assessed using data from the TRITON trial. All patients with available values for PVR and 6MWD were included: 110 patients randomized to double combination (macitentan/tadalafil/placebo), and 108 patients randomized to triple combination (macitentan/tadalafil/selexipag). The correlation between ΔPVR (log-transformed change from baseline to week 26 in PVR) and Δ6MWD (absolute change from baseline to week 26 in 6MWD) were assessed graphically in a scatter plot and regression analysis for the pooled treatment groups (placebo [double therapy] and selexipag [triple therapy]). A statistically significant correlation (ρ = -0.2568, p-value = 0.0004) was observed suggesting evidence of a correlation between ΔPVR and Δ6MWD.

Figure 17: Correlation between Log-transformed Changes in PVR and Absolute Changes in 6MWD from baseline to week 26



Bosentan studies:

A univariate linear regression analysis assessing Δ6MWD on ΔPVR was previously performed to evaluate the relationship between changes in hemodynamics and 6MWD in bosentan or placebo treated IPAH/HPAH patients (n = 141) using the bosentan studies. The pearson correlation coefficient was -0.46 (-0.58; -0.33) and the R squared was 0.22. To assess the percentage of the bosentan treatment effect on 6MWD that could be explained by changes in PVR, the final regression model was used to predict 6MWD in the individual bosentan studies. Within each study, ΔPVR explained 29% to 62% of the treatment effect on Δ6MWD.

Validation of PVR as a Surrogate Endpoint for 6MWD:

An analysis was performed to validate the potential of some or a combination of hemodynamic endpoints including PVR as a surrogate for 6MWD using the bosentan studies. Firstly, a regression analysis was used to identify a set of independent variables (ΔCI, ΔPVR, ΔPVRI, ΔRAPm, ΔPAPm, and ΔTPR) that best predicted

Δ6MWD; a linear combination of ΔPVRI and ΔRAPm was identified as the best predictor of Δ6MWD. Then a surrogacy evaluation using Prentice's criteria (Prentice 1989) was carried out to determine whether this linear combination of ΔPVRI and ΔRAPm could be considered as a surrogate for Δ6MWD in relation to treatment with bosentan. Results of this analysis demonstrated that changes in ΔRAPm and ΔPVRI were found to explain Δ6MWD, with 65% of the treatment effect being explained by hemodynamics. Rather than prove surrogacy of hemodynamics for 6MWD, this analysis demonstrates not only the relationship between ΔPVR and Δ6MWD but also that in the context of a well-defined patient population treated with bosentan or placebo in double-blind studies, generally accepted statistical criteria that describe surrogacy were met.

Association between ΔPVR and Time to Clinical Worsening / Disease Progression:

Data from SERAPHIN / AC-055-302 was used for an assessment of the treatment effect of PVR (logarithm of the ratio between PVR values at month 6 PVR and at baseline) as a surrogate endpoint on time to clinical worsening/disease progression, which was evaluated using the Prentice criteria (Prentice 1989) and the proportion of the treatment effect explained by PVR was estimated using Freedman proportion explained (Freedman 1992). ΔPVR was found to explain time to M/M event with approximately 41% of the treatment effect being explained by PVR.

Table 34: Criteria to establish Log(M6/BSL) as a Mediator of the Treatment Effect (macitentan 10 mg vs placebo) for Time to First CEC-confirmed M/M event up to EOT +7 days.

Prentice Criteria		Result (N=95)
1st	Treatment has a significant effect on the $\log_2$(Month 6/Baseline) in PVR	Geometric mean ratio vs. Placebo: 0.63 ($p < 0.0001$)
2nd	Treatment has a significant effect on the time to first confirmed CEC M/M event up to EOT+7days	HR vs. Placebo: 0.42 ($p = 0.0112$)
3rd	PVR as $\log_2$(Month 6/Baseline) has a significant effect on the time to first confirmed CEC M/M event up to EOT+7days	HR = 2.22 ($p = 0.0026$)
4th	Treatment effect on the time to first confirmed CEC M/M event up to EOT+7days is captured by the $\log_2$(Month 6/Baseline) in PVR	HR vs. Placebo: 0.59 ($p = 0.1650$)
	Freedman's Proportion Explained (%)	**40.5**

Applicants summary:

There is strong biological plausibility for PVR as a surrogate for clinical outcomes; PVR is indicative of the afterload burden on the RV. Persistently high PVR leads to RV dysfunction. Because outcomes of patients with PAH are determined by the RV function adapted to increased afterload, decreasing PVR from the early phase of treatment could prevent RV failure, leading to a better prognosis such as improved exercise capacity and delayed occurrence of M/M events. Review of the available literature, and analyses performed on data from PAH trials indicate that PVR is prognostic for clinical outcomes. There is consistent evidence in literature and from in-house data that treatment-induced changes in PVR are associated with effects on relevant clinical outcomes:

Analyses conducted on data from TRITON and SERAPHIN, 2 large phase 3 studies in PAH, showed that improvements in PVR are associated with improvements in exercise capacity and with a decreased risk of disease progression.

Several recent retrospective studies analyzed the predictive value of PAH-treatment induced reductions in PVR and found a clear link between decreases in PVR and improvement in outcome.

Surrogacy analyses showed that treatment induced effect on PVR explains treatment induced effect on 6MWD as follows. A study-level meta-analysis of PAH-therapy trials performed by the FDA, which regressed the ΔΔPVRI with the ΔΔ6MWD, resulted in an estimated slope of -0.047 (-0.064, -0.031) for predicted difference in 6MWD (meter) as a function of PVRI difference (dyn.sec/cm5.m2) (Stockbridge 2010). According to this relationship, a ΔΔPVRI of -319 dyn.sec/cm5.m2 allows prediction of 15 m for ΔΔ6MWD. A surrogacy analysis of 3 placebo-controlled studies of bosentan was performed using Prentice's criteria (Prentice 1989). Results of this analysis demonstrated that treatment induced changes in ΔRAPm and ΔPVRI explained treatment induced changes in Δ6MWD, with 65% of the treatment effect being explained by hemodynamics. Finally, a surrogacy analysis based on the SERAPHIN data indicates the effect on 6MWD and disease progression is explained by a reduction in PVR. The Freedman proportion (Freedman 1992) of the treatment effect on 6MWD or time to disease progression explained by the PVR treatment effect was 0.655 and 0.405, respectively.

CHMP early contact with ESC (on behalf of healthcare professionals) - responses

Background: Epidemiology and management of PAH

- Pulmonary arterial hypertension (PAH) is a rare life-threatening disease. Recent registry data from economically developed countries indicate an incidence and prevalence of 6 and 48–55 cases/million adults respectively. In newly diagnosed patients with PAH, the 2022 ESC/ERS Guidelines on PH recommend initial combination of drugs, especially in patients who do not have cardiopulmonary comorbidities (Humbert Eur Heart J 2023). More specifically, initial combination therapy with macitentan and tadalafil has a class I level of recommendation for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities.

Macitentan and tadalafil for the treatment of PAH

- Macitentan is an oral, dual endothelin receptor antagonist that has been found to reduce a composite endpoint of clinical worsening in patients with PAH, improve hemodynamics and exercise capacity measured by 6MWD (Galiè N et al. Eur Heart J 2017, Pulido T, et al. N Engl J Med 2013). In terms of side effects, significant anaemia with a reduction in Hb to ⩽8 g/dL was observed in 4.3% of patients receiving 10 mg of macitentan once daily (Pulido T, et al. N Engl J Med 2013).

- Tadalafil is a phosphodiesterase-5 inhibitor that has been shown to improve exercise capacity by 6MWD when prescribed as monotherapy (Galie et al. Circulation 2009) and delay clinical failure in patients receiving the drug in combination with ambrisentan 10 mg (Galie N, et al. N Engl J Med 2015). Most side effects are mild to moderate and mainly relate to vasodilation (headache, flushing, and epistaxis) when prescribed at the daily dose of 40 mg. It has also been shown to be associated with peripheral oedema, especially when combined with and ERA (Galie N, et al. N Engl J Med 2015, Chin K. Presented at ACC.23/WCC).

- The efficacy of the initial combination therapy is well-established, with persistent benefits over time, including functional status and QoL, in patients followed in PH centers.

Safety and tolerability of initial combination therapy

- The safety and tolerability of initial combination PAH therapy has also been reported in clinical trials.

- In the *AMBITION* trial, which used a different endothelin receptor antagonist (ambrisentan), the rate of discontinuation of a study drug and the rate of serious adverse events were similar in the three

study groups (ambrisentan/tadalafil combo, ambrisentan monotherapy, tadalafil monotherapy) (Galie N, et al. N Engl J Med 2015).

- In the *TRITON* trial (combination with selexipag+macitentan+tadalafil vs double combination with macitentan+ tadalafil), 5.6% patients in the initial double therapy group of macitentan plus tadalafil discontinued treatment prior to week 26 (Chin KM. J Am Coll Cardiol 2021).

- In the *OPTIMA* trial (an open-label study assessing the effects of macitentan + tadalafil on PVR), 6.5% of patients had an adverse event leading to study treatment discontinuation (both study drugs) (Sitbon O. Eur Respir J 2020).

A Due study top line results

- The recently presented A DUE study examined the safety and efficacy of a fixed-dose combination (FDC) of macitentan and tadalafil versus each of these drugs as monotherapy (Chin K. Presented at ACC.23/WCC). The primary endpoint was % change in pulmonary vascular resistance from baseline to 16 weeks. PVR was significantly decreased in the FDC group vs either monotherapy group: macitentan -23 vs. FDC -45%, $p \leqslant 0.0001$; tadalafil -22 vs. FDC -44%, $p \leqslant 0.0001$. As expected, patients in the FDC arm experienced more adverse events of special interest (mainly oedema in 20.6% and Hb decrease in 18.7%) compared to either monotherapy arm: oedema 14.3% in the macitentan group and 15.9% in the tadalafil group; Hb drop in 2.9% in the macitentan group vs 2.3% in the tadalafil group.

Considerations on the initial combination PAH therapy using macitentan plus tadalafil

- Macitentan and tadalafil have been in use for the treatment of PAH for several years, either alone or in combination. Initial and early combination treatment using these two compounds is increasing worldwide in countries where both drugs are approved. It has been shown that patients with "typical" PAH, i.e. without cardiopulmonary comorbidities, receive the greatest benefit from these drugs, suffering the fewest side effects and remain on this treatment for long periods (Souza R, et al. Adv Ther. 2022).

With regards to the timing of drug initiation and dose escalation, it is important to examine published clinical trials. In the AMBITION study, ambrisentan was given at an initial dose of 5 mg once daily for the first 8 weeks and 10 mg once daily thereafter; tadalafil was administered at a dose of 20 mg once daily for the first 4 weeks and 40 mg once daily thereafter. In the OPTIMA trial, macitentan 10 mg once daily and tadalafil 20 mg once daily were initiated; at day 8±3, the tadalafil dose was increased to 40 mg once daily. The dose of tadalafil could be decreased in case of tolerability issues. In real life, patients may be started on the initial combo treatment at the same time on day 1, or often proceed rapidly from monotherapy to early escalation (within approximately 1 month) to combined dual oral therapy. This may depend on the local circumstances and protocols (i.e. healthcare system, financial issues, stock in pharmacy, etc.) and physician preference. In most expert PH centers the practice is to start the 2 drugs within 2 weeks. Some centers prefer to start macitentan 10 mg and low-dose tadalafil 20 mg od concomitantly and up-titrate to 40 mg tadalafil dose in 1-2 weeks.

Pros and cons of FDC single pill

- A single pill fixed dose combination has the following advantages:

    - Patients receive "strong" and effective treatment soon after diagnosis. The clinical benefits of early combination therapy are established and patients are more likely to experience an rapid improvement in their symptoms and quality of life.

- Treatment delay ("inertia") is avoided. Slow up-titration of treatment can lead to delays to treatment and confusion for the patient.

- PAH patients without cardiopulmonary comorbidities, who are most likely to benefit from early combination therapy, are often young and active, and may be less compliant when prescribed multiple pills daily (2 tablets of tadalafil and 1 tablet of macitentan). FDC can overcome this and increase treatment adherence.

In contrast, the disadvantages of FDC are

- Adverse effects cannot be easily attributed to either of the medications, a reason why early sequential therapy is preferred by some expert to upfront combination therapy. FDC still has an important role to play, as it can be introduced as soon as up-titration of treatment has been achieved.

- FDC may not be suitable for patients in whom either macitentan or tadalafil need to be stopped, e.g., patients who are started on a soluble guanylate cyclase stimulator and tadalafil should be stopped.

Potential clinical scenarios

- The recently presented A DUE study reported on the efficacy and safety of FDC used in patients already on an ERA or PDE-5i and patients who were treatment naïve (though in the latter group, the rate of discontinuation due to side-effects was higher). Therefore, use of the FDC for upfront combination therapy or escalation from monotherapy appears reasonable.

  A pragmatic approach for patients in whom upfront treatment may not be deemed appropriate, may be to prescribe the FDC when patients are up-titrated and stable under dual oral combination. Of note, in Canada the combination pill (OPSYNVI) has been approved and is licensed for use in patients with PAH who are currently treated concomitantly with stable doses of macitentan 10mg and tadalafil 40mg (20mg x 2) as separate tablets.

Options and estimated relative percentages of the population to which the fix-dose therapy may be applicable are described below:

1) FDC initial therapy (macitentan 10/tadalafil 40) without dose escalation (mainly in PAH patients without cardiopulmonary comorbidities) 50%

2) monotherapy followed by FDC (in PAH patients with and without cardiopulmonary comorbidities) 25%

3) monotherapy followed by two drug therapy followed by FDC (mainly in PAH patients with cardiopulmonary comorbidities) 25%

Regarding EMA scenarios for fixed combination products:

1. **Add-on treatment of patients insufficiently responding to an existing therapy with one or more active substances:** This is not a possible scenario since the 2 active substances/drugs are indicated as a first line (initial) combination treatment.

2. **Substitution therapy in patients adequately controlled with two or more active substances used in combination:** This may be a possible scenario for patients who are stable and have no side effects from the already administered active substances/drugs. In this scenario, a patient may receive monotherapy with macitentan 10 mg or tadalafil 40mg (20mg x 2) (both sequences are allowed) and is switched to the fix-dose combination therapy. The other possibility is that the patient

is treated under stable doses of macitentan 10mg and tadalafil 40mg (20mg x 2) as separate tablets and is switched to the fix-dose combination therapy.

3. **Initial combination therapy for patients receiving previously neither of the substances.** This may be a possible scenario for patients who are started upfront with the FDC. As described previously this is the case particularly for patients without cardiopulmonary comorbidities ("classical" PAH). In an analysis of the A DUE trial which was recently presented in the ESC Congress 2023, adverse events, serious adverse events and adverse events leading to treatment discontinuation were reported by more treatment-naïve patients than those who had prior monotherapy treatment with an ERA or PDE-5 inhibitor (Grunig E, ESC Congress 2023). Therefore, in the case of treatment-naïve patients, additional precautions should be applied with pharmacovigilance and close follow-up for reporting of side effects.

Finally, regarding pharmacokinetic issues, there is no concern of drug-drug interaction between the active substances in the fixed combination medicinal product. The A DUE study demonstrated marked pulmonary hemodynamic improvement with a significant and robust reduction in pulmonary vascular resistance with the fixed combination vs monotherapies (Chin K et al. Presented at ACC.23/WCC).

2.6.6. Discussion on clinical efficacy

Rationale for FDC

Four main pathways are important in the treatment of PAH: the prostacyclin, nitric oxide (NO), endothelin (ET) and the Activin/TGF-β pathways (Humbert 2022, Humbert 2023, Sitbon 2012), and the medicinal products approved in the EU each target one of these mechanisms. The intent behind these drugs, whether administered as monotherapy or in combination, is to ameliorate vascular tone by addressing the underlying dysregulated processes that lead to pulmonary vasoconstriction. Recent PAH treatment guidelines advocate a risk-adapted approach for managing most patients, highlighting the importance of combination drug therapy. Although treatment options are available, PAH remains progressive and ultimately fatal. Current guidelines recommend combination in treatment-naïve patients as more effective therapeutic options to achieve and maintain low risk status (Galiè 2019b, Gaine 2017). However, the current ESC/ERS practice guidelines acknowledge that adherence to drug therapy in patients with PAH may be suboptimal (Kjellström 2020, Shah 2019, Humbert 2022). A single tablet combination of treatments with proven efficacy acting on 2 of the major pathways involved in the pathogenesis of PAH may provide synergistic treatment benefits to patients with PAH at a fixed dose, once a day, potentially representing an additional, and thereby novel, mode of action compared to other therapies approved for PAH.

Currently, no fixed dose combination tablet for the treatment of PAH is available in the EU. Patients with complex dosage regimens due to multiple medications and/or higher dose frequency, may be at risk for noncompliance (Ingersoll 2008). As the PAH population ages and presents with more comorbidities, the complexity of the regimen, and thus the risk of noncompliance, grows. In addition to adherence and persistence, a once-a-day single tablet is likely to add a potential safety benefit by reducing the risk of medication errors that lead to lost treatment benefits or adverse events (Böhm 2021). The rationale for a FDC M/T in general is supported, however it is not understood what the benefit is of initial combination therapy over sequential therapy (i.e. starting one monotherapy for one or two weeks and if tolerable switching to the FDC), given that this approach allows a gap to asses tolerability of the first treatment before starting the second treatment.

Furthermore, the pill-load will be reduced from three loose tablets (1 macitentan 10 mg and 2 tadalafil 20 mg tablets) to one FDC tablet of Yuvanci once daily, which might not be a huge impact on QoL. The claims regarding better adherence or contribution to patients' care remain hypothetical and are not supported by actual data. Although the pill-load is reduced, there were no differences in adherence or QoL among the

studies arms of the pivotal randomised trial. Notably, subjects also used dummy-controls in the randomised phase, making it impossible to draw conclusion on reduced burden.

Dose finding

The maintenance dose corresponding to the maintenance dose of the individual components of the fixed dose combination. The maintenance dose is considered acceptable.

The proposal to establish a fixed combination medicinal product containing M/T 10/20 mg as an up-titration dose for the treatment of PAH patients with M/T 10/40 mg FCMP was endorsed by the CHMP (EMA/SA/0000074632). The up-titration scheme is in line with the posology used in the pivotal trial with loose combinations. A similar up-titration scheme has been used in the Ambition trial for Ambrisentan and Tadalafil and is reflected in the SmPC of Volibris.

The proposed titration scheme depends on prior use of tadalafil. The titration scheme is proposed for treatment naïve patients and on macitentan monotherapy. Patients with prior use tadalafil (thus for add-on or substitution indication) in the maintenance dose of 40mg per day can immediately use the maintenance dose, rather than titration dose. Initially, no mention was made to patients on tadalafil 20 mg per day, due to e.g. tolerability issues, impaired kidney function or impaired liver function. Based on bioequivalence of the individual tablets macitentan 10mg and tadalafil 20 mg to M/T FDC 10/20 mg, and the approved tadalafil label, the Applicant subsequently agreed to amend the SmPC to include the use of the M/T FDC 10/20 mg single-tablet combination option for patients who are on 10 mg macitentan and 20 mg tadalafil as separate tablets due to either tolerability issues, impaired kidney function or impaired liver function.

Design and conduct of clinical studies

The main study is study AC-077A301, also known as and hereafter referred to as "A DUE". The A DUE study consists of a 16-week double-blind phase and an open label extension. When referring to A DUE in this report, this refers to the 16-week double-blind phase. A DUE is a prospective, multi-centre, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy. The rationale of the study was to demonstrate that macitentan 10 mg and tadalafil 40 mg as a fixed dose combination (M/T FDC) is superior to 10 mg of macitentan alone, and to 40 mg of tadalafil alone, as measured by the ratio of end of double-blind treatment (EDBT) to baseline pulmonary vascular resistance (PVR). This study evaluated the efficacy at 16 weeks against each of these 2 approved PAH therapies given as monotherapy.

The trial included adult males and females with a confirmed diagnosis of symptomatic PAH (WHO Group 1) in WHO FC II and III, with a confirmed hemodynamic evaluation at rest (through central reading), evaluated within 5 weeks prior to randomization. Patients had to either use a stable dose of ERA or PDE5i monotherapy for at least 3 months or have no use of PAH-specific treatment. Another important inclusion criterion was being able to perform a 6 minute walking test with a minimum distance of 100 meter and maximal distance of 450 meter. The minimum 6MWD is 100 m in order to avoid the imputation of missing values in participants who can hardly walk or cannot walk at all. The main exclusion criteria were use of prostanoids, soluble guanylate cyclase, combined ERA and PDE5i and strong CYP3A4 inducers and inhibitors. Furthermore, patients with haemoglobin<6.21 mmol/L (100g/L), patients with severe renal or hepatic impairment and patients on an exercise training program for cardiopulmonary rehabilitation were also excluded. Overall, the inclusion and exclusion criteria are considered acceptable.

Study treatments were M/T FDC, macitentan, tadalafil, and their respective matching placebos. M/T FDC was provided as film-coated tablets. Treatment allocation was stratified by treatment status at baseline, i.e. treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy. Participants also received matching

placebos for the 2 other study treatments to maintain the blind. Treatment-naïve participants were randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil. Participants on allowed ERA monotherapy were randomized in a 2:1 ratio to M/T FDC or macitentan. Participants on allowed PDE-5i monotherapy were randomized in a 2:1 ratio to M/T FDC or tadalafil.

The double-blind period consisted of a titration phase and a maintenance phase. The titration phase lasted two weeks. During the first week, patients were treated with a loose combination of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos. For patients on monotherapy with an ERA or PDE5i other than macitentan and tadalafil, this implied a switch in monotherapy. During the second week, patients in the M/T FDC and tadalafil arm were up-titrated from 20 mg to 40 mg tadalafil per day. Participants who were on an allowed dose of PDE-5i at baseline (40 mg tadalafil, 60–120 mg sildenafil, or 10 mg vardenafil daily) were not up-titrated and received 40 mg tadalafil starting on study Day 1. If a participant could not tolerate the higher tadalafil dose (or placebo) during the double-blind titration phase, the dose was to be decreased back to 20 mg daily. Within the first 2–3 weeks after decreasing the dose (up to and including Week 4 / Visit 5) and with the investigator's approval, the participant was allowed to be re-up-titrated to the tadalafil 40 mg daily dose (or its matching placebo equivalent). If the participant could not tolerate the 40 mg dose again on the 2nd attempt to up-titrate the tadalafil dose (or its matching placebo equivalent), then they were to stay on the 20 mg tadalafil daily dose (or its placebo equivalent) for the remainder of the double-blind treatment period. An issue with the current design, where patients treated with an ERA or PDE5 monotherapy were forced to switch to macitentan or tadalafil respectively, is that it makes it difficult to compare the true effect of treatment as the continuity of the control therapy is disrupted. Upon request, the Applicant provided subgroup analyses comparing those on macitentan or tadalafil monotherapy with those on other ERA or PDE5 therapies. Such analyses did not demonstrate an effect of switching from another ERA/PDE5i to macitentan and tadalafil in the monotherapy treatment arms. Furthermore, in all instances, the M/T FDC-treated participants showed a larger effect on PVR than those receiving monotherapy.

The primary endpoint for the current study was the change in pulmonary vascular resistance (PVR) expressed as the ratio of geometric means of end double-blind treatment to baseline. As was indicated in the CHMP scientific advices (EMA/CHMP/SAWP/123302/2019 and EMA/SA/0000074632), for a substitution indication only, it can be acceptable to show an additive value of the combination of M/T compared to treatment with the mono-components on the pulmonary vascular resistance (PVR) measurements in the pivotal study. The target effect size, as measured by the ratio of geometric means of the Week 16 / Baseline PVR values was assumed to be at least 0.75 for FDC compared to each monotherapy and to be consistent across the treatment naïve, prior-ERA, and prior- PDE-5i strata. This effect size was considered clinically relevant and supported, for a substitution indication only. This strategy is, however, not adequate to support a first line indication i.e. initial combination therapy with YUVANCI. Whilst PVR is a key diagnostic parameter and a prognostic risk estimator in PAH, a clinically relevant magnitude and timing of change in response to treatment is not defined and validated to be suitable for a pivotal study primary endpoint. For this reason, the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension (EMEA/CHMP/EWP/356954) does not support PVR as primary endpoint. In the latest CHMP scientific advice (EMA/SA/0000074632), it was stated that predefining a change in 6MWD as a primary endpoint would be acceptable and a clinically relevant and statistically significant effect would be considered as key evidence in support of the intended first line indication. However, a considerably larger study would be needed. In the context of both active substances of the fixed combination medicinal product being approved for a long time in this orphan disease and robust proof of concept being available for the combined treatment of ERAs and PDE5 inhibitors, it is understandable to explore alternative ways to generate evidence. In this context it is agreed that a pivotal study that indicates clinically relevant efficacy of the combination but has shortcomings regarding the robustness of the results could be supplemented by additional supportive evidence to strengthen the evidence level. Demonstration of a statistically significant and clinically relevant effect on PVR plus a clinically relevant positive trend for the 6MWD could be accepted as a "gatekeeper" for the acceptance of further supportive data. To be acceptable, it should be predefined what is considered a positive trend. It was then stated that for example, a numerical improvement in the 6MWD by 20 m or more, similar to what has been observed in the AMBITION trial (22m) for the ambrisentan/tadalafil combination therapy vs. monotherapy arms. A p-value of < 0.10, as a gatekeeper alpha indicative of a trend, should be

sufficient to allow for the acceptance of additional data needed for reassurance. In the subsequent discussion meeting with the Applicant, the Applicant stated that the A DUE trial was ongoing with a protocol specified interim analysis planned and performed in February 2022. Changes in the statistical analysis plan at this stage were not foreseen in order to not jeopardize the validity of the study. Predefinition of a trend to be achieved for the 6MWD was not planned. Considering the shorter observation period in A DUE, a treatment effect of 15 – 20m at week 16 was considered in-line with the somewhat larger treatment effect observed in the AMBITION trial at week 24. Although such a time dependent effect is conceivable, a thorough justification for the clinical relevance was expected in case the observed numerical effect on 6MWD would be smaller than 20 m. The same would apply if the p-value for the effect on the 6MWD was not within the range of what can be considered a statistical trend.

The total double-blind duration was 16 weeks, after which the study switched to an open label extension. The rationale to switch after 16 weeks (2 weeks titration and 14 weeks maintenance) to open label fixed combination medicinal product treatment in all patients was not entirely understood. The Applicant justified the duration of the DB period to avoid withholding M/T FDC therapy for a prolonged period of time for eligible candidates to receive combination therapy. The duration of the DB period of the A DUE study was limited to 16 weeks, which was considered sufficient to assess the effect of M/T FDC vs both monotherapies on the primary endpoint (change in PVR). Without a control group neither reliable conclusions on efficacy nor on safety can be drawn in the long-term maintenance phase. Considering that e.g. in the Ambition trial 6 MWD was assessed at week 24, prolonging the double-blind treatment period may allow assessing maintenance of a treatment effect and collecting more evaluable data on clinical endpoints and safety. In the latest CHMP scientific advice (EMA/SA/0000074632) this issue was also raised. During the subsequent discussion meeting the Applicant stated that a prolonged controlled treatment duration was not considered feasible since first line combination therapy is, in line with current treatment guidelines, widely recognized as the appropriate approach. This was acknowledged and may be particularly applied in specialized centres with a high adherence to accepted treatment standards.

Given the effect size assumptions, the sample size calculation can be followed and is acceptable. Of note, the study was underpowered for the first secondary endpoint 6MWD. Patient randomization was stratified according to prior treatment. Participants on ERA therapy at baseline are randomized 2:1 to M/T FDC or macitentan 10 mg, respectively. Participants on PDE-5i therapy at baseline are randomized 2:1 to M/T FDC or tadalafil 40 mg, respectively. Treatment-naïve participants at baseline are randomized 2:1:1 to M/T FDC, macitentan 10 mg, or tadalafil 40 mg, respectively. A Interactive Response Technology (IRT) system was used to randomize patients, which is acceptable. The first 16 weeks of this study was performed in a double-blind fashion. The investigator and study personnel, the participants, the Site Managers (SMs), sponsor personnel, and CRO personnel involved in the conduct of the study remained blinded to the study treatment until the final double-blind analysis.

The definitions of the analysis sets are considered standard and acceptable. The primary endpoint comparisons of the combination against each monotherapy were seen as co-primary endpoints and study success would only be declared when both were successful. Secondary endpoints would then be tested hierarchically. Around 50% of the information fraction, an interim analysis was planned to test for futility, efficacy and re-assess the sample size. A Hwang, Shih and DeCani alpha spending function was used to calculate the alpha spent at the interim. Together these methods will preserve the overall type I error rate and adequately handle multiplicity. The estimand proposed is a hybrid using treatment policy strategy for disease progression or dose adjustments and composite strategies for death and prohibited medication or discontinuation with or without disease progression. To target this estimand, worst observed case imputation was used in case of death and 75^{th} or 50^{th} percentile imputation in case of prohibited medication with or without disease progression. This is different from the estimand proposed during scientific advice (EMA/CHMP/SAWP/123302/2019), which was only considered acceptable for a substitution indication and a treatment policy strategy was advised for the other indications. The current estimand is somewhere in between and is considered acceptable for the substitution indication, while an estimand using a treatment policy strategy is again considered more appropriate for the other indications, since the current estimand ignores a potential lack of efficacy when prohibited medication is added by imputing the 50^{th} percentile (in

case of no accompanying disease progression) or the 75th percentile (in case of accompanying disease progression). Nevertheless, it can be understood that the company chose to define one primary estimand for the study and a secondary estimand using a treatment policy strategy was included as well. Furthermore, the number of intercurrent events was generally low, with only treatment discontinuation reaching around 10% and the rest of the intercurrent events in 1 or 2 cases per arm. Also the analysis using the different estimand strategies led to almost identical results. Therefore, the estimand definitions can be considered acceptable. The primary analysis was performed using an ANCOVA model including baseline value and stratification factors. Analysis will be performed on log-transformed values. This is considered a standard method for the primary endpoint and is acceptable. Several sensitivity analyses were planned to test the assumptions of the primary analysis. The first, using a treatment policy estimand, is formally not a sensitivity analysis (as it targets a different estimand) but is nevertheless considered of importance (see above). The other sensitivity analyses adequately test the assumptions regarding missing data and normality and are acceptable. Secondary endpoints were tested according to a similar estimand as for the primary endpoint, but using a treatment policy strategy in case of prohibited medication instead of a composite strategy. The secondary endpoint 6MWD and PAH-SYMPACT Symptom domain scores were tested using the same ANCOVA model as for the primary analysis, the proportion of participants who improved or remained stable was analysed using a logistic regression model with baseline and stratification factors as covariates. These are considered suitable methods for the respective endpoints. The interim analysis was planned for futility, efficacy and sample size re-assessment. Rules for the different conclusions were prespecified and the methods adequately protected the overall type I error rate. The statistical methods are acceptable.

Efficacy data and additional analyses

The first patient was screened on 15 October 2019 and the end of the double-blind period was 23 August 2022. A total of 294 patients were screened across 16 countries/territories and 187 were randomized (108 to M/T FDC, 35 to macitentan, and 44 to tadalafil). Roughly 92% of the patients completed the double-blind period, the most prevalent reason for discontinuation was due to an adverse event.

There was a total of 61 patients (57.0%) in the M/T FDC arm with a major protocol deviation in the double-blind period. The majority was of protocol deviations were related to the haemoglobin retest not being done on time, a right heart catheterization outside of the time window and biomarker samples being collected without patient consent. There were 23 (12.4%) patients who had at least 1 COVID-19-related protocol deviations.

Demographics and baseline disease characteristics of the study population were representative of the target patient population, with a roughly 75% females, a median age ranging from 48.0 to 54.5 years in the different groups and all participants were in WHO FC II or III. The leading aetiology was idiopathic PAH, followed by PAH associated with connective tissue disease and the median time since diagnosis in all groups was <0.5 years. The treatment groups were mostly balanced in terms of demographics and baseline disease characteristics, with a notable exception seen in WHO FC distribution. The M/T FDC group included a higher proportion of participants in WHO FC II (60.7%) compared to the macitentan (31.4%) and tadalafil (43.2%) groups.

In the original MAA for macitentan, subgroup analyses according to WHO FC demonstrated a marginally stronger effect of macitentan over placebo on first morbidity/mortality event in the WHO FC III/IV group as compared to I/II group. In the original MAA for tadalafil, subgroup analyses according to WHO FC status demonstrated a somewhat larger placebo corrected increase in 6MWD for the WHO III/IV group as compared to the WHO I/II group. Therefore, it can be expected that a lower proportion of WHO FC III in the M/T FDC group will more likely underestimate the effect size than overestimate it. The in-balance in WHO FC is therefore not considered problematic.

During the maintenance phase, the majority of patients (95.7-100%, depending on the stratum) received tadalafil 40mg at least once. The tadalafil dose was only adjusted for participants in the M/T FDC group. The tadalafil dose decreased from 40 mg to 20 mg once in 3 participants (2 due to an AE, and 1 for an

unspecified reason) and increased from 20 mg to 40 mg once in 2 participants. Mean compliance was comparable across groups. Mean and median compliance, calculated as the difference between dispensed and returned tablets divided by total tablets that should have been taken, was nearly 100%. The number of patients with compliance <80% was below 5% in each stratum.

In the full analysis set and the safety set one patient was excluded (The participant was randomized to M/T FDC but did not take the study intervention). Both the full analysis set and the safety set were identical and comprised of a total of 186 patients, of whom 105 contributed to the "treatment-naïve and prior ERA strata" and 130 to the "treatment-naïve and prior PDE-5i strata". In total 107 patients received the M/T FDC, which contributes to both prior mentioned strata. A total of 35 patients received macitentan monotherapy and 44 received tadalafil. Separate datasets were used for PAH sympact, EQ-5D-5L, WPAI analyses, which were somewhat smaller.

The primary efficacy endpoint (change in PVR expressed as the ratio of geometric means of EDBT to baseline) was met: a highly statistically significant and clinically meaningful treatment effect was observed for both the M/T FDC versus macitentan and the M/T FDC versus tadalafil comparisons. Based on the ANCOVA model, the median estimates of the geometric means ratios (95% adjusted RCL) were 0.71 (0.61, 0.82) between M/T FDC and macitentan (29% reduction in PVR with M/T FDC compared to macitentan) and 0.72 (0.64, 0.80) between M/T FDC and tadalafil (28% reduction in PVR with M/T FDC compared to tadalafil). Both treatment effects were highly statistically significant for both comparisons (2-sided adjusted p-values both <0.0001). The treatment effect was consistent across all subgroups, including treatment-naïve vs prior monotherapy (stronger effect in treatment-naïve but significant in both subgroups). The effect was also consistent in the prespecified sensitivity analyses. As stated in the CHMP scientific advice (EMA/CHMP/SAWP/123302/2019), for a substitution indication only, it can be acceptable to show additive value of the combination of macitentan/tadalafil compared to treatment with the mono-components on the PVR measurements. However, for the proposed add-on and initial treatment indications, this is not acceptable.

The difference in 6MWD change from baseline to end of the double-blind period was not statistically significant between M/T FDC and macitentan or between M/T FDC and tadalafil. Based on the ANCOVA model, the unbiased estimates of change from baseline to EDBT of M/T FDC versus macitentan was 16.04 m (-17.0,49.08; p=0.380) and of M/T FDC versus tadalafil was 25.37 m (-0.93,51.59; p=0.0591). The treatment effect of M/T vs macitentan was 20.4m (95% CI: -20.3; 61.1; P=0.32) in the treatment-naïve strata and 8.5m (95% CI: -40.0; 58.0; P=0.73) in the prior ERA strata. The treatment effect of M/T vs tadalafil was 33.0m (95% CI: -5.3; 71.4; P=0.09) in the treatment naïve strata and 25.9m (95% CI: 0.9; 50.9; P=0.04) in the prior PDE-5i strata.

There were no differences in change from baseline to EDBT (treatment effect, 95% CI) between groups in the PAH-SYMPACT cardiopulmonary domain score and PAH-SYMPACT cardiovascular domain score. It has to be noted that the PAH-SYMPACT is at an advanced stage of development but has not finally been qualified as a validated tool. There was numerically more WHO FC worsening reported in the M/T FDC group at EDBT compared with baseline due to a higher number of participants with intercurrent events and missing data that were imputed as worsening. Based on observed (i.e. non-imputed) WHO FC data, the proportion of participants who experienced a worsening in WHO FC for the M/T FDC vs macitentan comparison was 3.2% vs 2.9% and for the M/T FDC vs tadalafil comparison it was 2.5% vs 4.5%.

As stated in the scientific advice (EMA/SA/0000074632), the demonstration of a statistically significant and clinically relevant effect on PVR plus a clinically relevant positive trend for the 6MWD could be accepted as a "gatekeeper" for the acceptance of further supportive data. To be acceptable, it should be predefined what is considered a positive trend. For example, a numerical improvement in the 6MWD by 20 m or more (Ambition trial: 22 m), similar to what has been observed in the AMBITION trial for the ambrisentan/tadalafil combination therapy vs. monotherapy arms. A p-value of < 0.10, as a gatekeeper alpha indicative of a trend, should be sufficient to allow for the acceptance of additional data needed for reassurance. The results demonstrate that for the comparison of M/T FDC vs tadalafil comparison (e.g. add-on of macitentan), these gatekeeping criteria were met with roughly a 25 meter increase in 6MWD. However, for the comparison of M/T FDC vs macitentan, the criteria were not met, with a mere 16 meters increase, accompanied by a very

wide confidence interval. In a prespecified sensitivity analyses using rank-based, the effect size was even lower with only a 10 meters increase. Furthermore, subgroup analyses according to WHO FC demonstrated a decrease in 6MWD for patients of WHO FC III. Combined with a lack of an effect or relevant trend on quality of life and mortality/morbidity events, these results do not provide sufficient confidence in an added value of tadalafil on top of macitentan with regard to clinically relevant outcomes, precluding an add-on indication for tadalafil on top of macitentan and an initial treatment indication. The study was not powered to demonstrate a significant effect on 6MWD, which is considered a major weakness of the A DUE study, as it has repeatedly been advised to use 6MWD, rather than PVR, as the primary endpoint. In response, the Applicant has removed the add-on and initial treatment indications from the labelling.

Another issue is that the proposed indication refers to a general "treatment" indication, whereas the mono-component tadalafil is only registered to improve exercise capacity. However, since the combination therapy includes both tadalafil and macitentan, and macitentan has also demonstrated efficacy on morbidity and mortality events, it is considered appropriate to use a general treatment indication for the fixed dose combination, as this includes macitentan.

The results from the post-hoc combined double-blind and open-label extension indicate that the trend toward improvement of 6MWD is maintained throughout the open label extension. However, it appears that in patients treated with tadalafil in the DB, there is limited to no effect of starting M/T FDC on 6MWD. The Applicant was requested to comment on this phenomenon (e.g. whether these patients are in poorer health compared to the other groups). The Applicant reviewed baseline characteristics of the DB-macitentan and DB-tadalafil participants (NT-proBNP levels, WHO FC, PVR, and 6MWD), participants in the DB-tadalafil treatment group appear similar to the other groups in terms of health condition. Based on the available data, the Applicant ruled out that this observation is due to any significant imbalances in participant characteristics between DB-treatment groups and suggests it is more likely incidental in nature and to be interpreted in the context of relatively small participant numbers. Given the removal of add-on indications, this issue is also of less interest. Issue not further pursued.

The OL data in the prior ERA strata, however, demonstrates a trend toward reduced efficacy at week 120. This is likely due to the low number of participants that have reached this timepoint (n=2). Overall, without a control group neither reliable conclusions on efficacy can be drawn for the long-term maintenance phase. The results provide some supportive evidence on sustainment of the effect size.

Supportive data

Supportive analyses A

In supportive analyses A, an assessment was made to compare the effectiveness of macitentan and tadalafil versus macitentan monotherapy using retrospective data from completed clinical trials in treatment-naïve, newly diagnosed patients with PAH. An indirect treatment comparison with no common comparator was conducted using pooled patient level data from completed studies (TRITON, REPAIR, SERPAPHIN and ORCHESTRA).

These results demonstrate a treatment difference on 6MWD of 34m (95%CI: 14; 55m) and 42m (95% CI: 21; 62) at week 16 and 26 respectively, in favour of M/T over M. Furthermore, the proportion of patients with WHO FC improvements from baseline was also higher for the M/T arm and there was a numerical reduction in the overall risk of all-cause death or hospitalization.

However, the conclusions from these analyses have inherent methodological limitations. Although the inclusion and exclusion criteria of the completed studies in this analysis were similar, the heterogeneity in the study design and study conduct introduced a source of potential bias that could not be adjusted for. For example, differences in protocol objectives and in geographical regions. The analyses were further limited by the absence of randomization, as well as differences in study design. TRITON contributed to 87% of participants in the M+T arm whilst SYMPHONY contributed to 60% of participants in the M monotherapy arm.

Moreover, REPAIR contributed to both the M+T arm and the M monotherapy arm in the treatment comparison. Despite adjustments for clinically relevant covariates between the two treatment groups, the lack of randomization for the comparison of interest implicitly resulted in confounding. The results are therefore at best interpreted as supportive.

Supportive analyses B

In supportive analyses B, an assessment was made to compare the effectiveness of macitentan and tadalafil versus tadalafil monotherapy using retrospective data from completed clinical trials in treatment-naïve, newly diagnosed patients with PAH. An indirect treatment comparison with no common comparator was conducted using pooled patient level data from completed studies (TRITON, REPAIR, and AMBITION). The planned analyses resulted in inconclusive statistical evidence for the comparative effectiveness between macitentan + tadalafil and tadalafil monotherapy in treatment-naïve, newly diagnosed patients with PAH using pooled PLD from the TRITON/REPAIR trials and published aggregate data from the AMBITION trial. The indirect treatment comparison for the whole cohort prior to weighting for matched-adjusted indirect comparison (MAIC) demonstrated a 32m improvement in 6MWD in favour of M/T combination therapy. After weighting using covariates based on the REVEAL 2.0 risk score (gender, WHO FC, age, hypertension, etiology, prior diuretics, right arterial pressure, cardiac index, PVR, 6MWD and log[NT-proBNP], a 65% reduction from the original sample size was observed, suggesting a low degree of similarity between the patient populations compared prior to matching. The estimated mean difference of macitentan + tadalafil versus tadalafil after matching was 3.9m, whilst the result prior to matching was 32.5m in the AMBITION-like analysis set. Conversely, in the mFAS the estimated mean difference of macitentan + tadalafil versus tadalafil after matching was -2.1m, whilst the result prior to matching was 29.9m.

To better understand Analysis B results, a post hoc analysis was performed. The MAIC was repeated on the AMBITION-like analysis set using a clinically important subset of the original covariates (WHO FC, 6MWD and log[NT-proBNP]). Use of this approach resulted in down weighting from 111 to 89.8 after weighting M+T 10+40 mg arm (whereas it was 111 to 39.2 in the primary analysis). The results for change from baseline to Week 24 in 6MWD (31.6m [10.9, 52.4]) are consistent with the observed results in A DUE treatment-naïve participants.

The conclusion drawn from this analysis was significantly limited due to several factors affecting the statistical methodology for population-adjusted indirect comparisons. Firstly, the unanchored MAIC made a strong assumption that all baseline effect modifiers and prognostic factors were adequately addressed, which is implausible and potentially biased the results. As a result, the accuracy of the unanchored MAIC estimates remains uncertain, as no assessment of potential residual bias was conducted. Secondly, the absence of a common comparator in the indirect treatment comparison undermined the validity of randomization within the trials, introducing further challenges in making reliable comparisons. Thirdly, heterogeneity arising from differences in study design and conduct among the included trials added complexity to the analysis. Unfortunately, the MAIC method couldn't fully account for the resulting systematic error, leaving room for potential bias in the indirect comparison. In fact, the magnitude of bias could be substantial and might even exceed the estimated treatment effects. In conclusion, the findings of this analysis should be interpreted with caution, recognizing the limitations imposed by the unanchored MAIC approach and the potential for bias in the results. Further research, such as direct head-to-head trials or more robust statistical methods, may be necessary to obtain more reliable treatment comparisons that allow first-line indication.

Incorporation of ESC recommendations in clinical practice

To investigate to what degree initial combination therapy with ERA and PDE-5i is used as initial combination therapy, the Applicant included an DSP report, a survey and a targeted literature search.

The DSP report provides real world data on the implementation of the ESC/ERS guideline recommendations "Initial combination therapy with macitentan and tadalafil is recommended" and "Initial combination therapy with ambrisentan and tadalafil is recommended" in Europe. The report demonstrates that in 2022 roughly 22.3% of the surveyed physicians start with initial combination therapy of a PDE5i and ERA. Furthermore, the

results also demonstrate that while tadalafil is the most prescribed PDE5i, macitentan was the least prescribed ERA.

Overall, these findings indicate that the ESC/ERS guideline recommendation are not (yet) widely implemented in the European Union.

A survey was performed on PAH prescribing in cardiologists, pulmonologists and rheumatologists who have been managing PAH patients for at least 2 years in Europe. The survey demonstrated that initial dual therapy was started in 41% of the patients. ERA + PDE-5i represented 75% of drug class in dual-therapy received as initial treatment, of which 29% was macitentan + tadalafil, compared to 33% ambrisentan + tadalafil. Thus, a total of 31% (75% of 41%) of patients started on ERA + PDE-5i therapy, which is almost 50% higher than the percentage of the DSH real world data (22%).

The targeted literature search on PDE5i+ERA prescribing included 17 full text articles and 3 abstracts. The available data have been collected mainly through three large registries (The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension registry [COMPERA], the French PH Registry and the Swedish Pulmonary Arterial Hypertension Registry [SPAHR]). Overall, PAH patients with a variety of etiologies are included in the publications reviewed, covering the range of group 1 PAH subclassifications. In some older papers, with data collection periods mainly before 2015, the proportion of patients prescribed initial double combination therapy was approximately 10 – 20%. In more recent publications that included the largest number of patients, approximately 20 – 40% of patients were initiated on double combination therapy. There appears to be a gap between the recommendation in the 2015 ESC/ERS Guidelines for double combination therapy in most newly diagnosed patients and what is observed in clinical practice.

The DARWIN report demonstrated that in terms of PAH treatments, PDE-5 inhibitors, particularly sildenafil, were the primary choice as index treatment for newly diagnosed PAH patients. The study revealed an increasing trend in the prescription of PDE-5 inhibitors and ERAs in the year leading up to the PAH diagnosis. Monotherapy with PDE-5 inhibitors was the predominant treatment strategy for PAH, with less frequent use of combination therapy, usually involving bosentan. Notably, sildenafil was frequently used as a standalone treatment, while tadalafil was preferred in combination therapy, often in conjunction with bosentan or ambrisentan for dual therapy.

The ESC/ERS guideline on PAH recommends initial combination therapy of macitentan and tadalafil (class I recommendation, evidence level B). This recommendation is based on the publications by Chin et al. 2021 and Sitbon et al. 2020. Chin et a. 2021 is a publication of the TRITON trial, (The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension; NCT02558231), a multicenter, double-blind, randomized phase 3b study, evaluated initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral therapy in newly diagnosed, treatment-naive patients with PAH. Efficacy was assessed until the last patient randomized completed week 26 (end of main observation period). The primary endpoint was change in pulmonary vascular resistance (PVR) at week 26. Patients were assigned to initial triple (n = 123) or initial double therapy (n = 124). At week 26, both treatment strategies reduced PVR compared with baseline (by 54% and 52%), with no significant difference between groups (ratio of geometric means: 0.96; 95% confidence interval: 0.86-1.07; P = 0.42). Both 6MWD and NT-proBNP improved by week 26, with no difference between groups. Risk for disease progression (to end of main observation period) was reduced with initial triple versus initial double therapy (hazard ratio: 0.59; 95% confidence interval: 0.32-1.09). No mono-therapy control groups were included, so an actual benefit of initial double therapy (tadalafil + macitentan) over monotherapy (tadalafil or macitentan) cannot be assessed. Sitbon et al. 2020 describes the results from OPTIMA, a prospective, multicentre, single-arm, open-label, phase 4 study that explored the efficacy and safety of macitentan administered as initial oral combination therapy with tadalafil, in newly diagnosed, treatment-naïve PAH patients. The change from baseline in 6MWD was 35.8 (15.8 to 55.9) meter (P=0.0008). The geometric mean ratio of week 16 to baseline PVR was 0.53 (95% CI 0.47–0.59), representing a 47% reduction. No mono-therapy control groups were included, so an actual benefit of initial double therapy (tadalafil + macitentan) over monotherapy (tadalafil or macitentan) cannot be assessed.

Overall, the recommendation from the ESC/ERS guideline appears to be poorly backed by data in the real-world setting, and likely followed an extrapolation from the first-line combination of ambrisentan and tadalafil, which based on the results from the AMBITION trial. It is also unclear whether the results from ambrisentan and tadalafil can be extrapolated to macitentan and tadalafil. As stated in the CHMP scientific advice, a non-inferiority study against ambrisentan and tadalafil would have been preferred, but no such study was conducted by the Applicant.

PVR report

The Applicant has provided a PVR report, in which they investigated the correlations between ΔPVR and Δ6MWD and investigated whether PVR fulfils the Prentice criteria for a potential surrogate outcome. The analyses demonstrate that the correlation coefficient between ΔPVR and Δ6MWD was -0.31 in SERAPHIN, -0.26 in TRITON and -0.46 in bosentan studies. The proportion of the treatment effect explained (PTE)(fourth Prentice criterion) was 65.5% in the SERAPHIN data (without specifying a confidence interval) for 6MWD. No PTE analysis was conducted for TRITON. A PTE analysis was also conducted for time to clinical worsening / disease progression in SERPAHIN data, yielding a PTE of 40.5% without specifying the confidence interval.

Importantly, from a regulatory perspective, PVR is not considered a surrogate endpoint in PAH, but instead regarded as a pharmacodynamic biomarker, to be used as a secondary endpoint at best. While the submitted data by the Applicant is of interest, the current procedure is not fit for assessing whether or not PVR can be used as a surrogate endpoint. The Applicant is referred to the EMA qualification process.

There are two principal concerns with the introduction of any proposed surrogate variable. First, it may not be a true predictor of the clinical outcome of interest. For example, it may measure treatment activity associated with one specific pharmacological mechanism, but may not provide full information on the range of actions and ultimate effects of the treatment, whether positive or negative. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have ultimately been shown to be detrimental to the subjects' clinical outcome; conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates. Secondly, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects. Statistical criteria for validating surrogate variables have been proposed but the experience with their use is relatively limited.

With regard to the submitted data, the correlation coefficients between ΔPVR and Δ6MWD ranged from -0.26 to -0.46. A modification to surrogate criteria proposed by the Institute of Quality and Efficiency in Health Care (IQWiG Reports – Commission No. A10-05) and several articles (Prasad et al. 2015, Baker et al. 2018) defined the following relation between strength of correlation and the correlation coefficients: low correlation ($r \leq 0.7$), medium strength correlation ($0.7 < r < 0.85$), and high correlation ($0.85 \leq r$). Using these values, the correlation is considered low (weak).

Freedman et al. argued that the last Prentice criterion raises a conceptual difficulty since it requires the statistical test for treatment effect on the true endpoint to be nonsignificant after adjustment for the surrogate. The non-significance of this test does not prove that the effect of treatment upon the true endpoint is fully captured by the surrogate, and therefore Freedman et al. proposed to calculate the proportion of the treatment effect mediated by the surrogate. A general difficulty with interpreting many of such measures is that they are not directly linked to the effect of intervention on the true endpoint and, as a consequence, it is difficult to specify a target value that indicates a validated surrogate endpoint. In this paradigm, a valid surrogate would be one for which the PTE is equal to one. In practice, a surrogate would be deemed acceptable if the lower limit of its confidence interval of PTE was "sufficiently" large, which is not specifically defined. However, PTE will tend to be unstable when beta is close to zero, a situation that is likely to occur in practice. As Freedman et al. themselves acknowledged, the confidence limits of PE will tend to be rather wide (and sometimes even unbounded if Fieller confidence intervals are used), unless large sample sizes are available or a very strong effect of treatment on the true endpoint is observed. In this case, the confidence intervals were not provided by the Applicant, but given the relatively low PTE of 65.5% and 40.5% for 6MWD and time to clinical worsening, it is likely to assume that the lower bounds of the 95% CI is

not "sufficiently" large. In conclusion, the data submitted by the Applicant showed that improvements in PVR are associated with improvements in exercise capacity and with a decreased risk of disease progression. Nonetheless, PVR is not an accepted surrogate endpoint in PAH trials for other indications than the substitution indication.

2.6.7. Conclusions on the clinical efficacy

The A DUE trial demonstrated that M/T FDC resulted in a substantially greater reduction in PVR after 16 weeks of double-blind treatment than macitentan alone and tadalafil alone. This primary result was robust to sensitivity analyses and consistent in subgroup analyses. These data support efficacy in a substitution indication for the M/T FDC. The results demonstrate clinical efficacy of add-on macitentan on top of tadalafil. Therefore, the add-on indication for macitentan on top of tadalafil is considered acceptable. However, for the "ERA + treatment naïve stratum", the gatekeeping criterion was not reached, precluding assessment of supportive data. After raising this issue, the Applicant agreed to remove the proposed add-on and initial treatment indications from the product information.

The CHMP considered that efficacy in the proposed substitution indication has been sufficiently established.

2.6.8. Clinical safety

Introduction

The pivotal safety data included data from 186 patients evaluated in the Phase 3 A DUE DB period in which M/T FDC was compared with macitentan monotherapy and tadalafil monotherapy, supplemented by long-term safety data from the ongoing A DUE DB+OL period up to a data cut-off 31 Dec 2022. Additional safety data are provided from 4 completed Phase 3b/4 clinical trials and 3 observational studies in which macitentan and tadalafil were co-administered as a loose combination of separate tablets.

2.6.8.1. Patient exposure

Data from the following studies was considered:

Table 35: Summary of studies that provided safety data

	Study Design and Study Population	Comparator	Study Drug, Dose, and Duration	Number of Participants (Safety Population)
Pivotal Safety Data				
A DUE (AC-077A301) (DB period completed; OL period ongoing) Mod5.3.5.1/ADUE/CSR [DB primary analysis] Mod5.3.5.3/ISS/ADUE DB post-hoc/ [DB post-hoc analysis] Mod5.3.5.3/ISS/ADUE DB+OL/ [interim DB+OL analysis up to data cut-off of 31 Dec 2022]	Multicenter, prospective, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group sequential, adaptive Phase 3 clinical study that evaluated M/T 10/40 mg FDC compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg in patients with PAH (WHO Group 1, WHO FC II or III)	DB period: macitentan 10 mg, tadalafil 40 mg OL period: none (single-arm M/T 10/40 mg FDC)	DB period: M/T 10/40 mg FDC (od) for 16 weeks	35 M; 44 T; 107 M/T FDC (69 from DB-M/T FDC group were titrated initially with a loose combination of M 10 mg + T 20 mg during DB period)
			DB+OL period: M/T 10/40 mg FDC (od) at any time up to data cut-off date	185 (M/T FDC) (35 from DB-macitentan group were titrated initially with a loose combination of M 10 mg + T 20 mg during OL period)
Supportive Clinical Trials in Patients with PAH with Macitentan and Tadalafil as a Loose Combination of Tablets				
TRITON (AC-065A308) Mod5.3.5.3/ISS/TRITON/	Multicenter, prospective, double-blind, randomized, placebo-controlled, parallel-group, Phase 3b, efficacy and safety study in newly diagnosed, treatment-naïve patients with PAH (WHO Group 1)	Macitentan 10 mg (od) and tadalafil 40 mg (od) and placebo (bid) 26 weeks for primary efficacy/safety analysis [a] (include 1-week tadalafil titration + maintenance period); median 77 weeks	Macitentan 10 mg (od) and tadalafil 40 mg (od) and selexipag 200–1600 µg (bid)	127 (M+T+PBO) (Participants received titration dose of M 10 mg + T 20 mg for the first week and was up-titrated to T 40 mg per individual tolerability)
SYMPHONY (AC-055-401/ AC-055-402 [extension]) Mod5.3.5.3/ISS/SYMPHONY/	Multicenter, open-label, single-arm, Phase 3b study of macitentan in patients with PAH (Dana Point classification groups 1.1 to 1.4, WHO FC II to IV)	None	Macitentan 10 mg (od) 16 weeks (core study) + median 10.5 weeks (extension study)	73 (M+T) [b]
ORCHESTRA (AC-055-310/ AC-055-311 [extension]) Mod5.3.5.3/ISS/ORHCESTRA/	Prospective, multicenter, open-label, single-arm, Phase 3b study of macitentan in patients with PAH (Dana Point classification groups 1.1 to 1.4)	None	Macitentan 10 mg (od) 16 weeks (core study) + median 104 weeks (extension study)	36 (M+T) [b]
REPAIR (AC-055-403) Mod5.3.5.3/ISS/REPAIR	Multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on right ventricular remodelling in PAH (WHO Group 1, WHO FC I to III)	None	Macitentan 10 mg (od) Up to 52 weeks (median52.0 weeks)	30 (M+T) [b]
Supportive Observational Data in Patients with PAH with Macitentan and Tadalafil as a Loose Combination of Tablets				
OPUS/OrPHeUS (AC-055-503 [OPUS]/ AC-055-510 [OrPHeUS]) Mod5.3.5.3/ISS/OPUS-OrPHeUS/	OPUS: Multicenter, observational, prospective drug registry for new macitentan users in the US OrPHeUS: Multicenter, retrospective chart review	None	Macitentan	OPUS/OrPHeUS: 1336 (M+T) [b] (OPUS: 604, OrPHeUS: 732)

Narratives of the aforementioned studies (except A DUE):

Supportive Trials

TRITON was a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3b efficacy and safety study, in which the double regimen (macitentan, tadalafil, placebo) was compared to a triple oral regimen (macitentan, tadalafil, selexipag) in newly diagnosed (within 6 months of Day 1), participants with PAH (idiopathic, heritable, drug or toxin induced, or associated with connective tissue disease, HIV infection, or congenital heart disease; Simonneau 2013) who had not received prior PAH-specific treatment (ie, treatment-naïve). The primary objective of the study was to compare the effect of the 2 regimens on PVR at Week 26. Participants had the option to continue treatment until the last randomized participant completed 6 months. Safety endpoints included treatment-emergent AEs, vital signs, and laboratory values. The last participant last visit was completed on 5 May 2020.

SYMPHONY (AC-055-401) and its extension (AC-055-402) was a multicenter, open-label, single-arm, Phase 3b study conducted at multiple sites in the US in participants with PAH (Dana Point Clinical Classification Group 1, WHO FC II to IV) who were treatment-naïve or had been treated with a stable dose of background PAH therapy (including tadalafil) as part of standard of care. All participants received macitentan 10 mg od during the 16-week main study and continued on the same dose in the extension study until macitentan became commercially available in the US. The primary objective was to psychometrically validate the PAH-SYMPACT (a PRO). Safety endpoints included treatment-emergent AEs, vital signs, ECG abnormalities, and marked laboratory abnormalities. The last participant last visit for the main study and its extension was completed on 5 Oct 2015.

ORCHESTRA (AC-055-310) and its extension (AC-055-311) was a multicenter, open-label, single-arm, Phase 3b study conducted at multiple sites in France, Italy, and Spain in participants with symptomatic PAH (Dana Point Clinical Classification Group 1, WHO FC II or III). All participants received 10 mg macitentan od on top of any background PAH therapy (including tadalafil) as part of standard of care during the 16-week treatment period and continued on the same dose in the optional extension study until macitentan became commercially available in the respective country. The primary objective was to psychometrically validate the French, Italian and Spanish versions of the PAH-SYMPACT questionnaire. Safety endpoints included treatment-emergent AEs, vital signs, and lab abnormalities. The last participant last visit for the main study and its extension was completed on 17 Sep 2018.

REPAIR (AC-055-403) was a multicenter, single-arm, open-label, Phase 4 study in participants with symptomatic PAH (WHO FC I or II). Participants received 10 mg macitentan od on top of any background PAH therapy (including tadalafil) as part of standard of care during the 52-week treatment period. Participants in France completing the 52-week treatment period (core phase) had the possibility to continue macitentan treatment in an OLE phase. The primary objective was to evaluate the effects of macitentan on right ventricular and hemodynamic properties in participants with symptomatic PAH. Safety endpoints included treatment-emergent AEs, vital signs and marked laboratory abnormalities. REPAIR was completed on 8 Aug 2019.

Supportive Trial Publication

OPTIMA was a multicenter, prospective, single-arm, open-label, pilot Phase 4 study, in which newly diagnosed PAH patients (n=46) in WHO FC II or III received macitentan 10 mg and tadalafil 40 mg od (administered as a loose combination) (Sitbon 2020). The primary objective of the study was to compare the effect of the combination treatment on PVR at Week 16, with safety assessed through an extension period until the end of study. The conclusion in the publication is that safety and tolerability were generally consistent with previous data for macitentan in combination with PDE 5i.

Supportive Observational Studies

The OPUS registry (AC-055-503) was a multicenter, prospective, long-term, longitudinal, real-world, observational drug registry of new users of OPSUMIT (macitentan) in the US; the study was set up to fulfil a US post-marketing requirement to assess hepatotoxicity for OPSUMIT. At participating sites, all consecutive patients newly treated with macitentan (ie, initiation ≤30 days prior to or at the time of enrolment) were eligible, unless enrolled in an ongoing clinical trial. Patients were followed by their physician according to routine clinical practice, with data collected at enrolment and throughout the observation period until study end or until death, loss to follow-up, withdrawal of consent, or macitentan discontinuation with an elapsed time of 30 days after the last macitentan dosing day, whichever occurred first. The last observation for the last patient in the OPUS registry was 30 Jun 2020.

The OrPHeUS study (AC-055-310) was a multicenter, retrospective chart review of macitentan users who initiated macitentan therapy for the first time in the US, and was set up to complement OPUS to fulfill the US post marketing requirement. It aimed to include approximately 2200 new users of macitentan who were not already enrolled in OPUS. Patients could have been on other PAH therapy (including tadalafil) and could have initiated other PAH therapies (including tadalafil) as part of standard of care. Patients who initiated macitentan for the first time between 19 October 2013 (macitentan launch date) and 31 December 2016 (inclusive), were not enrolled in OPUS or in a clinical trial involving macitentan, and whose medical chart was available for data collection were eligible. Data were systematically collected as available from macitentan initiation until the earliest of macitentan discontinuation, last patient data available in the medical chart, patients' last day under the center's care, death, or end of the study observation period. The last observation for the last patient in the OrPHeUS study was 31 Mar 2017.

EXPOSURE (AC-065A401) is an ongoing, multicenter, international, prospective, real-world, observational, cohort study conducted at multiples sites in Europe and Canada to further characterize the safety profile of UPTRAVI (selexipag) when used in clinical practice and to describe clinical characteristics and outcomes of patients newly treated with selexipag compared to patients newly treated with any other PAH-specific therapy (including combination therapy with macitentan and tadalafil) who were never treated with selexipag, in the post marketing setting. EXPOSURE is a post-authorization safety study which is part of the European UPTRAVI Risk Management Plan. Patients with Group 1 PAH who recently (within 1 month) initiated treatment with selexipag or any other PAH-specific therapy are eligible for enrollment. Patients are followed by their physician according to clinical practice. The planned observation period for each patient enrolled in the study is at least 18 months or until the earliest of death, withdrawal of consent, loss to follow-up, or study end. Participants in EXPOSURE who were newly treated with selexipag (ie, UPTRAVI cohort) were excluded as all participants in this cohort were on therapies for the prostacyclin pathway and therefore not representative of the real-world population of patients treated with macitentan and tadalafil. Data collection for EXPOSURE is ongoing. Safety data through a cut-off of 30 Nov 2022 are included in this dossier.

An overview of the type of safety data provided per study, and the total extent of exposure is demonstrated is shown in the tables below.

Table 36: Overview of safety data provided per study

	A DUE Pivotal Study		Supportive Clinical Trials				Supportive Observational Studies	
	A DUE DB	**A DUE DB+OL**	**TRITON**	**SYMPHONY**	**ORCHESTRA**	**REPAIR**	**OPUS/OrPHeUS**	**EXPOSURE**
Disposition	×	×	×	×	×	×	×	×
Demographics and baseline	×	×	×	×	×	×	×	×
Prior and concomitant medications	×	×	×	×	×	×	(PAH-specific concomitant medications only)	(PAH-specific concomitant medications only)
Exposure	×	×	×	×	×	×	×	×
AEs	×	×	×	×	×	×	(Hepatic AEs and hepatic AESIs only; AEs, AESIs, and SAEs for OPUS only)	(AEs leading to interruption or discontinuation and pregnancies only)
Deaths	×	×	×	×	×	×	×	×
Laboratory (liver transaminases and hemoglobin)	(All labs available)	(All labs available)	×	×	×	×	(liver transaminases only)	--
Vital signs (blood pressure)	(All vital signs available)	(All vital signs available)	×	×	×	×	--	--

Table 37: Extent of exposure across studies.

Pivotal Study	Intervention	N	Median Duration of Exposure: Weeks (Range)	Cumulative Duration of Exposure			
				≥ 4 weeks	≥16 weeks	≥42 weeks	≥68 weeks
A DUE (AC-077A301) 16-week DB SS Population	M/T 10/40 mg FDC	107	16.14 (0.6, 21.1)	97 (90.7%)	69 (64.5%)	--	--
	Titration with macitentan 10mg + tadalafil 20 mg	*69*	*1.00 (0.6, 16.9)*	--	--	--	--
	Macitentan 10 mg	35	16.43 (15.1, 20.1)	35 (100.0%)	28 (80.0%)	--	--
	Tadalafil 40 mg	44	16.00 (11.0, 18.0)	44 (100.0%)	26 (59.1%)	--	--
	Titration with PBO + tadalafil 20 mg	*25*	*1.00 (1.0, 1.0)*	--	--	--	--
A DUE DB+OL[a] CSS Population	M/T 10/40 mg FDC (at any time during DB+OL period)	185[b]	59.86 (0.6; 151.6)	173 (93.5%)	165 (89.2%)	121 (65.4%)	80 (43.2%)
Supportive Trials	**Intervention**	**N**	**Months (Range)**	**≥ 1 month**	**≥ 3 months**	**≥ 6 months**	**≥ 12 months**
TRITON (AC-065A308)	Macitentan 10 mg + tadalafil 40 mg + PBO	127[c]	20.70 (0.1, 43.6)	121 (95.3%)	117 (92.1%)	116 (91.3%)	110 (86.6%)
SYMPHONY (AC-055-401/402)	Macitentan 10 mg + tadalafil (concomitant)	73	3.68 (0.0; 5.3)	65 (89.0%)	61 (83.6%)	--	--
ORCHESTRA (AC-055-310/311)	Macitentan 10 mg + tadalafil (concomitant)	36	14.09 (0.1, 48.3)	33 (91.7%)	30 (83.3%)	25 (69.4%)	21 (58.3%)
REPAIR (AC-055-403)	Macitentan 10 mg + tadalafil (concomitant)	30	11.91 (0.2, 13.4)	29 (96.7%)	28 (93.3%)	25 (83.3%)	11 (36.7%)
Observational Studies	**Intervention**	**N**	**Months (Range)**	**≥ 1 month**	**≥ 3 months**	**≥ 6 months**	**≥ 12 months**
OPUS/OrPHeUS (AC-055-503/510)	Macitentan + tadalafil	1336	14.28 (0.0, 67.1)	1215 (90.9%)	1063 (79.6%)	932 (69.8%)	739 (55.3%)
EXPOSURE (AC-065A401)	Macitentan + tadalafil	422	10.40 (0.0; 56.9)	363 (86.0%)	315 (74.6%)	274 (64.9%)	190 (45.0%)

Key: CSS=A DUE combined safety set, DB=double-blind, FDC=fixed dose combination, M=macitentan, OL=open-label, PBO=placebo, SS=A DUE safety set, T=tadalafil

a. Data are presented up to a cut-off date of 31 Dec 2022 for the Combination Safety Set

b. In addition to the 69 participants who titrated with macitentan 10 mg + tadalafil 20 mg at start of DB period, this cohort includes further 35 participants randomized to macitentan monotherapy arm who received a loose combination of macitentan 10 mg + tadalafil 20 mg over a 7-day titration period at start of OL period.

c. Per TRITON protocol, participants received macitentan 10 mg + tadalafil 20 mg from Day 1 to Day 7 (1 week). On Day 8 (±3 days), the dosage of tadalafil were increased to 40 mg depending on individual tolerability

This dossier summarizes the clinical safety data for 185 patients with PAH who received M/T FDC as well as supportive data from 266 patients with PAH in clinical trials and 1758 patients in observational studies who have been treated with a loose combination of macitentan and tadalafil.

As of the data cut-off date for this dossier, 186 participants received DB study treatment during the A DUE 16-week DB period, of whom 185 participants were exposed to M/T FDC at any time in the DB+OL period for a median duration of 59.86 weeks (range: 0.6–151.6). During the A DUE 16 week DB period, median treatment duration was similar across the M/T FDC, macitentan monotherapy, and tadalafil monotherapy groups, with 69 participants exposed to a loose combination of macitentan 10 mg and tadalafil 20 mg for a median duration of 1.00 week (range: 0.6–16.9) as needed for titration.

At the end of the A DUE DB period, 35/35 from DB-macitentan, 43/44 from DB-tadalafil, and 91/107 from DB-M/T FDC group continued receiving study treatment in the A DUE OL period.

Of a total of 2024 participants with PAH who have been treated with a loose combination of macitentan and tadalafil in supportive studies, 142/266 from clinical trials and 929/1758 from observational studies have been exposed to the combination for ⩾12 months.

2.6.8.2. Adverse events

Unless otherwise stated, AEs presented for A DUE safety set (i.e. treated during the A DUE 16-week DB period) are "treatment-emergent", ie, occurring after administration of the first dose of study treatment up to and including the start date of OL treatment or 30 days after end of DB treatment, whichever was earlier. For A DUE DB period, data comparisons were based on all participants receiving M/T FDC (ie, all strata) versus each monotherapy. For the A DUE DB+OL period, AEs presented for the combined safety set (ie, treated with M/T FDC at any time in study) included events after administration of the first dose of M/T FDC (in either DB or OL) up to either 30 days after end of M/T FDC treatment or data cut off, whichever was earlier.

Unless otherwise stated, the treatment-emergent period for supportive studies was defined as occurring after the first intake of the macitentan and tadalafil combination through the last dose of macitentan and tadalafil combination plus 30 days. For TRITON, the treatment-emergent period was defined from the first intake of any of 3 study medications (macitentan, tadalafil, or placebo) up to 30 days after the last intake of the last study medication.

In the A DUE 16-week DB period, the proportion of participants who experienced at least 1 AE in the M/T FDC group (82.2%) was higher than in the macitentan group (71.4%) and similar to the tadalafil group (79.5%). The proportion of participants randomized to M/T FDC who experienced at least 1 AE in the DB period was higher in the treatment-naïve stratum (87.8%) than in the prior ERA (76.2%) and the prior PDE-5i (78.4%) strata.

Table 38: Overall Summary of Treatment-emergent Adverse Events in the Double-blind Period; Safety Set (A DUE 16-week DB Period)

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

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.

In the A DUE DB+OL period, the overall incidence of AEs was 91.9% in participants treated with M/T FDC at any time up to the data cut-off date (ie, M/T FDC Total). In participants who received DB monotherapy and switched to OL M/T FDC, incidences of AEs and SAEs were comparable, although more participants from the DB-macitentan group discontinued study treatment compared to those who switched from DB-tadalafil.

In the supportive clinical trials, the majority of participants had at least 1 AE, with the highest incidence in the treatment-naïve study population in TRITON. The frequency of events varied based on the extent of exposure.

Table 39: Overall Summary of Treatment-emergent Adverse Events; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Median duration (range) of exposure, months	20.70 (0.1, 43.6)	3.680 (0.03; 5.26)	14.09 (0.1, 48.3)	11.91 (0.2, 13.4)
Subjects with 1 or more:				
AEs	124 (97.6%)	56 (76.7%)	32 (88.9%)	24 (80.0%)
AEs related to macitentan[a]	80 (63.0%)	--	--	--
AEs related to tadalafil[a]	92 (72.4%)	--	--	--
Serious AEs	48 (37.8%)	12 (16.4%)	14 (38.9%)	2 (6.7%)
Serious AEs related to macitentan[a]	4 (3.1%)	--	--	--
Serious AEs related to tadalafil[a]	4 (3.1%)	--	--	--
AEs leading to discontinuation of macitentan	19 (15.0%)	--	--	--
AEs leading to discontinuation of tadalafil	12 (9.4%)	--	--	--
AEs leading to death[b]	12 (9.4%)	0	6 (16.7%)	0

Key: AE = adverse event

a. Adverse events with missing relationship are considered as related to study treatment.

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

Note: Treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Note: For subjects who were never up-titrated and discontinued tadalafil 20 mg dose on or before Day 11, all TEAEs up to end of treatment plus 30 days are included. For all other subjects, TEAEs up to min of (Day 11, prior to day of up-titration) are included.

In the A DUE 16-week DB period, the most frequently reported AEs occurring in ⩾10% of participants in the M/T FDC group were headache and peripheral oedema; both also occurred with a frequency ⩾10% in the macitentan and tadalafil monotherapy groups. Other frequently reported AEs (⩾5% of participants) in the M/T FDC group included anaemia, decreased hemoglobin, hypotension, peripheral swelling, cough, myalgia, and nausea.

AEs occurring more frequently (difference >5%) in the M/T FDC group compared with both macitentan and tadalafil monotherapy included anaemia, decreased hemoglobin, and hypotension. Other AEs occurring more frequently in the M/T FDC group compared to macitentan monotherapy were myalgia and nausea. Peripheral swelling occurred more frequently with M/T FDC compared to tadalafil monotherapy, while diarrhea and arthralgia occurred more frequently with tadalafil monotherapy compared to M/T FDC, all with a difference in frequency >5%.

AEs of severe intensity were more frequent in the M/T FDC group (14.0%) than in the macitentan (5.7%) and tadalafil (6.8%) groups. Headache and cardiac failure AEs of severe intensity were reported for 2 participants each in the M/T FDC group, all others were reported in 1 participant each. There was no apparent pattern of AE intensity (mild, moderate, and severe) when looking at AEs by PT.

The higher frequency of AEs associated with anaemia in the M/T FDC group resulted in a higher frequency in the Blood and lymphatic system disorders SOC. Anaemia is evaluated as an AESI.

AEs in the Cardiac disorders SOC, driven by AEs of cardiac failure, were reported more frequently in the M/T FDC group than in the monotherapy groups.

More AEs were also observed in the M/T FDC group compared with monotherapy groups in Eye disorders and Nervous system disorders SOCs. For eye disorders, the difference was mainly driven by eyelid oedema, eye swelling, and periorbital oedema, with a tendency of events occurring earlier in the treatment (up to Day 12). For nervous system disorders, the difference was driven by headache (known to be associated with macitentan and tadalafil) and dizziness.

Gastrointestinal disorders, and Musculoskeletal and connective tissue disorders represent known events associated with tadalafil treatment and were reported with a greater frequency in the M/T FDC and tadalafil groups than in the macitentan group.

A greater frequency of Vascular disorder AEs in the M/T FDC group was driven by AEs of hypotension and flushing. Vascular disorders are known events associated with both monotherapies, and hypotension is evaluated as an AESI.

Table 40: Treatment-emergent Adverse Events Occurring in ≥2% Participants (M/T FDC All Strata) in the Double-blind Period by Preferred Term; Safety Set (A DUE 16-week DB Period)

	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
Subjects with 1 or more AEs	25 (71.4%)	59 (84.3%)	35 (79.5%)	72 (83.7%)	88 (82.2%)
Preferred term					
Headache	6 (17.1%)	12 (17.1%)	6 (13.6%)	14 (16.3%)	18 (16.8%)
Oedema peripheral	4 (11.4%)	9 (12.9%)	5 (11.4%)	12 (14.0%)	14 (13.1%)
Anaemia	0	6 (8.6%)	0	7 (8.1%)	8 (7.5%)
Haemoglobin decreased	0	3 (4.3%)	0	8 (9.3%)	8 (7.5%)
Hypotension	0	6 (8.6%)	0	5 (5.8%)	8 (7.5%)
Peripheral swelling	1 (2.9%)	7 (10.0%)	0	7 (8.1%)	7 (6.5%)
Cough	1 (2.9%)	5 (7.1%)	2 (4.5%)	6 (7.0%)	6 (5.6%)
Myalgia	0	5 (7.1%)	2 (4.5%)	4 (4.7%)	6 (5.6%)
Nausea	0	5 (7.1%)	3 (6.8%)	4 (4.7%)	6 (5.6%)
Back pain	1 (2.9%)	5 (7.1%)	4 (9.1%)	3 (3.5%)	5 (4.7%)
Diarrhoea	0	4 (5.7%)	6 (13.6%)	5 (5.8%)	5 (4.7%)
Arthralgia	2 (5.7%)	2 (2.9%)	4 (9.1%)	4 (4.7%)	4 (3.7%)
Cardiac failure	0	4 (5.7%)	1 (2.3%)	3 (3.5%)	4 (3.7%)
Dyspepsia	0	4 (5.7%)	3 (6.8%)	4 (4.7%)	4 (3.7%)
Dyspnoea	0	2 (2.9%)	2 (4.5%)	4 (4.7%)	4 (3.7%)
Nasal congestion	0	3 (4.3%)	0	3 (3.5%)	4 (3.7%)
Palpitations	1 (2.9%)	1 (1.4%)	2 (4.5%)	3 (3.5%)	4 (3.7%)
Pyrexia	0	2 (2.9%)	0	4 (4.7%)	4 (3.7%)
Vomiting	0	3 (4.3%)	2 (4.5%)	4 (4.7%)	4 (3.7%)
Angina pectoris	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%)
Dizziness	1 (2.9%)	2 (2.9%)	0	3 (3.5%)	3 (2.8%)
Dry mouth	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Epistaxis	0	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Fatigue	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	3 (2.8%)
Flushing	2 (5.7%)	3 (4.3%)	0	3 (3.5%)	3 (2.8%)
Hyperuricaemia	1 (2.9%)	3 (4.3%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
Nasopharyngitis	1 (2.9%)	1 (1.4%)	0	3 (3.5%)	3 (2.8%)
Non-cardiac chest pain	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)
Pain in extremity	0	2 (2.9%)	3 (6.8%)	2 (2.3%)	3 (2.8%)

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

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.

In the A DUE DB+OL period up to the data cut-off date, AEs reported with a frequency >10% in participants treated with M/T FDC at any time during the study (ie, M/T FDC Total) were COVID-19, headache, edema peripheral, and anemia. AEs reported with a frequency ⩾5% included hemoglobin decreased, cough, hypotension, upper respiratory tract infection, arthralgia, dyspnea, myalgia, back pain, palpitations, and pyrexia. Aside from COVID-19 and cough, which were consistent with study conduct during the pandemic, the types of common AEs observed remained comparable to the known safety profiles of macitentan and tadalafil.

The most frequently reported AEs in participants switching to M/T FDC from macitentan monotherapy were COVID-19 and hemoglobin decreased; for those switching from tadalafil monotherapy, the most frequently reported AEs were COVID-19, anemia, dyspnea, and pyrexia. No new safety concern was identified.

Overall, the pattern of frequently reported AEs in clinical trials with a loose combination of macitentan and tadalafil were consistent with findings from the A DUE 16 week DB period and the known safety profiles of the individual components macitentan and tadalafil. The AEs observed were consistent with the known symptomatology, complications, and underlying comorbidities associated with PAH. In TRITON, participants were newly diagnosed with PAH and had not received any PAH-specific treatment prior to start of the trial, whereas in SYMPHONY, ORCHESTRA, and REPAIR, >40% participants were already receiving PDE-5i prior to the start of combination treatment. The frequency of events varied due to differences between the design, duration, demographics, and baseline characteristics of the participants across the studies.

The most frequent AEs included headache, oedema AEs (e.g. peripheral oedema, peripheral swelling) and gastrointestinal AEs (e.g. diarrhea, nausea, dyspepsia and vomiting). Vasodilatory effects such as flushing and respiratory AEs (e.g. nasal congestion and AEs associated with upper respiratory tract infections) were also frequent. AEs associated with tadalafil such as back pain, myalgia and arthralgia were frequently reported.

Adverse Drug Reactions

Known ADRs for macitentan and tadalafil in PAH indications were considered for inclusion in the labeling documents for M/T FDC. Macitentan CCDS and tadalafil EU SmPC served as reference for ADRs observed with individual components.

A DUE data were reviewed for potential new ADRs; information on imbalance in AEs frequencies between treatment groups, SAE, and TEAE leading to discontinuation were considered for identification of potentially new ADRs. Conservatively, a threshold of 2% was selected for identifying AEs with imbalance for further review. TEAEs reported with a difference of more than 2% with M/T FDC group compared to either the macitentan or tadalafil groups were cardiac failure, diarrhea, dyspnoea, pyrexia, dry mouth, non-cardiac chest pain, cough, dizziness, and angina pectoris. The review of details of individual cases for these AEs did not show any particular pattern indicating potential new ADRs:

Cardiac failure
AEs denoting cardiac failure were reported in 6/107 (5.6%) participants in the M/T FDC group: cardiac failure in 4 (3.7%) participants, left ventricular failure in 1 (0.9%) participant, and right ventricular failure in 1 (0.9%) participant. In the monotherapy treatment groups, cardiac failure and cardiac failure chronic were reported in 1/44 (2.3%) participant each in the tadalafil group and no cardiac failure was reported in the macitentan group.
Of 8 total cases in the DB period denoting cardiac failure, 6 were observed in the M/T FDC group. Events were predominantly in treatment-naïve participants (5 of 6). Most participants were elderly ($\geqslant$65 years, 4 of 6). All patients with cardiac failure had pre-existing comorbidities associated with a higher risk of cardiac failure (eg, medical history of cardiomegaly, COPD, heart failure, hyperlipidemia, hypertension, interstitial pneumonia, atypical myobacterial infection, mitral regurgitation, atrial fibrillation). Out of 6 participants who experienced cardiac failure events in the M/T FDC group, 2 participants were not considered for further detailed analysis due to following reasons: the event was reported as secondary to PAH worsening on Day 1 for one participant, and the second participant discontinued M/T FDC due to hypotension on Day 4, started treatment with ambrisentan, and developed cardiac failure on Day 19. Among the remaining 4 participants, two cases out of four resolved while on treatment, whereas the other two were discontinued due to other adverse events [a newly established diagnosis of Pulmonary Veno-Occlusive Disease (exclusionary as per study protocol) and anaemia].

In the A DUE OL period where all participants received M/T FDC (data cut-off: 31 December 2022), an additional 6 participants (3 DB-M/T FDC, 2 DB-tadalafil, and 1 DB-macitentan) experienced events of cardiac failure (ie, right ventricular failure and cor pulmonale); there was no pattern observed with regard to age or

latency in the occurrence of these events. Confounding factors were identified for 5 participants, including a medical history of coronary artery bypass graft surgery, renal impairment, liver cirrhosis, hypertension, and left heart failure.

Cardiac failure was also evaluated in 4 supportive clinical trials in which participants were given macitentan 10 mg and tadalafil 40 mg as separate tablets (total N=266 from TRITON, ORCHESTRA, SYMPHONY, and REPAIR). Events denoting heart failure generally occurred later during treatment with a loose combination of macitentan and tadalafil. Of 22 total participants who experienced heart failure in the supportive studies, events occurred within 4 weeks of initiation of the loose combination in 5 participants. None of these events led to discontinuation of combination treatment, although macitentan was discontinued per protocol in a participant who was also diagnosed with PVOD. Concurrent peripheral edema/fluid retention AE was reported in 2 participants with significant comorbidities (e.g. severely reduced systolic function of dilated right ventricle, 2-vessel coronary artery disease). Notably, there were large differences in exposure between clinical trials (range 3.68 months to 20.70 months). Considering the pathophysiology of PAH, the review of cardiac failure events from A DUE and supportive studies did not provide conclusive evidence supporting a causal relationship between the administration of M/T FDC and occurrence of cardiac failure in participants with PAH. Therefore, the Applicant does not consider cardiac failure to be an ADR for M/T FDC.

Diarrhea

During the A DUE DB period, 5/107 (4.7%) participants in the M/T FDC group experienced an AE of diarrhea compared with 6/44 (13.6%) in the tadalafil group; no participant (0/35) in the macitentan group experienced diarrhea. All 5 events of diarrhea in the M/T FDC group were nonserious, mild to moderate, and did not lead to M/T FDC treatment discontinuation. In 4 participants, the event resolved; in one participant, the outcome resolved with sequelae (not further specified). Latency ranged from Day 1 to Day 61 of study treatment. Three events were assessed as related to study medication and 2 events were assessed as not related to study medication. Four cases reported one or more confounding factors that could have contributed to the AEs of diarrhea, including 1) concomitant medication of ibuprofen, pantoprazole, and magnesium were reported in 3 participants, 2) medical history of ulcerative colitis reported in 1 participant, and 3) 3 participants experienced concurrent AEs suggestive of other possible underlying causes such as gastrointestinal infection, e.g. pyrexia in one participant; nausea, decreased appetite, vomiting before and after diarrhea in the second participant; and AEs of nausea and vomiting 6 days after diarrhea in the third participant. Considering no clear latency pattern in cases occurring, the presence of confounding factors, and resolution while M/T FDC was continued in all cases, a causal relationship between M/T FDC and diarrhea is considered unlikely.

Dyspnea

During the A DUE DB period, 4/107 (3.7%) participants in the M/T FDC group experienced dyspnea compared with 2/44 (4.5%) participants treated with tadalafil; no participant (0/35) in the macitentan group experienced dyspnea. Of the 4 participants who reported dyspnea in the M/T FDC group, 2 events were serious and 2 were nonserious. Latency was 4, 14, 76 and 97 days. One participant with SAE of dyspnea discontinued treatment on Day 15 due to the event (and events of peripheral swelling and swelling face). The event resolved after 10 days and was assessed as severe and related to study medication. In the remaining 3 participants, no action was taken with study medication; two events resolved, one event was not resolved; event severity was moderate in all 3 cases; the event was assessed as related to study medication in 2 participants and not related in one participant. All 4 cases reported potential confounding factors. Two participants (including a participant who experienced dyspnea on Day 4) experienced concurrent fluid retention (peripheral edema/ swelling/swelling face). One participant with medical history of asthma experienced SAE of dyspnea on Day 76 concurrent to chest pain, palpitations, and hemiparesis of unknown origin. One participant had hemorrhoidal hemorrhage, anemia, and blood transfusion 1 day prior to onset of dyspnea. In addition, 2 participants developed mild nonserious exertional dyspnea during 6MWT which resolved while on treatment with M/T FDC. Considering no clear latency pattern in cases occurring, the presence of confounding factors, and resolution while on treatment with M/T FDC in most cases, and the fact that dyspnea is a common presentation of the underlying disease (PAH), a causal relationship between M/T FDC and dyspnea is considered unlikely.

Pyrexia

During the A DUE DB period, 4/107 (3.7%) participants in the M/T FDC group experienced a total of 6 AEs of pyrexia; no participants in the macitentan and tadalafil treatment groups experienced pyrexia (0/35 and 0/44, respectively). All events were nonserious, mild or moderate, and all resolved while M/T FDC was continued. Latency ranged from 6 to 88 days. Pyrexia occurred in close time relationship with upper respiratory tract infection in one participant. One other participant had a medical history of gout; additionally, one episode of pyrexia was concurrent with diarrhea, suggesting an underlying gastrointestinal infection. Considering no clear latency pattern in DB or OL, transient nature of the events, and presence of confounding factors in most cases, a causal relationship between M/T FDC and pyrexia is determined to be unlikely.

Dry mouth

During the A DUE DB period, 3/107 (2.8%) participants in the M/T FDC group experienced AEs of dry mouths; no participants in the macitentan and tadalafil treatment groups experienced dry mouth (0/35 and 0/44, respectively). All events were nonserious, mild, and all resolved while M/T FDC was continued. Latency varied from 6 to 13 days. In one participant, dry mouth occurred in the presence of ongoing unspecified digestive problems and concurrently to flushing and ankle edema. In another participant, dry mouth was concurrent with multiple events of edema/fluid retention and thirst. No additional AEs of dry mouth were reported during the OL period. Although events of dry mouth occurred early after M/T FDC initiation, considering the transient nature of the events and presence of confounding factors in 2 of 3 cases, there is insufficient evidence supporting a causal relationship between M/T FDC and dry mouth. Of note is that the number of events is too small to draw any reasonable conclusions.

Non-cardiac chest pain

During the A DUE DB period, 3/107 (2.8%) participants in the M/T FDC group experienced AE of non-cardiac chest pain compared with 3/44 (6.8%) participants treated with tadalafil; no participant (0/35) in the macitentan treatment group reported non-cardiac chest pain. All 3 events of non-cardiac chest pain in the M/T FDC group were nonserious, of which one was considered severe in intensity. No action was taken with the study medication due to the event in any of the 3 participants. The event resolved in 2 participants; in one participant, outcome was not reported. The events occurred on Day 28, Day 47, and Day 87 of study treatment. Participants in all 3 cases reported potential confounding factors: medical history of non-cardiac chest pain, esophagitis, post herpetic neuralgia in one participant; Barrett's esophagus in a second participant; and concurrent cough and subsequent upper respiratory tract infection in a third participant. No additional AEs of non-cardiac chest pain were reported during the OL period. Considering no clear latency pattern, transient nature of the events, and presence of confounding factors in all 3 cases, a causal relationship between M/T FDC and non-cardiac chest pain is considered unlikely. Of note is that there were too few events to draw any reasonable conclusions.

Cough

During the A DUE DB period, 6/107 (5.6%) participants in the M/T FDC group experienced AEs of cough compared with 2/44 (4.5%) participants in the tadalafil group and 1/35 (2.9%) participants in the macitentan group. All events were nonserious, mild or moderate, and none led to M/T FDC discontinuation. Latency varied from 8 to 117 days. All 6 participants had potential confounding factors (eg, medical history of COPD, emphysema, Sjögren's syndrome, asthma, tobacco use, and gastroesophageal reflux disease) or reported cough concurrent/adjacent to events of nasal congestion/pyrexia/upper respiratory tract infection or concurrent with Sjögren's syndrome. Considering no clear latency pattern and the presence of confounding factors in the majority of events, a causal relationship between M/T FDC and cough is considered unlikely.

Dizziness

During the A DUE DB period, 3/107 (2.8%) participants in the M/T FDC group and 1/35 (2.9%) participant in the macitentan treatment group experienced AEs of dizziness; no participants (0/44) in the tadalafil treatment group experienced dizziness. Two additional AEs denoting dizziness (dizziness exertional and dizziness postural) were reported in 2 participants from the M/T FDC group. All 5 events of dizziness in the M/T FDC group were nonserious, mild or moderate, and none led to treatment discontinuation. All but one event resolved. The events occurred on Days 2, 3, 8, 11, and 51 of study treatment. All events were

assessed as not related to study medication. One AE of dizziness was reported as related to concomitant medication and another event occurred after physical exertion.

During the A DUE OL period, 4 more participants (2 DB-M/T FDC and 2 DB-macitentan) experienced AEs of dizziness on Days 10, 84, 186, and 197, respectively. All events were nonserious, mild or moderate, and all but 1 event (dizziness exertional) were assessed as not related to study medication. None led to M/T FDC discontinuation and all resolved while M/T FDC was continued. Considering transient nature of the events, no clear pattern of latency, there is not enough evidence supporting a causal relationship between M/T FDC and dizziness.

Angina pectoris
Four AEs of angina pectoris (reported as cardiac chest pain) occurred in the A DUE study: 3 participants in the M/T FDC group and 1 participant in the macitentan group.

No events of angina pectoris occurred in the tadalafil group (0/44).

All 3 AEs of angina pectoris in the M/T FDC group were reported as nonserious, mild or moderate, and none led to treatment discontinuation. Occurrence was confounded by medical history of significant cardiovascular comorbidity such as ischemic heart disease, hypertension, dyslipidemia, and diabetes mellitus in 2 participants and underlying scleroderma in the third participant. No event of angina pectoris was considered related to study medication by the investigator. While unstable angina pectoris is a known ADR associated with the use of tadalafil and is reflected accordingly in the M/T FDC labelling documents, based on the review of the cases presented above, considering the small number of cases, an unclear latency pattern, significant cardiovascular comorbidities, risk factors, and the fact that chest pain can be a presentation of the underlying PAH (Oldroyd 2023), there was insufficient evidence to add angina as an additional ADR for M/T FDC.

Based on the performed assessments, no new ADRs were identified for M/T FDC.

Hypertension
The event of hypertension, which is included in the tadalafil EU SmPC as an ADR, was not selected as an ADR for M/T FDC based on the mechanism of action of the combination and the lack of events observed in the A DUE 16-week DB period.

Known ADRs
A summary of known ADRs from labelling documents of individual components that were observed in A DUE and not observed in A DUE are presented below. Where appropriate, ADRs denoting the same medical concept have been grouped. Alignment with local labels of individual components is ensured.

Table 41: A summary of known ADRs from labelling documents of individual components that were observed in A DUE and not observed in A DUE

Known ADRs for macitentan and tadalafil observed in A DUE DB period	Known ADRs as per labeling documents of individual components not observed in A DUE DB period (list of PTs)
• Edema/fluid retention (Oedema peripheral[a], Peripheral swelling[a], Generalised oedema[a], Swelling[a], Bone marrow oedema[a], Joint swelling[a], Fluid retention[a]); Chest pain[b]; Swelling face[b] • Nausea[b], Dyspepsia[b], Vomiting[b], Abdominal discomfort[b], Abdominal pain[b], Gastroesophageal reflux disease[b] • Headache[c], Migraine[b], Syncope[b] • Nasopharyngitis[c], Influenza[a], Urinary tract infection[a], Upper respiratory tract infection[b] • Myalgia[b], Back pain[b], Pain in extremity[b] • Nasal congestion[c], Epistaxis[b] • Palpitations[b], Tachycardia[b] • Transaminases increased[a] • Anemia/hemoglobin decreased (Anaemia[a], Iron deficiency anaemia[a], Anaemia of chronic disease[a], Haemoglobin decreased[a], Normochromic anaemia[a], Pancytopenia[a]) • Hypotension[c], Flushing[c], Hot flush[c] • Rash[c] • Vision blurred[b] • Heavy menstrual bleeding[b], Intermenstrual bleeding[b], Vaginal haemorrhage[b] • Hypersensitivity[c], Angioedema[c]	• Seizure[b] • Transient amnesia[b] • Stroke[b] • Non-arteritic anterior ischemic optic neuropathy[b] • Retinal vascular occlusion[b] • Visual field defect[b] • Tinnitus[b] • Sudden hearing loss[b] • Sudden cardiac death[b] • Myocardial infarction[b] • Urticaria[b] • Stevens-Johnson syndrome[b] • Exfoliative dermatitis[b] • Priapism[b] • Prolonged erections[b] • Unstable angina pectoris[b] • Ventricular arrythmia[b] • Hyperhidrosis[b] • Haematuria[b] • Penile haemorrhage[b] • Haematospermia[b] • Bronchitis[a] • Pharyngitis[a]

a. ADR seen with macitentan
b. ADR seen with tadalafil
c. ADR seen with both macitentan and tadalafil

Leukopenia and Thrombocytopenia were included as ADRs in M/T FDC SmPC in alignment with Opsumit SmPC.

Central serous chorioretinopathy was added as an ADR for tadalafil in PAH indication during the dossier review and is now also considered an ADR in M/T FDC SmPC.

The incidence of treatment discontinuation due to AEs among participants receiving M/T FDC in the DB phase of the study was 8.4%. The following ADRs led to treatment discontinuation in the M/T FDC group in the DB period: anaemia and haemoglobin decreased (1.9% grouped); oedema peripheral and peripheral swelling (1.9% grouped); swelling face (0.9%); hypersensitivity (0.9%); angiooedema (0.9%); myalgia (0.9%); transaminases increased (0.9%); and hypotension (0.9%).

The following ADRs led to treatment discontinuation of M/T FDC treatment in the DB+OL period: anaemia and haemoglobin decreased (1.6% grouped); oedema peripheral and peripheral swelling (1.1% grouped); swelling face (0.5%); hypersensitivity (0.5%); angiooedema (0.5%); transaminases increased (0.5%); ALT

increased (0.5%); AST increased (0.5%); nausea (0.5%); palpitations (0.5%); myalgia (0.5%); and hypotension (0.5%).

Adverse Events During Titration Period with Macitentan 10 mg + Tadalafil 20 mg

A loose combination of macitentan 10 mg + tadalafil 20 mg was given as part of a 7-day titration period to 69 participants with PAH in A DUE DB period and 35 participants randomized to DB macitentan who transitioned to the M/T FDC in the OL period, as well as 127 participants in the double combination group in TRITON. In addition, in the OPTIMA study of the macitentan and tadalafil combination in treatment-naïve patients with PAH, all 46 participants received macitentan 10 mg and were titrated from a starting dose of tadalafil 20 mg to tadalafil 40 mg once daily, the majority within 8±3 days. Tadalafil dose reductions to 20 mg once daily occurred in 2 participants, both between Day 15 and week 16.

During the initial 7-day titration period in the A DUE 16-week DB period, participants in the prior ERA and treatment-naïve strata who were randomized to M/T FDC were titrated with macitentan 10 mg and tadalafil 20 mg, and participants in the treatment-naïve stratum who were randomized to tadalafil were titrated with tadalafil 20 mg; after the titration period, participants may have been up-titrated to the maintenance dose in accordance with their assigned treatment. In the M/T FDC group, the frequency of AEs was higher in participants in the treatment-naïve and prior ERA strata who received the titration dose than in those on prior PDE-5i therapy who started directly on the maintenance dose (i.e. macitentan 10 mg + tadalafil 40 mg). Similarly, in participants randomized to tadalafil monotherapy, treatment-naïve participants who received tadalafil 20 mg titration during first week of DB treatment had a higher frequency of AEs than those who had prior PDE-5i therapy and started directly on the tadalafil 40 mg maintenance dose.

No new safety concerns were identified during treatment with macitentan 10 mg + tadalafil 20 mg. As in the overall 16-week DB period, headache was the most frequently reported AE during the titration phase, with a frequency >10% in the M/T FDC group:

- M/T FDC: 12.5%, 19.0%, and 10.8% in the treatment naïve, prior ERA, and prior PDE-5i strata, respectively;
- Macitentan: 8.3% and 18.2% in the treatment naïve and prior ERA strata, respectively;
- Tadalafil: 8.0% and 5.3% in the treatment naïve and prior PDE-5i strata, respectively.

All AEs leading to discontinuation of study intervention were in the M/T FDC group, and included myalgia, hypersensitivity, angiooedema (treatment-naïve participants), hypotension (prior ERA), and oedema peripheral (prior PDE-5i).

Table 42: Overall Summary of Treatment-emergent Adverse Events During the Titration Phase by Stratum; Safety Set (A DUE 16-week DB Period)

	Treatment-naïve stratum			Prior ERA stratum		Prior PDE-5i stratum [a]	
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC
Analysis set: Safety	24	25	48[b]	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%)
Related AEs [c]	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 [d]	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: EOT-DB = End of treatment in double-blind treatment period.

a. Participants in the prior PDE-5i strata started with tadalafil 40 mg or a combination of macitentan 10 mg + tadalafil 40 mg on Day 1 if they were already on a stable dose of PDE-5i at baseline (ie, tadalafil 40 mg, sildenafil 60–120 mg, or vardenafil 10 mg od) (see A DUE study protocol Section 3.1.1)
b. One treatment-naïve participant was excluded from the analysis as the participant mistakenly took M/T FDC tablets as soon as Day 1 and did not undergo titration part.
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.
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 up-titrate, and up to EOT-DB + 30 days for patients who do not up-titrate
- for Macitentan and M/T FDC or Tadalafil patients previously treated by PDE-5i: first intake of study + 7 days (included)

2.6.8.3. Serious adverse events/deaths/other significant events

During the A DUE 16-week DB period, SAEs were reported more frequently in the M/T FDC group than in the macitentan and tadalafil groups; within the M/T FDC group, SAEs were reported by more treatment-naïve participants than those who have had prior treatment with an ERA or a PDE-5i (8/49 [16.3%] treatment-naïve, 3/21 [14.3%] prior ERA, and 4/37 [10.8%] prior PDE-5i). The only SOC with a notable imbalance in SAEs was Cardiac disorders. The imbalance was mainly driven by AEs denoting heart failure (i.e. cardiac failure, left and right ventricular failure).

Cardiac failure and dyspnoea were the only SAEs by PT that occurred in more than 1 participant during the DB period. Most SAEs were considered not related to study intervention by the investigator. Treatment-related SAEs in the M/T FDC group included cardiac failure, dyspnoea, anaemia, peripheral swelling, right ventricular failure, and swelling face, each reported once.

Table 43: Treatment-emergent Serious Adverse Events in the Double-blind Period by System Organ Class and Preferred Term; Safety Set (A DUE 16-week DB Period)

System organ class Preferred term	Treatment-naïve and prior ERA strata Macitentan	 M/T FDC	Treatment-naïve and prior PDE-5i strata Tadalafil	 M/T FDC	All strata 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%)
Cardiac disorders	1 (2.9%)	5 (7.1%)	1 (2.3%)	6 (7.0%)	7 (6.5%)
Cardiac failure	0	2 (2.9%)	1 (2.3%)	1 (1.2%)	2 (1.9%)
Atrial flutter	0	0	0	1 (1.2%)	1 (0.9%)
Coronary artery disease	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Left ventricular failure	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Palpitations	0	0	0	1 (1.2%)	1 (0.9%)
Right ventricular failure	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Angina pectoris	1 (2.9%)	0	0	0	0
Infections and infestations	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 pneumonia	1 (2.9%)	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Gastroenteritis clostridial	0	0	0	1 (1.2%)	1 (0.9%)
Influenza	0	1 (1.4%)	0	0	1 (0.9%)
Pneumonia	1 (2.9%)	0	1 (2.3%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.9%)	2 (2.9%)	1 (2.3%)	3 (3.5%)	3 (2.8%)
Dyspnoea	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Pulmonary veno-occlusive disease	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Asthma	1 (2.9%)	0	0	0	0
Haemoptysis	0	0	1 (2.3%)	0	0
General disorders and administration site conditions	0	1 (1.4%)	0	2 (2.3%)	2 (1.9%)
Chest pain	0	0	0	1 (1.2%)	1 (0.9%)
Peripheral swelling	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Swelling face	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Nervous system disorders	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Hemiparesis	0	0	0	1 (1.2%)	1 (0.9%)
Horner's syndrome	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Cerebral infarction	0	0	1 (2.3%)	0	0
Blood and lymphatic system disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Anaemia	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Gastrointestinal disorders	0	1 (1.4%)	1 (2.3%)	0	1 (0.9%)
Tongue cyst	0	1 (1.4%)	0	0	1 (0.9%)
Oesophageal ulcer	0	0	1 (2.3%)	0	0
Musculoskeletal and connective tissue disorders	0	1 (1.4%)	0	0	1 (0.9%)
Osteonecrosis	0	1 (1.4%)	0	0	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (1.2%)	1 (0.9%)
Mucinous cystadenocarcinoma ovary	0	0	0	1 (1.2%)	1 (0.9%)
Reproductive system and breast disorders	0	0	0	1 (1.2%)	1 (0.9%)
Endometriosis	0	0	0	1 (1.2%)	1 (0.9%)
Vascular disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Hypotension	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

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: 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.

In the A DUE DB+OL period, the overall incidence of SAEs was 24.3% in participants treated with M/T FDC at any time up to the data cut-off date (ie, M/T FDC Total). In participants randomized to DB-M/T FDC, COVID-19 (1 from DB and 4 from OL period) and right ventricular failure (1 from DB and 2 from OL period) were the most frequently reported SAEs. Other SAEs reported in 2 participants included cardiac failure (all from DB period), COVID-19 pneumonia (1 from DB and 1 from OL period), dyspnoea (all from DB period), and pneumonia (all from OL period). Remaining SAEs were each reported in 1 participant, with no observable pattern. SAEs were reported by approximately 20% of participants previously in DB monotherapy groups (macitentan or tadalafil) while on treatment with OL M/T FDC. Right ventricular failure was reported in 1 participant from each DB monotherapy group. No pattern was observed in other SAEs, which were each reported in 1 participant.

Compared to A DUE 16-week DB period, there were generally more SAEs in the supportive trials and studies, as consistent with a longer duration of treatment. In both TRITON and ORCHESTRA, approximately 40% of participants experienced an SAE, which were most frequently reported (>10%) in the SOCs of Respiratory, thoracic and mediastinal disorders, Cardiac disorders, and Infections and infestations. SAEs of PAH and right ventricular failure were reported in >5% participants in TRITON and >5% (ie, $\geqslant$2 participants) in ORCHESTRA; in addition, SAEs of atrial fibrillation and seizure were reported in >5% participants in ORCHESTRA. Other SAEs occurred with a frequency <5% in both studies. No new safety concerns were observed in comparison with findings from A DUE.

In SYMPHONY and REPAIR, which had shorter treatment exposure, 12/73 (16.4%) and 2/30 (6.7%) of participants experienced an SAE, respectively. All SAEs occurred with a frequency <5%. There were no observable trends in comparison with findings from A DUE.

Table 44: Treatment-emergent Serious Adverse Events Occurring in >2% Participants by System Organ Class and Preferred Term; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

System organ class Preferred term	TRITON M+T	SYMPHONY M+T	ORCHESTRA[b] M+T	REPAIR M+T
Analysis set: SCS-Safety	127	73	36	30
Median duration (range) of exposure, months	20.70 (0.1, 43.6)	3.680 (0.03; 5.26)	14.09 (0.1, 48.3)	11.91 (0.2, 13.4)
Subjects with 1 or more SAEs	48 (37.8%)	12 (16.4%)	14 (38.9%)	2 (6.7%)
Respiratory, thoracic and mediastinal disorders	16 (12.6%)	--	6 (16.7%)	--
Pulmonary arterial hypertension	8 (6.3%)	--	3 (8.3%)	--
Acute respiratory failure	5 (3.9%)	--	1 (2.8%)	--
Pulmonary veno-occlusive disease	3 (2.4%)	--	--	--
Dyspnoea	--	--	1 (2.8%)	--
Hypoxia	--	--	1 (2.8%)	--
Pulmonary fibrosis	--	--	1 (2.8%)	--
Respiratory failure	--	--	1 (2.8%)	--
Cardiac disorders	15 (11.8%)	--	5 (13.9%)	--
Right ventricular failure	8 (6.3%)	--	4 (11.1%)	--
Pericardial effusion	3 (2.4%)	--	--	--
Atrial fibrillation	--	--	2 (5.6%)	--
Cardiac failure congestive	--	--	1 (2.8%)	--
Infections and infestations	15 (11.8%)	--	4 (11.1%)	--
Pneumonia	4 (3.1%)	--	1 (2.8%)	--
Sepsis	3 (2.4%)	--	1 (2.8%)	--
Septic shock	--	--	1 (2.8%)	--
Erysipelas	--	--	1 (2.8%)	--
Fallopian tube abscess	--	--	1 (2.8%)	--
General disorders and administration site conditions	8 (6.3%)	--	1 (2.8%)	1 (3.3%)
Non-cardiac chest pain	3 (2.4%)	--	--	--
Death	--	--	1 (2.8%)	--
Malaise	--	--	1 (2.8%)	--
Therapeutic response decreased	--	--	--	1 (3.3%)
Nervous system disorders	8 (6.3%)	--	3 (8.3%)	1 (3.3%)
Syncope	6 (4.7%)	--	--	1 (3.3%)
Seizure	--	--	2 (5.6%)	--
Dizziness	--	--	1 (2.8%)	--
Blood and lymphatic system disorders	--	3 (4.1%)	1 (2.8%)	--
Anaemia	--	2 (2.7%)	1 (2.8%)	--
Gastrointestinal disorders	--	3 (4.1%)	1 (2.8%)	--
Small intestinal obstruction	--	2 (2.7%)	--	--
Rectal haemorrhage			1 (2.8%)	
Surgical and medical procedures	--	2 (2.7%)	3 (8.3%)	--
Transfusion	--	2 (2.7%)	--	--
Abortion induced	--	--	1 (2.8%)	--
Cholecystectomy	--	--	1 (2.8%)	--
Lung transplant	--	--	1 (2.8%)	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	--	--	2 (5.6%)	--
Breast cancer	--	--	1 (2.8%)	--
Lung neoplasm	--	--	1 (2.8%)	--
Hepatobiliary disorders	--	--	1 (2.8%)	--
Cholecystitis acute	--	--	1 (2.8%)	--
Injury, poisoning and procedural complications	--	--	1 (2.8%)	--
Hip fracture	--	--	1 (2.8%)	--
Product issues	--	--	1 (2.8%)	--
Device material issue	--	--	1 (2.8%)	--
Renal and urinary disorders	--	--	1 (2.8%)	--
Acute kidney injury	--	--	1 (2.8%)	--
Vascular disorders	--	--	1 (2.8%)	--
Shock haemorrhagic	--	--	1 (2.8%)	--

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: For TRITON, treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Deaths

During the A DUE 16-week DB period, there were 3 deaths (2 treatment-emergent) in the M/T FDC group and none in the macitentan and tadalafil groups. None were assessed by the investigators as related to study treatment. As of the data cut-off date, 2 deaths (1 treatment-emergent) occurred during the A DUE OL period, both from the DB-M/T FDC group.

Compared to A DUE 16-week DB period, there were more deaths in TRITON and ORCHESTRA, as consistent with a longer duration of treatment in these clinical trials. In TRITON and ORCHESTRA, right ventricular failure, which was consistent with the underlying PAH and comorbidities, was the only event that led to death in >1 participant in both clinical trials. In addition, in ORCHESTRA, there were 2 participants who died from seizure. No apparent trends were observed in other AEs leading to death from clinical trials.

In OPUS/OrPHeUS, 176/1336 (13.2%) participants died during the study (median duration of exposure of 14.28 months). Aside from disease progression (ie, PTs of PAH [1.9%], disease progression [1.0%]) and unclassified reasons of death (ie, PTs of death [5.2%] and cause of death not classified [1.4%]), dyspnoea and respiratory failure were the most frequently reported AEs leading to death (both 1.0%).

In EXPOSURE, after disease progression, the most frequently reported AE leading to death was right heart failure, which may also be associated with worsening of PAH. In all 3 observational studies, other AEs leading to death were uncommon. Findings from observational studies are consistent with published data on the 1-year mortality rate for patients with PAH (McLaughlin 2009).

Other significant adverse events

Cardiac disorders

Events of cardiac disorders that occurred during the A DUE DB period were further investigated. Cardiac disorders were reported in 16 (15.0%) of participants in the M/T FDC group compared to 2 (5.7%) in the macitentan group and 4 (9.1%) in the tadalafil group. The difference was mainly driven by AEs denoting cardiac failure reported in 4 (3.7%) participants, left ventricular failure in 1 (0.9%) participant, and right ventricular failure in 1 (0.9%) participant in the M/T FDC group. Cardiac failure and cardiac failure chronic were reported in 1 (2.3%) participant each in the tadalafil group. There was no cardiac failure reported in the macitentan group.

- Overall, 8 participants (6 in the M/T FDC group, 2 in the tadalafil group) experienced an AE denoting cardiac failure (cardiac failure, left and right heart failure). Within the M/T FDC group, 2 participants had concurrent fluid retention at the onset of cardiac failure.
- Except for 1 participant in the tadalafil group, all cardiac failure AEs occurred during the first month of DB exposure to study intervention.
- 5 of 8 participants with AEs denoting cardiac failure were treatment-naïve (all in the M/T FDC group) and 5 of 8 participants were ⩾65 years old (4 in the M/T FDC group and 1 in tadalafil group).
- 5 of the 8 cardiac failure AEs were reported as serious, of which 1 was fatal.

In summary, AEs denoting cardiac failure were reported more frequently in participants in the M/T FDC group during the 16-week DB period. Events occurred within 1 month of treatment initiation and were generally clinically manageable while participants continued on study intervention. Most participants with such AEs were 65 years or older, were treatment-naïve, and had pre-existing comorbidities associated with a higher risk of cardiac failure. Of the 4 treatment-naïve, elderly participants in the M/T FDC group who experienced

events denoting cardiac failure, two cases out of four resolved while on treatment, whereas the other two were discontinued due to other adverse events [a newly established diagnosis of Pulmonary Veno-Occlusive Disease (exclusionary as per study protocol) and anaemia].

Menstrual Bleeding

For macitentan, menstrual disorders (primarily bleeding) are currently listed as a potential risk in the European risk management plan (OPSUMIT RMP). For tadalafil, menstrual disorders are currently listed as a common ADR.

In the A DUE 16-week DB period, a higher proportion of female participants from the M/T FDC group reported 1 or more AEs from the Reproductive system and breast disorders SOC (M/T FDC 6.1%, macitentan 3.4%, and tadalafil 2.9%. This imbalance was driven mainly by menstrual/vaginal hemorrhage AEs that occurred only in the M/T FDC group and all were in the prior PDE-5i stratum. There were 4 AEs related to menstrual bleeding: heavy menstrual bleeding (n=2), intermenstrual bleeding (n=1), and vaginal hemorrhage (n=1). In addition to prior treatment with a PDE-5i, all participants with abnormal menstrual bleeding events had concomitant medications known to increase the risk of menstrual bleeding disorders (eg, anticoagulants or intrauterine devices), prior medical history of menstrual disorders (eg, irregular menses, ovarian resection, metrorrhagia), and/or concurrent potentially confounding AEs (eg, endometrial polyp, cervicitis, adenomyosis, cervical ectopy).

AEs of anaemia/haemoglobin decreased were reported in 3 participants with menstrual bleeding disorders: 2 already had ongoing decreased haemoglobin prior to the bleeding events (8 days prior in 1 participant, who also had concurrent iron deficiency, and 76 days prior in the other) and 1 participant had decreased haemoglobin of 115 g/L 2 days after the bleeding event resolved.

In summary, menstrual bleeding disorders were reported in a higher proportion of female participants from the M/T FDC group during the 16-week DB period, all in the prior PDE-5i stratum. The events were manageable and did not lead to discontinuations of study intervention.

AEs of Special Interest

AEs of special interest for the A DUE study were predefined as anaemia, oedema, hypotension, and liver events, which were selected based on the well-characterized safety profiles of the M/T FDC components.

Hepatic events

A summary of participants who had at least 1 hepatic AESI in the A DUE 16-week DB period is displayed in the table below.

- No hepatic disorder AESI were reported as serious, and all but 1 AESI were reported as mild to moderate intensity.
- 1 participant (M/T FDC, prior PDE-5i) with risk factors in medical history experienced an AESI of increased transaminases of severe intensity. The participant experienced elevated ALT and AST >3×ULN on Days 113 and 121, respectively, reaching highest elevation on Day 127 (ALT 18.8×ULN and AST 7.5×ULN); total bilirubin remained normal. Study intervention was discontinued at the AESI onset, and the AESI resolved 58 days later.
- 1 participant (tadalafil, treatment-naïve) had an AESI of increased transaminases due to an AST increase to 3.6×ULN on Day 58, which led to treatment discontinuation. The AESI remained unresolved at cut-off.

- 1 participant (tadalafil, treatment-naïve) had an AESI of increased ALT due to an ALT increase to 5.1×ULN on Day 56, which led to interruption of study intervention. After 10 days of interruption of study intervention, ALT decreased to 2.1×ULN and study intervention was reintroduced. After a steady decline, liver transaminases normalized by Day 84.

Liver aminotransferase increases are known events associated with macitentan. Hepatic AESIs were infrequently reported across all treatment groups during the DB period. No imbalance in incidence of markedly abnormal AST and/or ALT was observed between treatment groups, and no participant met criteria for potential Hy's law (i.e. ALT and/or AST ⩾3×ULN and total bilirubin ⩾2×ULN) during the DB period. No new safety concern was identified in participants receiving M/T FDC during the DB period.

Table 45: Treatment-emergent Hepatic AESIs in the Double-blind Period; Safety Set (A DUE 16-week DB Period)

	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
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					
Transaminases increased	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Alanine aminotransferase increased	1 (2.9%)	0	1 (2.3%)	0	0
Aspartate aminotransferase increased	1 (2.9%)	0	2 (4.5%)	0	0
Blood alkaline phosphatase increased	1 (2.9%)	0	0	0	0
Hepatic steatosis	0	0	1 (2.3%)	0	0
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
Subjects with 1 or more fatal AESIs	0	0	0	0	0
Subjects with 1 or more AESIs leading to treatment discontinuation	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Transaminases increased	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)

Key: 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.

In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of hepatic AESIs was 4.08 events per 100 patient-years. The overall incidence of hepatic events was 4.9% in participants treated with M/T FDC at any time up to the data cut-off. Of the 107 participants randomized to DB-M/T FDC, 6 (5.6%) had a hepatic AESI, of which 1 was previously described in the DB period. 5 participants had hepatic events only during the OL period; all were mild or moderate in intensity. Participants with hepatic AESIs in the OL period are summarized below.

- 1 participant discontinued OL treatment due to DILI (drug-induced hepatitis). Participant's ALT/AST was >3×ULN on Day 148, with highest elevation observed on Day 155 (ALT 8.6×ULN and AST 6.2×ULN). Total bilirubin and ALP remained within normal limits. The event was reported as moderate in intensity and resolved after treatment discontinuation.

- 1 participant with relevant risk factors had ALT, AST, ALP, bilirubin increased, and ocular icterus. Participant had ALT 1.7×ULN and AST 5.3×ULN on Day 217 (AST/ALT ratio of 3.1), with total bilirubin 1.2×ULN. The participant discontinued OL study treatment on Day 223 due to elevated ALT and AST. The elevated ALP and ocular icterus resolved. Following initial improvement, AST increased to 5.8×ULN on Day 257, with ALT <3×ULN and total bilirubin within normal limits. On Day 266, more than 30 days after treatment discontinuation, total bilirubin increased to 2.6×ULN, with AST 4.3×ULN and ALT <2×ULN.

- 1 participant had SAEs of hepatic cirrhosis (assessed as related to hepatic congestion), portal hypertension, and varices esophageal, who died during the OL period due to right ventricular failure (the participant had multiple episodes of right ventricular failure).

- In the remaining 2 participants, 1 had AESIs of hepatic steatosis and hepatitis B, and 1 had an AESI of transaminase increased, with ALT 1.9×ULN and AST 3.0×ULN on Day 211. In all 3 events, no action was taken with the study treatment. The hepatitis B was resolving; the hepatic steatosis and transaminase increased were ongoing at the time of the data cut-off.

Of the 78 participants who switched from DB monotherapy to OL M/T FDC, hepatic AESIs were reported in 3 participants and were all mild in intensity. None were SAEs and 1 AESI of hepatitis B led to treatment discontinuation.

- 1 participant (DB-macitentan) with medical history of hepatitis B carrier and hepatic steatosis had an AESI of varices esophageal and discontinued OL treatment due to AESI of hepatitis B flare. Participant had ALT and AST >3×ULN on OL Day 94, with maximum elevation at 7.13×ULN on OL Day 101; both ALT and AST normalized on OL Day 179. Total bilirubin remained within normal limits. Both events resolved.

- In the 2 remaining participants (both DB-tadalafil), 1 had an AESI of hepatitis B antibody abnormal and 1 participant had AESIs of ALT increased, AST increased, and hepatitis C. In both participants, ALT and AST remained below 2×ULN, with total bilirubin within normal limits. No action was taken with study treatment. The hepatitis B antibody abnormal was ongoing at the time of data cut-off; the other 3 events resolved.

Comparison Across Supportive Clinical Trials

The table below shows the incidence rates of hepatic AESIs in the supportive clinical trials. Compared to the M/T FDC group from the A DUE 16-week DB period, more participants in TRITON and ORCHESTRA had hepatic AESIs. No hepatic AESIs were reported in REPAIR or SYMPHONY. No participant met criteria for

potential Hys law (ie, ALT and/or AST ⩾3×ULN and total bilirubin ⩾2×ULN) and 6 participants, all from TRITON, had markedly elevated ALT/AST (i.e. ⩾5×ULN). Overall, hepatic AESIs observed with a loose combination of macitentan and tadalafil were generally mild or moderate in intensity.

Table 46: Exposure-adjusted Incidence Rate of Hepatic AESIs; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Subjects with at least one AE	15 (11.8%)	0	5 (13.9%)	0
Subject-Years of Exposure (SYE)a	215.35	19.88	49.67	26.60
Exposure-Adjusted Incidence Rate (EAIR) per 100 SYEb	6.97	-	10.07	-
95% CLc	(4.20, 11.55)	-	(4.19, 24.19)	-

Key: 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: For TRITON, treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Note: For SYMPHONY, ORCHESTRA, REPAIR, Treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

Anaemia

In A DUE 16-week DB period, anaemia AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups. Similar findings were observed in markedly abnormal haemoglobin values.

Most participants with anaemia AESI were treatment-naïve: 11 of 20 participants with anaemia AESI in the M/T FDC group and both participants with anaemia AESI in the macitentan and tadalafil groups.

Within the M/T FDC group, incidence of anaemia AESIs was comparable between the treatment-naïve and prior PDE-5i strata (11/49 [22.4%] and 8/37 [21.6%], respectively), and lower in the prior ERA stratum (1/21 [4.8%]).

In summary, anaemia AESI were disproportionally reported in participants in the M/T FDC group compared to the macitentan and tadalafil groups during the DB period. In total, 3 participants with an AE of anaemia received red blood cell transfusions, but only 1 participant required transfusion for correction of low haemoglobin due to anaemia. Anaemia is a known event associated with macitentan and was reported in 12% of participants with PAH in the tadalafil monotherapy group of the AMBITION study (Galié 2015). The frequency in the M/T FDC group was higher than is routinely observed with macitentan monotherapy. All but 1 anaemia AESI were reported as mild to moderate, and they were clinically manageable. The pattern of occurrence was consistent with known safety profile of macitentan in participants with PAH. No new safety concern was identified in participants receiving M/T FDC during the DB period.

Table 47: Treatment-emergent Anaemia AESIs in the Double-blind Period; Safety Set (A DUE 16-week DB Period)

	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
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					
Anaemia	0	6 (8.6%)	0	7 (8.1%)	8 (7.5%)
Haemoglobin decreased	0	3 (4.3%)	0	8 (9.3%)	8 (7.5%)
Iron deficiency anaemia	1 (2.9%)	2 (2.9%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Anaemia of chronic disease	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Normochromic anaemia	0	0	0	1 (1.2%)	1 (0.9%)
Pancytopenia	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%)
Anaemia	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%)
Anaemia	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Haemoglobin decreased	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Key: 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.

In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of anaemia AESIs was 23.27 events per 100 patient-years. The overall incidence of anaemia AESIs was 22.2% in participants treated with M/T FDC at any time up to the data cut-off.

Of the 107 participants randomized to DB-M/T FDC, 29 (27.1%) had an anaemia AESI, of which 20 were described in the DB period. 9 participants had anaemia AESIs only during the OL period, and all events were mild or moderate in intensity. There was 1 SAE reported during the OL period in a participant (PDE 5i

stratum) with a non-serious anaemia AESI reported during the DB period. The SAE of normochromic anaemia was severe in intensity and resolved after treatment interruption. In the DB-M/T FDC group, no anaemia AESI with an onset during the OL period led to treatment discontinuation. 2 participants received blood transfusion (1 for AESI of anaemia and 1 for gastrointestinal bleeding without a concurrent AE of anaemia).

Of the 78 participants transitioning from DB monotherapy to OL M/T FDC, anaemia AESIs were reported in 12 participants during the OL period and were all mild or moderate in intensity. None were SAEs and 1 AESI of haemoglobin decreased led to treatment discontinuation in a participant who received DB-macitentan. 3 participants received blood transfusion: 2 from DB-tadalafil (1 with AESI of anaemia as well as concurrent AE of uterine polyp) and 1 from DB-macitentan.

Comparison Across Supportive Clinical Trials

The table below shows the incidence rates of anaemia AESIs in the supportive clinical trials. The incidence of anaemia AESIs was comparable between the M/T FDC group from A DUE 16-week DB period and supportive trials with a loose combination of macitentan and tadalafil. Overall, anaemia AESIs in supportive trials were generally mild or moderate in intensity, and few participants required transfusion. No new safety concerns were identified, and events were manageable with routine monitoring of haemoglobin values.

Table 48: Exposure-adjusted Incidence Rate of Anaemia AESIs; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Subjects with at least one AE	24 (18.9%)	10 (13.7%)	4 (11.1%)	3 (10.0%)
Subject-Years of Exposure[a]	194.85	18.71	50.87	25.14
Exposure-Adjusted Incidence Rate (EAIR) per 100 subject-years of exposure[b]	12.32	53.44	7.86	11.93
95% CL[c]	(8.26, 18.38)	(28.75, 99.32)	(2.95, 20.95)	(3.85, 37.01)

Key: AESI = Adverse event of special interest; 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: For TRITON, treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Note: For SYMPHONY, ORCHESTRA, and REPAIR, treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

In the supportive studies, the frequency of participants with an anaemia AESI was as follows:

- TRITON: 24/127 (18.9%), of which 2 (1.6%) were severe in intensity. 2 participants reported SAEs (anaemia, decreased hemoglobin, iron deficiency anaemia), and 2 participants discontinued macitentan due to AEs of anaemia. 54.6% of events resolved. During the study, 6/127 (4.7%) participants received blood and related products as a concomitant treatment for any reason.
- SYMPHONY: 10/73 (13.7%), of which 2 (2.7%) were severe in intensity. 3 participants had SAEs (anaemia and microcytic anaemia). 50.0% of events resolved. No participants reported blood transfusion as a concomitant treatment during the study.

- ORCHESTRA: 4/36 (11.1%), of which 1 (2.8%) was severe in intensity. 1 participant experienced an SAE of anaemia. The majority (66.7%) of events resolved. 1 (2.8%) received whole blood as a concomitant treatment during the study.

- REPAIR: 3/30 (10.0%), all mild in intensity. One event (33.3%) resolved. No participants reported blood transfusion as a concomitant treatment during the study.

In the OPUS registry, the exposure-adjusted event rate for a first anaemia AESI was 7.21 events per 100 person-years. Anaemia AESIs were reported in 64/604 (10.6%) participants.

Hypotension

In A DUE 16-week DB period, hypotension AESI, a known event associated with both macitentan and tadalafil, only occurred in participants treated with M/T FDC. Events occurred within 4 weeks of study treatment for 5 participants and after 4 weeks of treatment for 3 participants.

- AESI of hypotension were reported in 3 participants in the treatment-naïve stratum, 3 in the prior ERA stratum, and 2 in the prior PDE-5i stratum.

- All hypotension AESI were of mild or moderate intensity.

- In 6 participants, the hypotension AESI resolved while study intervention was continued (n=4) or following interruption of study intervention (n=2), of which 1 was an SAE.

    - 1 participant (M/T FDC, treatment-naïve) experienced an SAE of orthostatic hypotension of moderate intensity on Day 126. The participant was hospitalized for COVID-19 pneumonia with hypoxemia. Study intervention was interrupted, and the SAE resolved. The investigator assessed the event as not related to study intervention but rather to COVID-19 pneumonia related autonomic dysfunction.

- 1 participant (M/T FDC, prior ERA) discontinued study intervention due to hypotension; the participant later experienced worsening of heart failure and died; the hypotension AESI was unresolved at the time of death.

- The remaining participant (M/T FDC, treatment-naïve) had a mild event of hypotension on Day 22, which was assessed as related to the study intervention. No action was taken with the study intervention, and the outcome was unavailable at the time of data cut-off.

In summary, hypotension AESIs were generally clinically manageable. Although all AESI of hypotension during the DB period occurred in the M/T FDC group, the concomitant introduction of 2 vasodilators to participants with or without prior PAH treatments did not raise any new safety concerns.

Table 49: Treatment-emergent Hypotension AESIs in the Double-blind Period; Safety Set (A DUE 16 week DB Period)

	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
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					
Hypotension	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%)
Hypotension	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%)
Hypotension	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.

In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of hypotension AESIs was 5.57 events per 100 patient-years. The overall incidence of hypotension AESIs was 6.5% in participants treated with M/T FDC at any time up to the data cut-off.

Of the 107 participants randomized to DB-M/T FDC, 10 (9.3%) had a hypotension AESI, of which 8 were described in the DB period. 2 participants had hypotension AESIs only during the OL period (1 on OL Day 1 and the other on OL Day 179), and both events were moderate in intensity, non-serious, and did not lead to treatment discontinuation.

Of the 78 participants transitioning from DB monotherapy to OL M/T FDC, hypotension AESIs were reported in 2 participants during the OL period and both events were mild in intensity. None were SAEs and none led to treatment discontinuation.

In the OPUS registry, the exposure-adjusted event rate for a first hypotension AESI was 3.53 events per 100 person-years. Hypotension AESIs were reported in 34/604 (5.6%) participants.

The table below shows the incidence rates of hypotension AESIs in the supportive clinical trials. Overall, the incidence of hypotension AESIs was comparable between the M/T FDC group from A DUE 16 week DB period and supportive trials with a loose combination of tadalafil and macitentan. In the supportive trials, events were predominantly mild in intensity and most events resolved. No new safety concern was identified.

Table 50: Exposure-adjusted Incidence Rate of Hypotension AESIs; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Subjects with at least one AE	11 (8.7%)	1 (1.4%)	1 (2.8%)	1 (3.3%)
Subject-Years of Exposure (SYE)a	209.43	19.75	54.26	25.56
Exposure-Adjusted Incidence Rate (EAIR) per 100 SYEb	5.25	5.06	1.84	3.91
95% CLc	(2.91, 9.48)	(0.71, 35.95)	(0.26, 13.08)	(0.55, 27.78)

Key: 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: For TRITON, treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Note: For SYMPHONY, ORCHESTRA, and REPAIR, treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

Oedema

In A DUE 16-week DB period, oedema AESI were reported more frequently in M/T FDC group as compared to the macitentan and tadalafil groups.

- Most participants with oedema AESI were treatment-naïve: 15/22 participants with oedema AESI in the M/T FDC group, 5/5 participants with oedema AESI in the macitentan group, and 4/7 participants with oedema AESI in the tadalafil group.
- All but 1 oedema AESI were of mild or moderate intensity; 1 severe intensity AESI was reported as an SAE.
- In the M/T FDC group, oedema AESI (notably peripheral oedema) were more frequently reported in elderly participants (⩾65 years) and female participants. Within the M/T FDC group, 18 participants had

a first oedema event occurring within 4 weeks of study treatment and 4 participants had a first oedema event occurring after 4 weeks of study treatment.

- 1 participant (tadalafil, treatment-naïve) experienced a non-serious AESI of peripheral oedema, which led to treatment discontinuation after the participant switched to OL M/T FDC.

Oedema and fluid retention are known events associated with macitentan; in the AMBITION study, peripheral oedema was reported in 28% of participants with PAH in the tadalafil monotherapy group (Galié 2015). Therefore, the frequency observed in the M/T FDC group, though somewhat higher than compared to the monotherapy groups, is in line with the expected frequency. The AESI of oedema were manageable, and few participants discontinued study intervention due to oedema AESI during the DB period.

Table 51: Treatment-emergent Oedema and Fluid Retention AESIs in the Double-blind Period; Safety Set (A DUE 16 week DB Period)

	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
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					
Oedema peripheral	4 (11.4%)	9 (12.9%)	5 (11.4%)	12 (14.0%)	14 (13.1%)
Peripheral swelling	1 (2.9%)	7 (10.0%)	0	7 (8.1%)	7 (6.5%)
Bone marrow oedema	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Generalised oedema	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Swelling	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Fluid retention	0	0	1 (2.3%)	0	0
Joint swelling	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%)
Peripheral swelling	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%)
Oedema peripheral	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Peripheral swelling	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)

Key: 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

In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of oedema AESIs was 17.21 events per 100 patient-years. The overall incidence of oedema AESIs was 17.3% in participants treated with M/T FDC at any time up to the data cut-off.

Of the 107 participants randomized to DB-M/T FDC, 24 (22.4%) had an oedema AESI, of which 22 were described in the DB period. 2 participants had oedema AESIs only during the OL period, and both events were mild or moderate in intensity. Neither were SAEs and neither led to treatment discontinuation.

Of the 78 participants transitioning from DB monotherapy to OL M/T FDC, oedema AESIs were reported in 8 participants during the OL period and were all mild or moderate in intensity. The onset of oedema was within 4 weeks of switching to M/T FDC for 4 participants and after 4 weeks of treatment with M/T FDC in 4 participants. None were SAEs and none led to treatment discontinuation.

The table below shows the incidence rates of oedema AESIs in the supportive clinical trials. Overall, oedema AESIs were predominantly mild or moderate in intensity, with few meeting criteria for an SAE. In supportive trials, more than 60% of events resolved. Findings were consistent with the known safety profiles of macitentan and tadalafil.

In the OPUS registry, the exposure-adjusted event rate for a first oedema AESI was 19.14 events per 100 person-years. Oedema AESIs were reported in 156/604 (25.8%) participants.

Table 52: Exposure-adjusted Incidence Rate of Oedema AESIs; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Subjects with at least one AE	62 (48.8%)	19 (26.0%)	2 (5.6%)	7 (23.3%)
Subject-Years of Exposure (SYE)a	121.98	16.79	52.62	20.94
Exposure-Adjusted Incidence Rate (EAIR) per 100 SYEb	50.83	113.17	3.80	33.42
95% CLc	(39.63, 65.19)	(72.19, 177.43)	(0.95, 15.20)	(15.93, 70.11)

Key: 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: For TRITON, treatment-emergent period is defined from the first intake of study treatment through the last dose of study treatment plus 30 days.

Note: For SYMPHONY, ORCHESTRA, and REPAIR, treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

2.6.8.4. Laboratory findings

Liver enzymes

In the A DUE 16-week DB period, there was 1 participant in the M/T FDC group, 2 participants in the tadalafil group, and none in the macitentan group with markedly abnormal AST and/or ALT. Both participants had hepatic AESIs during the DB period and are described in the AESI section.

Of the participants treated with M/T FDC at any time during the A DUE DB+OL period up to the data cut-off, 2/178 (1.1%) had ALT or AST≥8×ULN (1 previously described in DB period), 2/178 (1.1%) had ALT or AST

between 5× to 8×ULN (both during the OL period), and 2/178 (1.1%) had ALT and/or AST between 3× to 5×ULN (both during the OL period). No participant met criteria for potential Hy's law (ie, ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN).

Table 53: Treatment-emergent Liver Abnormalities by Treatment Group; Safety Set (A DUE 16 week DB Period)

	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: 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

Mean Change from Baseline in Liver Transaminases

Decreases in the concentration of liver enzymes (ie, ALT, AST, ALP, and bilirubin) were greater in magnitude in the M/T FDC group compared to the monotherapy groups during the 16-week DB period. Changes from baseline in liver transaminases are also provided up to 52 weeks of treatment with M/T FDC (i.e. Week 42 in the DB-M/T FDC group and Week 52 in the DB monotherapy groups.

- For ALT, mean change from baseline at Week 16 was -4.0 U/L (n=78), 0 U/L (n=28), and -0.7 U/L (n=35) for M/T FDC, macitentan, and tadalafil, respectively. After 52 weeks of treatment with M/T FDC, mean change from baseline in ALT was -5.64 U/L (n=112).

- For AST, mean change from baseline at Week 16 was -1.6 U/L (n=77), 0.6 U/L (n=28), and 1.1 U/L (n=35) for M/T FDC, macitentan, and tadalafil, respectively. After 52 weeks of treatment with M/T FDC, mean change from baseline in AST was -3.75 U/L (n=113).

- For bilirubin, mean change from baseline at Week 16 was -3.486 µmol/L (n=81), -0.060 µmol/L (n=29), and 1.417 µmol/L (n=35) for M/T FDC, macitentan, and tadalafil, respectively. After 52 weeks of treatment with M/T FDC, mean change from baseline in bilirubin was -3.358 µmol/L (n=107).

In supportive trials, no participant met criteria for potential Hy's law and few participants had markedly elevated ALT/AST (i.e. ≥5×ULN). Overall, the incidence and severity of liver enzyme abnormalities in supportive trials were comparable to findings from the A DUE 16-week DB period.

In OPUS/OrPHeUS, 15/895 (1.7%) had AST and/or ALT ≥5×ULN during the observation period. For those with AST, ALT, and bilirubin data, 4/853 (0.5%) had ALT/AST ≥3×ULN and total bilirubin ≥2×ULN at the same time, and 5/853 (0.6%) had ALT/AST ≥3×ULN and total bilirubin ≥2×ULN at any time.

Table 54: Treatment-emergent Liver Abnormalities; SCS-S (TRITON, SYMPHONY, ORCHESTRA, REPAIR)

	TRITON M+T	SYMPHONY M+T	ORCHESTRA M+T	REPAIR M+T
Analysis set: SCS-S	127	73	36	30
Median duration (range) of exposure, months	20.70 (0.1, 43.6)	3.680 (0.03; 5.26)	14.09 (0.1, 48.3)	11.91 (0.2, 13.4)
ALT (U/L) and/or AST (U/L) [a]				
N	121	41	31	30
>= 3xULN and < 5xULN	5 (4.1%)	0	1 (3.2%)	0
>= 5xULN and < 8xULN	3 (2.5%)	0	0	0
>= 8xULN	3 (2.5%)	0	0	0
ALT (U/L) and/or AST (U/L) and BILI (µmol/L)				
N	121	41	31	30
ALT and/or AST >= 3xULN and BILI >= 2xULN at the same time [b,c]	0	0	0	0
ALT and/or AST >= 3xULN and BILI >= 2xULN at any time [c]	0	0	0	0

Key: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BILI = Bilirubin; ULN = Upper limit of normal

a. These categories are mutually exclusive, a subject is counted once according to the highest treatment-emergent result.
b. ALT or AST collected on the same day as bilirubin.
c. ALT or AST and bilirubin increased compared to baseline.

Note: Treatment-emergent period is defined from the first intake of macitentan and tadalafil combination treatment through the last dose of macitentan and tadalafil combination treatment plus 30 days.

Note: N is the number of subjects with at least 1 postbaseline value during the treatment-emergent period for the specified lab tests.

Hemoglobin

In the A DUE 16-week DB period, decreased haemoglobin was more frequently observed in the M/T FDC group than in the macitentan and tadalafil groups. In the M/T FDC group, clinically significant decreases relative to baseline (≥50 g/L) were observed in 3/100 (3.0%) participants and absolute haemoglobin (<80 g/L) in 2/100 (2.0%) participants. 1 participant had both haemoglobin <80 g/L and a decrease from baseline >50 g/L and was treated with transfusion of packed red blood cells.

Table 55: Treatment-emergent Haemoglobin Abnormalities by Treatment Group; Safety Set (A DUE 16 week DB Period)

	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

In the A DUE DB+OL period up to the data cut-off, clinically significant decreases in haemoglobin relative to baseline (≥50 g/L) were observed in 5/174 (2.9%) participants treated with M/T FDC at any time: 3 were described in the DB period and 2 had a decrease only during OL period. Similarly, 4/174 (2.3%) had marked decreases in absolute haemoglobin (<80 g/L), with 2 described in the DB period and 2 with a marked decrease <80 g/L only during OL period.

Mean Change from Baseline in Hemoglobin

Mean haemoglobin decrease was greater in magnitude in the M/T FDC group than in the macitentan and tadalafil groups during the DB period: mean change from baseline at Week 16: -13.9 g/L versus 6.8 g/L and 0.8 g/L, respectively. After 52 weeks of treatment with M/T FDC (i.e. Week 42 in the DB-M/T FDC group and Week 52 in the DB monotherapy groups), mean change from baseline was -9.5 g/L.

With the exception of TRITON, the incidence of substantial decrease relative to baseline (⩾50 g/L) and substantial decrease in absolute hemoglobin were comparable between the M/T FDC group in A DUE 16-week DB period and supportive trials with a loose combination of macitentan and tadalafil. However, the incidence of anemia AESIs was comparable between TRITON and A DUE DB period.

Renal clearance

In the A DUE 16-week DB period, mean eGFR remained stable in the M/T FDC arm. The incidence of eGFR <60 mL/min/1.73m2 was comparable between treatment groups. There were 2 participants (both in M/T FDC group) with eGFR <30 mL/min/1.73m2: 1 participant (treatment-naïve stratum) had an associated renal AE of blood creatinine increased. The other participant (prior PDE 5i stratum) had a low eGFR at baseline (35.3 mL/min/1.73m2), which decreased to 24.5 mL/min/1.73m2 on Day 33 and returned to baseline at Day 61 through the end of DB treatment. Neither participant discontinued study treatment during the DB period.

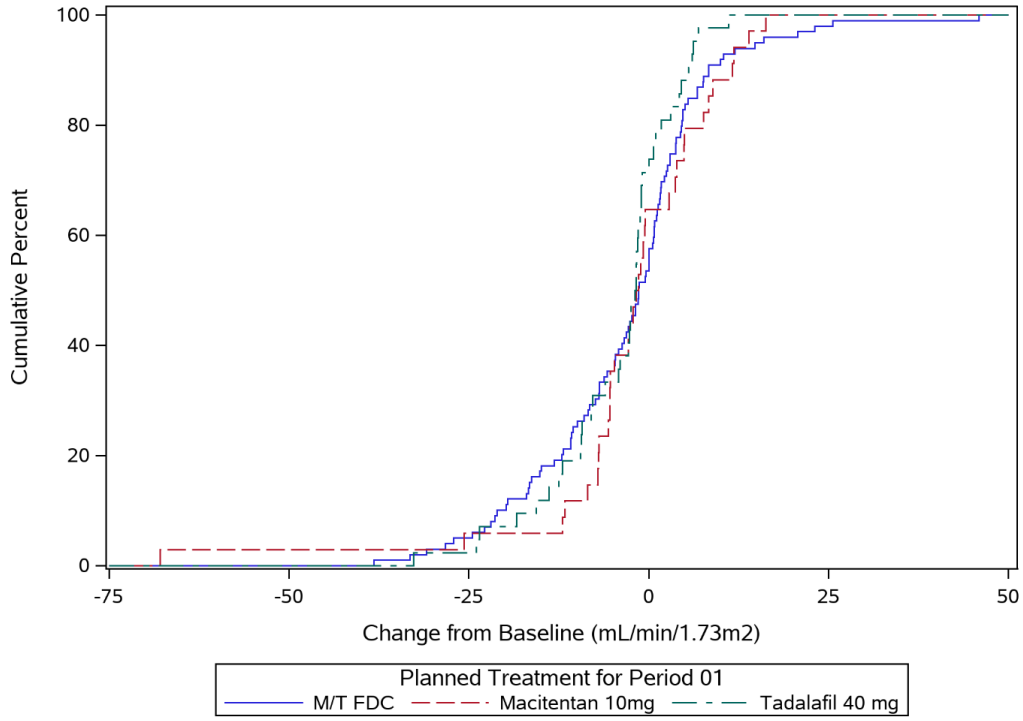
Table 56: Treatment-emergent Renal Laboratory Abnormalities by Treatment Group; Safety Set (A DUE 16 week DB Period)

	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%)
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: 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

A cumulative distribution function curve of worst change from baseline in eGFR during the DB period is shown in the figure below. The overlap between the treatment groups indicates a lack of major differences between treatments on eGFR. Decrease from baseline ≥25 mL/min/1.73m^2 were observed in 5 participants in the M/T FDC group, 2 in the macitentan group, and 1 in the tadalafil group. None of these participants discontinued study treatment.

Figure 20: Cumulative Distribution Function of eGFR Worst Change from Baseline; Safety Set (A DUE 16 week DB Period)



Leukocytes and platelets

At baseline, patients in the M/T FDC group had higher baseline leukocytes (7.3 $x10^9$/L) as compared to the macitentan and tadalafil groups (6.6 $x10^9$/L and 6.5 $x10^9$/L, respectively). After 16 weeks, the patients in the M/T group experienced a larger decrease in leukocytes (1.37 $x10^9$/L) as compared to those in the macitentan and tadalafil groups (0.55 $x10^9$/L and 0.57 $x10^9$/L, respectively).

During the A DUE DB+OL period, treatment-emergent markedly abnormal leukocytes <3×10^9/L were reported for 15/174 (8.6%) participants treated with M/T FDC at any time.

At baseline, patients in the M/T FDC group had similar baseline platelets (237 $x10^9$/L) as compared to the macitentan and tadalafil groups (218 $x10^9$/L and 230 $x10^9$/L, respectively). After 16 weeks, the patients in the M/T group and macitentan group experienced a larger decrease in platelets (16.2 $x10^9$/L and 19.3 $x10^9$/L, respectively) as compared to those in the tadalafil groups (5.6 $x10^9$/L).

During the A DUE DB+OL period, treatment emergent markedly abnormal platelets <75×10^9/L were reported in 4/174 (2.3%) participants treated with M/T FDC at any time.

Table 57: Number and Percentage of Subjects With Treatment-emergent Markedly Abnormal Laboratory Values in the Combined Double-blind and Open-label Period

	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
Leukocytes (10^9/L)				
N	33	41	100	174
WBC < 2.0	1 (3.0%)	1 (2.4%)	3 (3.0%)	5 (2.9%)
WBC < 3.0	3 (9.1%)	1 (2.4%)	11 (11.0%)	15 (8.6%)
Platelets (10^9/L)				
N	33	41	100	174
PLAT < 50	0	0	1 (1.0%)	1 (0.6%)
PLAT < 75	1 (3.0%)	1 (2.4%)	2 (2.0%)	4 (2.3%)

Note: A postbaseline marked abnormality is considered treatment-emergent if it is worse than the baseline abnormality or if baseline is missing.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Safety in special groups were evaluated for patients with PAH who were treated with M/T FDC or a loose combination of macitentan and tadalafil.

There were no new safety findings associated with intrinsic or extrinsic factors in A DUE or the supportive clinical trials that would alter the interpretation of the safety profiles as presented in the prescribing information of the individual components of the M/T FDC.

Intrinsic factors

Age

In the A DUE 16-week DB period, there were fewer elderly participants (age ≥65 years) compared to adults (age 18-64 years) across the macitentan, tadalafil, and M/T FDC groups. More participants treated with M/T FDC in the ≥65 years age group reported an AE compared to the 18-64 years age group. Cardiac and musculoskeletal AEs were reported more frequently in elderly participants (≥65 years: 25.0% for both SOCs) versus younger participants (18-64 years: 12.6% and 19.5%, respectively), which is consistent with aging. As shown below, AESIs of anaemia and oedema were also reported more frequently in elderly participants. No new safety concerns were observed for the ≥65 years age group.

- For the 18-64 years age group treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of Gastrointestinal disorders, Nervous system disorders, and General disorders and administration site conditions. Headache (17.2%) was the only AE reported with frequency >10%.
- For the ≥65 years age group treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of General disorders and administration site conditions, Infections and infestations, and Blood and lymphatic system disorders (driven by anaemia). AEs reported with a frequency >10% were oedema peripheral (30.0%), anaemia (25.0%), and headache (15.0%). For comparison, the corresponding incidences in the 18-64 years age group were 9.2%, 3.4%, and 17.2%, respectively.

- Anaemia AESIs in participants treated with M/T FDC: Anaemia AESIs were more frequently reported in the ≥65 years age group (6/20 [30.0%]) compared to the 18-64 years age group (14/87 [16.1%]). There was 1 severe event, which occurred in the 18-64 years age group; all other events were mild or moderate in intensity. There was 1 SAE, which occurred in the ≥65 years age group and led to discontinuation. In addition, 1 participant in the 18-64 years age group discontinued DB treatment due to an anaemia AESI.

  Blood transfusion was given to a total of 7 participants on M/T FDC: 5 participants (2 in ≥65 years and 3 in 18-64 years subgroup) experienced AESIs of anaemia as described above and 2 (in 18-64 years subgroup) received transfusion with concurrent AEs of uterine polyp and gastrointestinal bleeding but no concurrent AEs of anaemia. No age-related imbalance was identified.

- Oedema AESIs in participants treated with M/T FDC: Oedema AESIs were more frequently reported in the ≥65 years age group (7/20 [35.0%]) compared to the 18-64 years age group (15/87 [17.2%]). There was 1 SAE, which occurred in the ≥65 years age group, was severe, and led to discontinuation of DB treatment. All other events were mild or moderate in intensity. 1 participant in the 18-64 years age group discontinued DB treatment due to an oedema AESI.

Table 58: AEs according to age brackets

	M/T FDC			
	Age <65	Age 65-74	Age 75-84	Age 85+
Analysis set: Combination Safety Set	147	26	12	0
Total AEs	136 (92.5%)	25 (96.2%)	12 (100.0%)	0
Serious AEs – Total	29 (19.7%)	11 (42.3%)	9 (75.0%)	0
- Fatal	2 (1.4%)	1 (3.8%)	1 (8.3%)	0
- Hospitalization/prolong existing hospitalization	27 (18.4%)	9 (34.6%)	9 (75.0%)	0
- Life-threatening	1 (0.7%)	1 (3.8%)	4 (33.3%)	0
- Disability/incapacity	0	1 (3.8%)	0	0
- Other (medically significant)	4 (2.7%)	1 (3.8%)	0	0
AE leading to drop-out	13 (8.8%)	1 (3.8%)	3 (25.0%)	0
Psychiatric disorders	3 (2.0%)	1 (3.8%)	1 (8.3%)	0
Nervous system disorders	35 (23.8%)	5 (19.2%)	2 (16.7%)	0
Accidents and injuries	12 (8.2%)	3 (11.5%)	2 (16.7%)	0
Cardiac disorders	25 (17.0%)	4 (15.4%)	4 (33.3%)	0
Vascular disorders	12 (8.2%)	5 (19.2%)	3 (25.0%)	0
Cerebrovascular disorders	1 (0.7%)	0	1 (8.3%)	0
Infections and infestations	78 (53.1%)	11 (42.3%)	6 (50.0%)	0
Anticholinergic syndrome	22 (15.0%)	4 (15.4%)	1 (8.3%)	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black-outs, syncope, dizziness, ataxia, fractures	13 (8.8%)	3 (11.5%)	1 (8.3%)	0
Postural hypotension	0	0	0	0
Falls	0	2 (7.7%)	0	0
Syncopes	3 (2.0%)	1 (3.8%)	0	0
Black-outs	0	0	0	0
Dizziness	7 (4.8%)	1 (3.8%)	1 (8.3%)	0
Ataxia	0	0	0	0
Fractures	3 (2.0%)	1 (3.8%)	0	0
Other AEs appearing more frequently in older patients[b]				
Anaemia	12 (8.2%)	5 (19.2%)	3 (25.0%)	0
Arthralgia	7 (4.8%)	3 (11.5%)	1 (8.3%)	0
Back pain	6 (4.1%)	2 (7.7%)	2 (16.7%)	0
Dyspnoea	9 (6.1%)	4 (15.4%)	0	0

	M/T FDC			
	Age <65	Age 65-74	Age 75-84	Age 85+
Gastritis	4 (2.7%)	3 (11.5%)	0	0
Nausea	6 (4.1%)	3 (11.5%)	0	0
Oedema peripheral	14 (9.5%)	5 (19.2%)	2 (16.7%)	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 (ie, 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.
Adverse events are coded using MedDRA Version 25.1.
b. PTs with frequency >10% in any age subgroup are presented.

No new safety concerns by age group were identified in the A DUE DB+OL period or from the supportive clinical trials.

Sex

In the A DUE 16-week DB period, there were fewer male participants with PAH compared to female participants across the macitentan, tadalafil, and M/T FDC groups. Incidence of AEs was comparable between female and male participants treated with M/T FDC. As described below, AESIs of anaemia were comparable between subgroups, but oedema AESIs were reported more frequently in female participants. No new safety concerns were observed for either subgroup.

- For female participants treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of General disorders and administration site conditions and Gastrointestinal disorders. AEs reported with a frequency >10% were headache (17.1%) and oedema peripheral (14.6%). For comparison, the corresponding incidences in male participants were 16.0% and 8.0%, respectively.

- For male participants treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of Infections and infestations (driven by COVID-19-related events), Nervous system disorders, and Respiratory, thoracic and mediastinal disorders. AEs reported with a frequency >10% were headache (16.0%), COVID-19 (12.0%), dizziness (12.0%), and pyrexia (12.0%). For comparison, the corresponding incidences in female participants were 17.1%, 0%, 0%, and 1.2%, respectively.

- Anaemia AESIs in participants treated with M/T FDC: Anaemia AESIs were reported in 16/82 (19.5%) female participants and 4/25 (16.0%) male participants. There was 1 severe event, which occurred in the male subgroup; all other events were mild or moderate in intensity. 2 participants, both female, discontinued DB treatment (due to 1 SAE of anaemia and 1 AESI of haemoglobin decreased. No male participant on DB-M/T FDC had an SAE or discontinued treatment due to an anaemia AESI.

- Oedema AESIs in participants treated with M/T FDC: Oedema AESIs were reported more frequently in female participants (18/82 [22.0%]) compared to male participants (4/25 [16.0%]). There was 1 SAE, which occurred in a female participant, was severe, and led to discontinuation of DB treatment. All other events were mild or moderate in intensity. 1 additional female participant discontinued DB treatment due to an oedema AESI. No male participant had an SAE or discontinued treatment due to an oedema AESI.

Considering the ratio of female and male participants treated with M/T FDC at any time during the A DUE DB+OL period, no major differences in incidence of AEs was observed by sex. Incidence of AEs in supportive clinical trials was generally comparable between female and male subgroups, with the exception of REPAIR due to the low number (<10 participants) in the male subgroup. Despite occasional imbalances by PTs in each trial, no clinically meaningful trend was identified across clinical trials. No new safety concerns were observed between male and female participants.

Race

In the A DUE 16-week DB period, fewer AEs were reported for Asian participants treated with M/T FDC compared with white participants, although the incidence in both race subgroups were comparable to the overall study population. AESIs of anaemia were reported more frequently in Asian participants, but oedema AESIs were reported more frequently in white participants. No new safety concerns were observed for either subgroup.

- For white participants treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of Gastrointestinal disorders, General disorders and administration site conditions and Nervous system disorders. AEs reported with a frequency >10% were headache (21.2%), oedema peripheral (15.2%), and hypotension (12.1%).

- For Asian participants treated with M/T FDC, AEs were reported with a frequency >25% in the SOCs of General disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders. AEs reported with a frequency >10% were anaemia (11.1%), oedema peripheral (11.1%), and myalgia (11.1%).

- Anaemia AESIs in participants treated with M/T FDC: Anaemia AESIs were reported more frequently in Asian participants (9/36 [25.0%]) compared to white participants (10/66 [15.2%]). 1 Asian participant had an SAE, which was severe and led to discontinuation of DB treatment. All other events were mild or moderate in severity. No white participant had an SAE or discontinued DB treatment due to an anaemia AESI.

- Oedema AESIs in participants treated with M/T FDC: Oedema AESIs were reported more frequently in white participants (16/66 [24.2%]) white participants compared to Asian participants (6/36 [16.7%]). There was 1 SAE, which occurred in a white participant, was severe, and led to discontinuation of DB treatment. All other events were mild or moderate in intensity. 1 additional white participant discontinued due to an oedema AESI. No Asian participant had an SAE or discontinued DB treatment due to an oedema AESI.

No new safety concerns by race were identified in the A DUE DB+OL period.

Renal impairment

In order to support labelling proposals, a post-hoc analysis of data from participants treated with M/T FDC at any time during the A DUE DB+OL period were analyzed by renal impairment, defined by severity at baseline: no impairment (eGFR ⩾90 mL/min/1.73 m2), mild impairment (eGFR 60 to <90 mL/min/1.73 m2), moderate (eGFR 30 to <60 mL/min/1.73 m2), and severe (eGFR <30 mL/min/1.73 m2). At baseline, there were 42% participants with no renal impairment, 44% with mild impairment, and 14% with moderate impairment; per protocol, participants with severe renal impairment at baseline were excluded.

The overall incidence of AEs was generally comparable across subgroups, with a difference ⩾5% observed only between participants with moderate impairment and no impairment. No pattern was identified between subgroups from a review of AEs by SOC and PT. There were more SAEs in participants with mild or moderate renal impairment compared to those with no impairment, although there were no particular PT driving the imbalance of SAEs in the mild or moderate subgroups. The level of renal impairment at baseline had no observable impact on the incidence of AEs leading to treatment discontinuation. More AESIs of hypotension were reported in participants with renal impairment, incidence of hypotension AESIs was higher in participants with moderate renal impairment (15.4%) compared with those with mild or no impairment (8.6% and 1.3%, respectively). All events were mild or moderate in intensity. Incidences of other AESI categories were comparable between participants with different levels of renal impairment.

External factors

Administration with food

A food-effect study (67896062PAH1006 Group 2, n=15) involving administration of the M/T 10/40 mg FDC formulation to healthy participants under fasting conditions and with a high-fat meal indicated no food effect with macitentan, and that the Cmax of tadalafil increased by 45% while AUC remained unchanged. This increase in Cmax of tadalafil is not clinically significant, therefore the M/T 10/40 mg FDC formulation could be taken without regard to meals.

A second food-effect study (67896062PAH1002, n=40) conducted in healthy participants who received M/T 10/20 mg FDC under fasting conditions and with a high-fat, high-calorie meal showed an absence of food effect on the respective Cmax and AUC of macitentan and tadalafil. The M/T 10/20 mg FDC formulation could also be taken without regard to meals.

With or Without Prior PAH-specific Therapy

The A DUE population was stratified by prior treatment and included 98 treatment-naïve participants, 32 previously treated with ERA, and 56 previously treated with PDE-5i. A tabulated overview comparing safety data in patients with or without prior treatment is shown below.

Table 59: Overview of AEs by Stratum

	Treatment-naïve			Prior ERA strata		Prior PDE-5i strata		Pre-treated
	Macitentan	Tadalafil	M/T FDC	Macitentan	M/T FDC	Tadalafil	M/T FDC	M/T FDC
Analysis set: Safety	24	25	49	11	21	19	37	58
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%)	45 (77.6%)
Subjects with 1 or more SAEs	2 (8.3%)	3 (12.0%)	8 (16.3%)	1 (9.1%)	3 (14.3%)	1 (5.3%)	4 (10.8%)	7 (12.1%)
Subjects with 1 or more AEs leading to discontinuation of double-blind study treatment	0	2 (8.0%)	6 (12.2%)	0	1 (4.8%)	0	2 (5.4%)	3 (5.2%)
Subjects with 1 or more hypotension AESIs	0	0	3 (6.1%)	0	3 (14.3%)	0	2 (5.4%)	5 (8.6%)
Subjects with 1 or more anemia AESIs	1 (4.2%)	1 (4.0%)	11 (22.4%)	0	1 (4.8%)	0	8 (21.6%)	9 (15.5%)
Subjects with 1 or more edema/fluid retention AESIs	5 (20.8%)	4 (16.0%)	15 (30.6%)	0	2 (9.5%)	3 (15.8%)	5 (13.5%)	7 (12.1%)
Subjects with 1 or more hepatic disorder AESIs	1 (4.2%)	3 (12.0%)	0	0	0	1 (5.3%)	1 (2.7%)	1 (1.7%)
Incidence by SOC								
Musculoskeletal and connective tissue disorders	2 (8.3%)	9 (36.0%)	12 (24.5%)	1 (9.1%)	7 (33.3%)	6 (31.6%)	3 (8.1%)	10 (17.2%)
Gastrointestinal disorders	2 (8.3%)	8 (32.0%)	12 (24.5%)	2 (18.2%)	5 (23.8%)	5 (26.3%)	11 (29.7%)	16 (27.6%)
General disorders and administration site conditions	7 (29.2%)	6 (24.0%)	16 (32.7%)	2 (18.2%)	4 (19.0%)	3 (15.8%)	10 (27.0%)	14 (24.1%)
Infections and infestations	5 (20.8%)	3 (12.0%)	12 (24.5%)	2 (18.2%)	4 (19.0%)	4 (21.1%)	6 (16.2%)	10 (17.2%)
Nervous system disorders	3 (12.5%)	5 (20.0%)	14 (28.6%)	3 (27.3%)	4 (19.0%)	4 (21.1%)	9 (24.3%)	13 (22.4%)
Respiratory, thoracic and mediastinal disorders	3 (12.5%)	4 (16.0%)	11 (22.4%)	2 (18.2%)	3 (14.3%)	4 (21.1%)	7 (18.9%)	10 (17.2%)
Vascular disorders	2 (8.3%)	0	7 (14.3%)	0	3 (14.3%)	0	3 (8.1%)	6 (10.3%)
Cardiac disorders	1 (4.2%)	1 (4.0%)	10 (20.4%)	1 (9.1%)	2 (9.5%)	3 (15.8%)	4 (10.8%)	6 (10.3%)
Eye disorders	1 (4.2%)	1 (4.0%)	4 (8.2%)	0	2 (9.5%)	1 (5.3%)	2 (5.4%)	4 (6.9%)
Skin and subcutaneous tissue disorders	2 (8.3%)	1 (4.0%)	4 (8.2%)	0	2 (9.5%)	2 (10.5%)	3 (8.1%)	5 (8.6%)
Blood and lymphatic system disorders	2 (8.3%)	1 (4.0%)	9 (18.4%)	0	1 (4.8%)	0	3 (8.1%)	4 (6.9%)
Injury, poisoning and procedural complications	1 (4.2%)	0	2 (4.1%)	2 (18.2%)	1 (4.8%)	1 (5.3%)	1 (2.7%)	2 (3.4%)
Investigations	3 (12.5%)	3 (12.0%)	8 (16.3%)	1 (9.1%)	1 (4.8%)	2 (10.5%)	7 (18.9%)	8 (13.8%)
Congenital, familial and genetic disorders	0	1 (4.0%)	0	0	0	0	0	0
Ear and labyrinth disorders	2 (8.3%)	1 (4.0%)	0	0	0	0	0	0
Hepatobiliary disorders	0	1 (4.0%)	0	0	0	0	0	0
Immune system disorders	1 (4.2%)	0	1 (2.0%)	0	0	0	0	0
Metabolism and nutrition disorders	2 (8.3%)	3 (12.0%)	8 (16.3%)	3 (27.3%)	0	3 (15.8%)	3 (8.1%)	3 (5.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.2%)	0	0	0	0	0	1 (2.7%)	1 (1.7%)

The number of patients with any AE in the treatment naïve group were 71%, 80% and 88% in the macitentan, tadalafil and M/T FDC arms, respectively. In pre-treated patients AEs were experienced in 78% of patients in the M/T FDC arm. The number of patients with any SAE in the treatment naïve group were 8.3%, 12.0% and 16.3% in the macitentan, tadalafil and M/T FDC arms, respectively. In pre-treated patients AEs were experienced in 12.1% of patients in the M/T FDC arm. The number of patients with AESI of anemia in the treatment naïve group were 4%, 4% and 22% in the macitentan, tadalafil and M/T FDC arms, respectively. In pre-treated patients AEs were experienced in 16% of patients in the M/T FDC arm. The number of patients with AESI of edema in the treatment naïve group were 21%, 16% and 31% in the macitentan, tadalafil and M/T FDC arms, respectively. In pre-treated patients AEs were experienced in 16% of patients in the M/T FDC arm.

Within the M/T FDC group, treatment-naïve participants were older, with 16/49 (32.7%) in the ≥65 age group compared with the prior ERA or PDE-5i strata (1/21 [4.8%] and 3/37 [8.1%], respectively). Compared with the prior treatment strata, more treatment-naïve participants experienced AEs while on treatment with M/T FDC during the DB period, with a higher incidence of SAEs and AEs leading to discontinuation. No pattern in PT was observed for SAEs or AEs leading to discontinuation, although most discontinuations of DB-M/T FDC in the treatment-naïve stratum occurred during the first 4 weeks of the DB period. No treatment-emergent death occurred in treatment-naïve participants on M/T FDC during the DB or the OL period.

During the 16-week DB period, AEs reported with a frequency >10% in treatment-naïve participants treated with M/T FDC included headache (8/49 [16.3%]), oedema peripheral (7/49 [14.3%]), peripheral swelling (7/49 [14.3%]), anaemia (5/49 [10.2%]), and cough (5/49 [10.2%]). AEs reported with a frequency >5% included diarrhoea (4/49 [8.2%]), dyspepsia (4/49 [8.2%]), as well as back pain, cardiac failure, flushing, haemoglobin decreased, hyperuricemia, hypotension, myalgia, nausea, and vomiting (3/49 [6.1%] each).

Within the M/T FDC group, the most frequently reported AEs (frequency >2 participants) reported in the DB period in the prior ERA stratum were headache (4/21 [19.0%]) and hypotension (3/21 [14.3%]); the most frequently reported AEs in the prior PDE-5i stratum were headache (6/37 [16.2%]), haemoglobin decreased (5/37 [13.5%]), oedema peripheral (5/37 [13.5%]), and palpitations (3/37 [8.1%]).

Incidence of AESIs in treatment-naïve vs prior-treatment strata treated with M/T FDC during the DB period are summarized below.

- Hepatic AESIs: Within the M/T FDC group during the DB period, only 1 participant had a hepatic AESI, which occurred in the prior PDE-5i stratum and led to treatment discontinuation.

- Anaemia AESIs: Within the M/T FDC group during the DB period, incidence of anaemia AESIs was comparable between the treatment-naïve and prior PDE-5i strata (11/49 [22.4%] and 8/37 [21.6%], respectively), and lower in the prior ERA stratum (1/21 [4.8%]). 2 treatment-naïve participants received blood transfusion, 1 as treatment for an SAE (anaemia), which led to treatment discontinuation, and another as prophylactic procedure prior to Week 16 RHC. One participant in the prior PDE-5i stratum who had severe AE of anaemia received blood transfusion at the time of an AE of hemorrhoidal hemorrhage.

- Hypotension AESIs: Within the M/T FDC group during the DB period, a greater proportion of participants in the prior ERA stratum had hypotension AESIs (3/21 [14.3%] prior ERA) compared with the 2 other strata (3/49 [6.1%] treatment-naïve and 2/37 [5.4%] prior PDE 5i; 1 treatment-naïve participant had an SAE (orthostatic hypotension) and 1 participant from the prior ERA stratum discontinued treatment due to a hypotension AESI.

- Oedema AESIs: Within the M/T FDC group during the DB period, oedema AESIs were reported more frequently in the treatment-naïve stratum (15/49 [30.6%]) compared with the prior treatment strata (2/21 [9.5%] prior ERA, and 5/37 [13.5%] prior PDE-5i. One treatment-naïve participant discontinued treatment due to an SAE (peripheral swelling); 1 participant in the prior PDE-5i stratum discontinued treatment due to an oedema AESI.

In supportive clinical trials, higher incidences of AEs were observed in the treatment-naïve TRITON study population, compared with a mixed population in SYMPHONY, ORCHESTRA, and REPAIR, in which >40% were previously treated with a PDE-5i. However, median duration of exposure was also longest in TRITON and was a confounding factor.

Geographical region

No new safety concerns by geographical region were identified in the A DUE DB+OL period.

2.6.8.7. Immunological events

Hypersensitivity was experienced by one patient in the M/T FDC group of the A DUE trial. Hypersensitivity is sufficiently reflected in the SmPC, based on previous data from the individual components.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Based on the known characteristics of macitentan and tadalafil, no PK interaction is expected between these individual components in M/T FDC. Based on the information of the individual components, in the presence of strong CYP3A4 inhibitors, exposure of M/T FDC could be increased. Co-administration of M/T FDC with strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, ritonavir, voriconazole, clarithromycin, telithromycin, nefazodone, and saquinavir) should be avoided. Based on the information of the individual components, in the presence of strong CYP3A4 inducers, exposure and efficacy of M/T FDC could be reduced. Co-administration of M/T FDC with strong CYP3A4 inducers (e.g. rifampicin) should be avoided. As M/T FDC contains macitentan and tadalafil, the interactions associated with each component should be considered.

2.6.8.9. Discontinuation due to adverse events

- During the A DUE 16-week DB period, AEs leading to discontinuation of study intervention were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups. There was no trend based on individual PTs or SOCs. Most AEs leading to discontinuation were known events associated with macitentan or tadalafil, and thus identified as AESIs in this study.
- More than half of the 9 participants in the M/T FDC group who discontinued study intervention during the DB period were treatment-naïve (6/49 [12.2%] treatment-naïve, 1/21 [4.8%] prior ERA, and 2/37 [5.4%] prior PDE-5i).
- 5 participants in the M/T FDC group (3 treatment-naïve, 1 prior ERA, 1 prior PDE-5i) discontinued during the first 2 weeks due to hypotension, angiooedema, myalgia, hypersensitivity, or peripheral oedema.
- 2 participants in the M/T FDC group (treatment-naïve) discontinued per protocol requirement due to haemoglobin abnormalities: 1 due to interruption of more than 14 days caused by severe anaemia and 1 due to a haemoglobin decrease of >50g/L.
- 2 participants discontinued per protocol requirement due to elevation of liver enzymes: 1 participant in the M/T FDC group (prior PDE-5i) and 1 participant in the tadalafil group (treatment-naïve).
- AEs leading to discontinuation of study intervention (PVOD, anaemia, dyspnoea, peripheral swelling, swelling face) were reported as serious in 3 participants in the M/T FDC group (treatment-naïve). The participant with PVOD was incidentally diagnosed during the DB treatment period and subsequently discontinued by the investigator. Of note, PVOD was an exclusion criterion for the trial.

Table 60: Treatment-emergent Adverse Events Leading to Premature Discontinuation of Study Treatment in the Double-blind Period by System Organ Class and Preferred Term; Safety Set (A DUE 16-week DB Period)

System organ class Preferred term	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
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%)
General disorders and administration site conditions	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Oedema peripheral	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Peripheral swelling	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Swelling face	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Investigations	0	1 (1.4%)	1 (2.3%)	2 (2.3%)	2 (1.9%)
Haemoglobin decreased	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Transaminases increased	0	0	1 (2.3%)	1 (1.2%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	0	2 (2.9%)	0	2 (2.3%)	2 (1.9%)
Dyspnoea	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Pulmonary veno-occlusive disease	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Blood and lymphatic system disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Anaemia	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Immune system disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Hypersensitivity	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Musculoskeletal and connective tissue disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Myalgia	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Skin and subcutaneous tissue disorders	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Angioedema	0	1 (1.4%)	0	1 (1.2%)	1 (0.9%)
Vascular disorders	0	1 (1.4%)	0	0	1 (0.9%)
Hypotension	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.

In the A DUE DB+OL period, the overall incidence of AEs that led to discontinuation was 9.2% in participants treated with M/T FDC at any time up to the data cut-off date. 12/107 (11.2%) participants randomized to DB-M/T FDC discontinued study treatment due to an AE, of which 3 discontinued during the OL period (due to COVID-19, DILI, and 1 participant with ALT increased, AST increased, and nausea). In addition, after initiating OL M/T FDC, 4 participants from the DB-macitentan group discontinued (due to hemoglobin decreased, conjunctivitis, hepatitis B, and PAH), and 1 participant from the DB-tadalafil group discontinued (due to gastric disorder and palpitations).

Comparison Across Supportive Clinical Trials

In TRITON, 19/127 (15.0%) of participants discontinued macitentan and 12/127 (9.4%) discontinued tadalafil due to an AE. Anaemia, liver function test increased, and PVOD were each reported for 2 (1.6%) participants who discontinued macitentan. No other AE leading to discontinuation was reported for more than 1 participant for macitentan or tadalafil. The reasons for discontinuation are consistent with the known safety profiles of macitentan and tadalafil, and the higher incidence of discontinuation is consistent with a longer duration of treatment compared to the A DUE 16-week DB period.

As tadalafil was a concomitant medication rather than a study intervention in SYMPHONY, ORCHESTRA, and REPAIR, summaries of AEs leading to discontinuation are not available for the combination of macitentan and tadalafil.

Observational studies

In EXPOSURE, 84/422 (19.9%) participants had AEs that led to the interruption or discontinuation of macitentan and/or tadalafil treatment, including dyspnoea (3.6%), death (1.2%), fluid retention (1.2%), and nausea (1.2%); other events led to treatment interruption or discontinuation in <1% participants. Findings were consistent with a broader PAH population.

As tadalafil was a concomitant medication in OPUS, the reason for discontinuation for tadalafil was not provided; summaries of AE leading to discontinuation are therefore not available for the combination of macitentan and tadalafil.

2.6.8.10. Post marketing experience

OPSYNVI (M/T 10/40 mg FDC) is approved in Canada and Argentina in patients with PAH who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg as separate tablets.

An estimated 54 patients have been exposed to commercially available M/T FDC from launch through 10 September 2023.

Review of the safety data from the marketed use of M/T FDC did not reveal any new significant safety concerns. The safety profile of M/T FDC remains similar to the profile established during clinical trials with individual components (macitentan and tadalafil).

2.6.9. Discussion on clinical safety

Exposure

The pivotal safety analysis included data from 186 patients evaluated in the Phase 3 A DUE DB period in which M/T FDC was compared with macitentan monotherapy and tadalafil monotherapy, supplemented by long-term safety data from the ongoing A DUE DB+OL period up to a data cut-off 31 Dec 2022. Additional safety data are provided from 4 completed Phase 3b/4 clinical trials and 3 observational studies in which macitentan and tadalafil were co-administered as a loose combination of separate tablets. As of the data cut-off date for this dossier, 186 participants received DB study treatment during the A DUE 16-week DB period, of whom 185 participants were exposed to M/T FDC at any time in the DB+OL period for a median duration of 59.86 weeks (range: 0.6–151.6). Of a total of 2024 participants with PAH who have been treated with a loose combination of macitentan and tadalafil in supportive studies, 142/266 from clinical trials and 929/1758 from observational studies have been exposed to the combination for ≥12 months.

Adverse events

In the A DUE 16-week DB period, the proportion of participants who experienced at least 1 AE in the M/T FDC group (82.2%) was higher than in the macitentan group (71.4%) and approximately similar to the tadalafil group (79.5%). In the A DUE 16-week DB period, the most frequently reported AEs occurring in ≥10% of participants in the M/T FDC group were headache and peripheral oedema; both also occurred with a frequency ≥10% in the macitentan and tadalafil monotherapy groups. Other frequently reported AEs (≥5% of participants) in the M/T FDC group included anaemia, decreased haemoglobin, hypotension, peripheral swelling, cough, myalgia, and nausea. AEs occurring more frequently (difference >5%) in the M/T FDC group compared with both macitentan and tadalafil monotherapy included anaemia, decreased haemoglobin, and hypotension. Other AEs occurring more frequently in the M/T FDC group compared to macitentan monotherapy were myalgia and nausea. Overall, there was a higher incidence of AEs in the M/T FDC as compared to the monotherapies, but these AEs were in line with the AEs listed in the labelling of macitentan and tadalafil. AEs of severe intensity were more frequent in the M/T FDC group (14.0%) than in the macitentan (5.7%) and tadalafil (6.8%) groups. Headache and cardiac failure AEs of severe intensity were reported for 2 participants each in the M/T FDC group, all others were reported in 1 participant each. There was no apparent pattern of AE intensity (mild, moderate, and severe) when looking at AEs by PT. Overall, the pattern of frequently reported AEs in the supportive clinical trials and observational studies with a loose combination of macitentan and tadalafil were consistent with findings from the A DUE 16 week DB period and the known safety profiles of the individual components macitentan and tadalafil.

During the initial 7-day titration period in the A DUE 16-week DB period, participants in the prior ERA and treatment-naïve strata who were randomized to M/T FDC were titrated with macitentan 10 mg and tadalafil 20 mg, and participants in the treatment-naïve stratum who were randomized to tadalafil were titrated with tadalafil 20 mg. In the M/T FDC group, the frequency of AEs was higher in participants in the treatment-naïve and prior ERA strata who received the titration dose than in those on prior PDE-5i therapy who started directly on the maintenance dose. With regard to the titration phase, despite the higher frequency of AEs, no new safety concerns were identified during treatment with macitentan 10 mg + tadalafil 20 mg. As in the overall 16-week DB period, headache was the most frequently reported AE during the titration phase, with a frequency >10% in the M/T FDC group.

A DUE data were reviewed for potential new adverse drug reactions. A threshold of 2% was selected for identifying AEs with imbalance for further review. TEAEs reported with a difference of more than 2% with M/T FDC group compared to either the macitentan or tadalafil groups were cardiac failure, diarrhea, dyspnoea, pyrexia, dry mouth, non-cardiac chest pain, cough, dizziness, and angina pectoris. The review details were provided for each of these TEAEs under ADR assessment. For all of these events (cardiac failure, diarrhea, dyspnea, pyrexia, dry mouth, non-cardiac chest pain, cough, dizziness, and angina pectoris), the Applicant has discussed the potential of a causal relationship to be unlikely. This was based on patterns of latency, transient nature of event, presence of confounding factors, and resolution of AE while on treatment. The provided discussions are reasonable and acceptable.

Overall, the summary of clinical safety provides comparisons of M/T FDC vs monotherapies in the DB of A DUE for the strata "treatment-naïve and prior ERA" and "treatment-naïve and prior PDE-5i". The Applicant was requested to also provide a comparison of M/T FDC vs monotherapies for "treatment-naïve" and "prior treatment" separately. These analyses demonstrated that within M/T FDC treated patients, AEs, SAE, AESI of anemia and edema each occurred more often in treatment naïve patients as compared to pretreated patients. This further pleads for a sequential treatment, rather than initial treatment with M/T FDC.

Serious adverse events

As expected, treatment-naïve participants may be more prone than pre-treated participants to experiencing AEs known to be associated with the use of macitentan and tadalafil. SAEs were reported more frequently in the M/T FDC group than in the macitentan and tadalafil groups, both those related and unrelated to

treatment. SAEs were reported most frequently in patients that were on M/T FDC while treatment-naïve, pleading for a sequential treatment rather than initial combination therapy. Treatment-related SAEs in the M/T FDC group included cardiac failure, dyspnoea, anaemia, peripheral swelling, right ventricular failure, and swelling face, each reported once. Serious adverse events were reported more often in the supportive trials, which might be related to the longer treatment duration.

During the A DUE 16-week DB period, there were 3 deaths (2 treatment-emergent) in the M/T FDC group and none in the macitentan and tadalafil groups. None were assessed by the investigators as related to study treatment. Compared to A DUE 16-week DB period, there were more deaths in TRITON (9.4%) and ORCHESTRA (16.7%), as consistent with a longer duration of treatment in these clinical trials. In TRITON and ORCHESTRA, right ventricular failure, was the only event that led to death in >1 participant in both clinical trials. In addition, in ORCHESTRA, there were 2 participants who died from seizure. The Applicant states that no apparent trends were observed in other AEs leading to death from clinical trials. Although no definite conclusion can be drawn with the short-term data, no safety issue with regard to mortality is raised. Furthermore, findings from observational studies (13% and 10% mortality rate in OPUS/OrPHeUS and EXPOSURE) are consistent with published data on the 1-year mortality rate for patients with PAH (McLaughlin 2009).

Other significant adverse events that were investigated were cardiac disorders and menstrual bleeding. Cardiac disorders were reported in 16 (15.0%) of participants in the M/T FDC group compared to 2 (5.7%) in the macitentan group and 4 (9.1%) in the tadalafil group. The difference was mainly driven by AEs denoting cardiac failure reported in 4 (3.7%) participants, left ventricular failure in 1 (0.9%) participant, and right ventricular failure in 1 (0.9%) participant in the M/T FDC group. Events occurred within 1 month of treatment initiation and were generally clinically manageable while participants continued on study intervention. Most participants with such AEs were 65 years or older, were treatment-naïve, and had pre-existing comorbidities associated with a higher risk of cardiac failure. Of the 4 treatment-naïve, elderly participants in the M/T FDC group who experienced events denoting cardiac failure, two cases out of four resolved while on treatment, whereas the other two were discontinued due to other adverse events [a newly established diagnosis of Pulmonary Veno-Occlusive Disease (exclusionary as per study protocol) and anaemia].

For macitentan, menstrual disorders (primarily bleeding) are currently listed as a potential risk in the European risk management plan (OPSUMIT RMP). For tadalafil, menstrual disorders are currently listed as a common ADR. In the A DUE 16-week DB period, a higher proportion of female participants from the M/T FDC group reported 1 or more AEs from the Reproductive system and breast disorders SOC (M/T FDC 6.1%, macitentan 3.4%, and tadalafil 2.9%). This imbalance was driven mainly by menstrual/vaginal hemorrhage AEs that occurred only in the M/T FDC group and all were in the prior PDE-5i stratum. There were 4 AEs related to menstrual bleeding: heavy menstrual bleeding (n=2), intermenstrual bleeding (n=1), and vaginal hemorrhage (n=1). The events were manageable and did not lead to discontinuations of study intervention.

Discontinuations

During the A DUE trial, AEs leading to discontinuation of study intervention were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (8.4% vs 0% vs 4.5%). There was no trend based on individual PTs or SOCs. Most AEs leading to discontinuation were known events associated with macitentan or tadalafil, and thus identified as AESIs in this study. More than half of the 9 participants in the M/T FDC group who discontinued study intervention during the DB period were treatment-naïve. 5 participants in the M/T FDC group (3 treatment-naïve, 1 prior ERA, 1 prior PDE-5i) discontinued during the first 2 weeks due to hypotension, angiooedema, myalgia, hypersensitivity, or peripheral oedema. In the A DUE DB+OL period, the overall incidence of AEs that led to discontinuation was 9.2% in participants treated with M/T FDC at any time up to the data cut-off date. Somewhat higher incidence of discontinuation were previously found in TRITON (15%) and for AEs leading to interruptions and discontinuations in EXPOSURE (19.9%), consistent with a longer treatment duration and the broader PAH population. Overall, these data

indicate that there is an increased risk of discontinuation when treated with the FDC M/T as compared to the monotherapy arms. Furthermore, the discontinuation rate was highest in those that were treatment-naïve.

Adverse events of special interest

AEs of special interest for the A DUE study were predefined as hepatic events, anaemia, hypotension and oedema, which were selected based on the well-characterized safety profiles of the M/T FDC components.

Liver aminotransferase increases are known events associated with macitentan. Hepatic AESIs were infrequently reported across all treatment groups during the DB period (0.9% vs 2.9% vs 9.1% for M/T FDC, macitentan and tadalafil, respectively). No imbalance in incidence of markedly abnormal AST and/or ALT was observed between treatment groups, and no participant met criteria for potential Hy's law. In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of hepatic AESIs was 4.08 events per 100 patient-years. The overall incidence of hepatic events was 4.9% in participants treated with M/T FDC at any time up to the data cut-off. Compared to the M/T FDC group from the A DUE 16-week DB period, more participants in TRITON (11.8%) and ORCHESTRA (13.9%) had hepatic AESIs.

Anaemia AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (18.7% vs 2.9% vs 2.3%), which is reflected in the labelling. Most participants with anaemia AESI were treatment-naïve: 11 of 20 participants with anaemia AESI in the M/T FDC group and both participants with anaemia AESI in the macitentan and tadalafil groups. In total, 3 participants with an AE of anaemia received red blood cell transfusions, but only 1 participant required transfusion for correction of low haemoglobin due to anaemia. Anaemia is a known event associated with macitentan and was reported in 12% of participants with PAH in the tadalafil monotherapy group of the AMBITION study (Galié 2015). The frequency in the M/T FDC group was higher than is routinely observed with macitentan monotherapy. All but 1 anaemia AESI were reported as mild to moderate, and they were clinically manageable. In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of anaemia AESIs was 23.27 events per 100 patient-years. The overall incidence of anaemia AESIs was 22.2% in participants treated with M/T FDC at any time up to the data cut-off.

Hypotension AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (7.5% vs 0% vs 0%), which is reflected in the product information. All hypotension AESI were of mild or moderate intensity. In 6 participants, the hypotension AESI resolved while study intervention was continued (n=4) or following interruption of study intervention (n=2), of which 1 was an SAE. In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of hypotension AESIs was 5.57 events per 100 patient-years. The overall incidence of hypotension AESIs was 6.5% in participants treated with M/T FDC at any time up to the data cut-off.

Oedema AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (20.6% vs 14.3% vs 15.9%), which is reflected in the product information. Most participants with oedema AESI were treatment-naïve: 15/22 participants with oedema AESI in the M/T FDC group, 5/5 participants with oedema AESI in the macitentan group, and 4/7 participants with oedema AESI in the tadalafil group. All but 1 oedema AESI were of mild or moderate intensity. Oedema and fluid retention are known events associated with macitentan; in the AMBITION study, peripheral oedema was reported in 28% of participants with PAH in the tadalafil monotherapy group (Galié 2015). Therefore, the frequency observed in the M/T FDC group, though somewhat higher than compared to the monotherapy groups, is in line with the expected frequency. In A DUE DB+OL period up to the data cut-off date, the exposure-adjusted incidence rate of oedema AESIs was 17.21 events per 100 patient-years. The overall incidence of oedema AESIs was 17.3% in participants treated with M/T FDC at any time up to the data cut-off.

Laboratory data

Laboratory investigations of interest were liver enzymes, haemoglobin and renal clearance. Laboratory investigations performed in the A DUE DB trial demonstrated that there was 1 participant in the M/T FDC group, 2 participants in the tadalafil group, and none in the macitentan group with markedly abnormal AST and/or ALT. Continuous analyses demonstrated that decreases in the concentration of liver enzymes (ie, ALT, AST, ALP, and bilirubin) were greater in magnitude in the M/T FDC group compared to the monotherapy groups during the 16-week DB period.

In the A DUE 16-week DB period, decreased haemoglobin was more frequently observed in the M/T FDC group than in the macitentan and tadalafil groups. In the M/T FDC group, clinically significant decreases in haemoglobin relative to baseline (≥50 g/L) were observed in 3/100 (3.0%) participants and absolute haemoglobin (<80 g/L) in 2/100 (2.0%) participants. Mean haemoglobin decrease was greater in magnitude in the M/T FDC group than in the macitentan and tadalafil groups during the DB period: mean change from baseline at Week 16: -13.9 g/L versus 6.8 g/L and 0.8 g/L, respectively. Regarding renal clearance, the incidence of eGFR <60 mL/min/1.73m2 was comparable between treatment groups, with continuous analyses showing no indication of an adverse effect on eGFR.

Intrinsic and extrinsic factors

There were no new safety findings associated with intrinsic or extrinsic factors in A DUE or the supportive clinical trials that would alter the interpretation of the safety profiles as presented in the prescribing information of the individual components of the M/T FDC.

Cardiac and musculoskeletal AEs were reported more frequently in elderly participants (≥65 years: 25.0% for both SOCs) versus younger participants (18-64 years: 12.6% and 19.5%, respectively), which is consistent with aging. Incidence of AEs was comparable between female and male participants treated with M/T FDC. Oedema AESIs were reported more frequently in female participants. AESIs of anaemia were reported more frequently in Asian participants, but oedema AESIs were reported more frequently in white participants. No new safety concerns were observed for either subgroup.

There were more SAEs in participants with mild or moderate renal impairment compared to those with no impairment, although there were no particular PT driving the imbalance of SAEs in the mild or moderate subgroups. More AESIs of hypotension were reported in participants with renal impairment, incidence of hypotension AESIs was higher in participants with moderate renal impairment (15.4%) compared with those with mild or no impairment (8.6% and 1.3%, respectively). All events were mild or moderate in intensity. Incidences of other AESI categories were comparable between participants with different levels of renal impairment.

Compared with the prior treatment strata, more treatment-naïve participants experienced AEs while on treatment with M/T FDC during the DB period, with a higher incidence of SAEs and AEs leading to discontinuation. No pattern in PT was observed for SAEs or AEs leading to discontinuation, although most discontinuations of DB-M/T FDC in the treatment-naïve stratum occurred during the first 4 weeks of the DB period. No treatment-emergent death occurred in treatment-naïve participants on M/T FDC during the DB or the OL period.

Within the M/T FDC group during the DB period, incidence of anaemia AESIs was comparable between the treatment-naïve and prior PDE-5i strata (11/49 [22.4%] and 8/37 [21.6%], respectively), and lower in the prior ERA stratum (1/21 [4.8%]). Within the M/T FDC group during the DB period, a greater proportion of participants in the prior ERA stratum had hypotension AESIs (3/21 [14.3%] prior ERA) compared with the 2 other strata (3/49 [6.1%] treatment-naïve and 2/37 [5.4%] prior PDE 5i). Within the M/T FDC group during the DB period, oedema AESIs were reported more frequently in the treatment-naïve stratum (15/49 [30.6%]) compared with the prior treatment strata (2/21 [9.5%] prior ERA, and 5/37 [13.5%] prior PDE-5i.

These results indicate that patients on FDC M/T that were treatment-naïve overall had higher risk for AESI than those on prior therapy.

2.6.10. Conclusions on the clinical safety

The safety profile for macitentan and tadalafil as monotherapies is well established in patients with PAH. Results from the A DUE pivotal Phase 3 study show that the overall nature of AEs with the M/T 10/40 mg FDC was consistent with the expected safety profile of macitentan and tadalafil. The studies TRITON, REPAIR, SYMPHONY, ORCHESTRA, and OPUS/ORPHEUS provide supportive safety data for the loose combination of macitentan and tadalafil, consistent with A DUE results.

In the M/T 10/40 mg FDC group the overall incidence of treatment discontinuations due to AEs was 8.4%, with the majority of the discontinuations on M/T FDC occurring in the treatment-naïve patients. Discontinuations were more frequently reported during the first 4 weeks of treatment with study intervention, primarily in treatment-naïve participants. As expected, treatment-naïve participants may be more prone than pre-treated participants to experiencing AEs known to be associated with the use of macitentan and tadalafil. Serious AEs that occurred during the study were consistent with expectations in the study population and followed no apparent pattern. M/T FDC led to a higher incidence of the adverse events of special interest, anaemia, hypotension and oedema. The safety profile of the M/T 10/40 mg FDC is largely consistent with the well-established and expected safety profile of the individual components, macitentan and tadalafil. Importantly, no new safety signals were observed with the M/T 10/40 mg FDC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 61: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity Teratogenicity
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 62: Description of routine risk minimisation measures by safety concern

Safety concern	Routine Risk minimisation activities	Pharmacovigilance activities

Important identified risk		
Hepatotoxicity	**Routine risk minimization measures**: SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you take Yuvanci). PL Section 4 (Possible side effects). Warning that M/T FDC is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or elevated baseline values of aminotransferases (AST and/or ALT>3×ULN) is given in SmPC Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), and 4.4 (Special warnings and precautions for use). Recommendation that liver enzyme tests be obtained prior to initiation of M/T FDC and repeated monthly during treatment is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation that patients should be monitored for signs of hepatic injury is given in SmPC Section 4.4 (Special warnings and precautions for use). Recommendation to discontinue M/T FDC if sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.

	symptoms of liver injury is given in SmPC Section 4.4 (Special warnings and precautions for use). This section also notes that reinitiating of M/T FDC may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury; the advice of a hepatologist is recommended. Warning to patients not to take M/T FDC and to speak to their doctor if they have liver disease or if they have very high levels of liver enzymes in their blood is provided in PL Section 2 (What you need to know before you take Yuvanci). Patients are informed that their doctor will carry out laboratory tests to test whether their liver is working properly prior to initiation and during treatment, as needed, with M/T FDC in PL Section 2 (What you need to know before you take Yuvanci). Recommendation for patients to speak to their doctor immediately if they notice signs of liver impairment is given in PL Section 2 (What you need to know before you take Yuvanci). This section also contains a recommendation for patients to speak to their doctor if they have a serious liver problem before taking M/T FDC. **Legal status**: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.	

Teratogenicity	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction). SmPC Section 4.6 (Fertility, pregnancy and lactation). SmPC Section 5.3 (Preclinical safety data). PL Section 2 (What you need to know before take Yuvanci). Warning that use of M/T FDC is contraindicated during pregnancy and in women of childbearing potential who are not using reliable contraception due to teratogenicity identified in animal studies with macitentan is given in SmPC Section 4.6 (Fertility, pregnancy and lactation). Appropriate warnings are also given in SmPC Section 4.3 (Contraindications). Recommendation that M/T FDC treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practiced is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendation that women should not become pregnant for 1 month after discontinuation of M/T FDC is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Macitentan – Tadalafil FDC Pregnancy and Outcome Follow-up Questionnaire (TV-eFRM-16843). **Additional pharmacovigilance activities:** None proposed.

	lactation). Recommendation for use of monthly pregnancy tests during treatment with M/T FDC to allow for early detection of pregnancy is given in SmPC Sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation). Recommendations for patients to use a reliable form of birth control (contraception) whilst taking M/T FDC and to not take M/T FDC if they are pregnant, are planning to become pregnant, or could be pregnant because they are not using reliable birth control are given in PL Section 2 (What you need to know before you take Yuvanci). Warning that treatment with M/T FDC must not be taken during pregnancy is provided in PL Section 2 (What you need to know before you take Yuvanci). This section contains recommendations for patients to consult their doctor immediately if they become pregnant or think they may be pregnant while taking M/T FDC or shortly after stopping M/T FDC (up to 1 month). Recommendations for patients to have a pregnancy test before initiation of M/T FDC and every month during treatment are given in PL Section 2 (What you need to know before you take Yuvanci). **Legal status:** Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Card.	

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Although the pathogenesis of PAH is not completely understood, it likely involves an imbalance in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants that are probably consequences of pulmonary endothelial cell dysfunction and/or injury.

The initially proposed indication is:

"Yuvanci is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III who are:

- *treatment-naïve to any PAH specific therapy.*
- *on treatment with macitentan or tadalafil.*
- *already treated with the combination of macitentan and tadalafil as separate tablets"*

As such, with the proposed indication, the Applicant is applying for three different therapeutic scenarios in which the M/T FDC may be used, i.e., initial combination therapy, add-on therapy, and substitution therapy.

However, in response to the raised issues following the assessment of all available data, the wording of the indication was later amended to include only substitution therapy:

"Yuvanci is indicated as substitution therapy for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets."

3.1.2. Available therapies and unmet medical need

In the European Union (EU), multiple medicinal products have gained approval for PAH treatment. These drugs predominantly focus on pathways that either directly or indirectly enhance blood flow through the pulmonary vasculature. The main pathways targeted by these drugs are the endothelin-1 pathway, the nitric oxide pathway, the prostacyclin pathway and the activin/TGFβ pathway. The intent behind these drugs, whether administered as monotherapy or in combination, is to ameliorate vascular tone by addressing the underlying dysregulated processes that lead to pulmonary vasoconstriction.

Endothelin-1 (ET-1), another hormone with vasoactive properties produced by endothelial cells, functions as a vasoconstrictor. In the context of PAH, dysregulated ET-1 production contributes to heightened pulmonary vascular resistance. ET-1 engages cell surface receptors known as Endothelin-A (ETA) and Endothelin-B (ETB), expressed on vascular smooth muscle cells (VSMCs) and endothelial cells respectively. Blocking these endothelin receptors has demonstrated the ability to counteract the vasoconstrictive effects of ET-1. Several approved drugs, including bosentan, ambrisentan, and macitentan, fall into the category of endothelin receptor antagonists (ERAs) and function by inhibiting one or both of these receptors. Clinical studies have attested to their capacity to decrease pulmonary vascular resistance and enhance exercise capacity.

However, the use of ERAs has been associated with hepatotoxicity, even leading to the withdrawal of one such drug, sitaxentan.

Phosphodiesterase type-5 inhibitors (PDE5i) represent a class of compounds extensively used in PAH treatment. Proper functioning of vascular smooth muscle cells (VSMCs) to maintain vascular tone relies on adequate levels of cyclic guanosine monophosphate (cGMP) and nitric oxide (NO). PDE5, highly expressed in the VSMCs of pulmonary vasculature and upregulated in PAH, contributes to cGMP breakdown, resulting in vasoconstriction. PDE5 inhibitors, such as sildenafil and tadalafil, intervene by preventing the degradation of cGMP, thereby maintaining its levels and promoting vasodilation.

Riociguat, distinct from PDE5 inhibitors, operates as a stimulator of soluble guanylate cyclase. This enzyme is responsible for converting guanosine triphosphate (GTP) into cGMP. Clinical trials involving riociguat and PDE5 inhibitors have generated evidence of improvements in disease symptoms and exercise tolerance. Prostacyclins, potent vasodilatory hormones primarily released by endothelial cells, have played a pivotal role in the development of targeted PAH therapy. Epoprostenol, the initial therapy of this kind, is typically reserved for class III and IV patients due to its continuous intravenous infusion requirement, necessitating a permanent catheter. While newer-generation prostacyclins, such as treprostinil, offer improved physiochemical properties, they too demand continuous infusion, meticulous dose titration, and safety monitoring. Notably, inhaled and oral prostacyclins have mitigated some challenges associated with continuous infusion. Selexipag, an oral prostacyclin receptor agonist, has emerged as a recent option, exhibiting the ability to slow PAH disease progression when added to existing treatments.

Recent PAH treatment guidelines advocate a risk-adapted approach for managing most patients, highlighting the importance of combination drug therapy. Although treatment options are available, PAH remains progressive and ultimately fatal. Current guidelines recommend combination in treatment-naïve patients as more effective therapeutic options to achieve and maintain low risk status (Galiè 2019b, Gaine 2017). However, the current ESC/ERS practice guidelines acknowledge that adherence to drug therapy in patients with PAH may be suboptimal (Kjellström 2020, Shah 2019, Humbert 2022). A single tablet combination of treatments with proven efficacy acting on 2 of the major pathways involved in the pathogenesis of PAH could provide synergistic treatment benefits to patients with PAH at a fixed dose, once a day, representing an additional, and thereby novel, mode of action compared to other therapies approved for PAH. Currently, no fixed dose combination (FDC) tablet for the treatment of PAH is available in the EU. Patients with complex dosage regimens due to multiple medications and/or higher dose frequency, may be at risk for noncompliance (Ingersoll 2008). As the PAH population ages and presents with more comorbidities, the complexity of the regimen, and thus the risk of noncompliance, grows. In addition to adherence and persistence, a once-a-day single tablet might add a potential safety benefit by reducing the risk of medication errors that lead to lost treatment benefits or adverse events (Böhm 2021). However, this remains a hypothetical issue, without any related supportive data being provided in the current dossier.

3.1.3. Main clinical studies

The main study is study AC-077A301, also known as and hereafter referred to as "A DUE". The A DUE study consists of a 16-week double-blind phase and an open-label extension. When referring to A DUE in this report, this refers to the 16-week double-blind phase. A DUE is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding FDC in subjects with PAH, followed by an open-label treatment period with macitentan and tadalafil FDC therapy. The rationale of the study was to demonstrate that macitentan 10 mg and tadalafil 40 mg as a FDC (M/T FDC) is superior to 10 mg of macitentan alone, and to 40 mg of tadalafil alone, as measured by the ratio of end of double-blind treatment (EDBT) to baseline pulmonary vascular resistance (PVR). The key secondary outcome was change in 6MWD. Randomization was stratified by prior background PAH treatment at study entry (treatment naïve, ERA, or PDE5i).

For the comparison between M/T FDC and macitentan 10 mg, only participants randomized to M/T FDC or macitentan 10 mg in the treatment-naïve or prior-ERA strata will be included. For the comparison between M/T FDC and tadalafil 40 mg, only participants randomized to M/T FDC or tadalafil 40 mg in the treatment-naïve or prior-PDE-5i strata will be included. For the subsequent sections, the strata "treatment-naive and prior ERA strata" can be considered as the comparison of M/T FDC versus macitentan, and thus the added value of tadalafil. The strata "treatment-naive and prior PDE-5i strata" can be considered as the comparison of M/T FDC versus tadalafil, and thus the added value of macitentan.

To support the substitution indication, the focus is on the effect on PVR. To support the add-on and first-line indication the focus is on the combination of an effect on PVR, combined with a trend on 6MWD, which serves as a gatekeeper for additional supportive data:

In supportive analyses A (supporting add-on and initial treatment), an assessment was made to compare the effectiveness of macitentan and tadalafil versus macitentan monotherapy using retrospective data from completed clinical trials in treatment-naïve, newly diagnosed treatment-naïve patients with PAH. An indirect treatment comparison with no common comparator was conducted using pooled patient level data from completed studies (TRITON, REPAIR, SERPAPHIN and ORCHESTRA).

In supportive analyses B (supporting add-on and initial treatment), an assessment was made to compare the effectiveness of macitentan and tadalafil versus tadalafil monotherapy using retrospective data from completed clinical trials in treatment-naïve, newly diagnosed naïve patients with PAH. An indirect treatment comparison with no common comparator was conducted using pooled patient level and external aggregate data from completed studies (TRITON, REPAIR, and AMBITION).

3.2. Favourable effects

Pulmonary vascular resistance

The change in PVR (ratio of week 16 to baseline) was 0.55 (0.50; 0.60) in the M/T FDC arm of the treatment-naive and prior ERA strata and 0.56 (0.52; 0.60) in the M/T FDC arm of the treatment-naive and prior PDE5i strata, whereas the change in PVR was 0.77 (0.69; 0.87) in the macitentan arm of the treatment-naïve and prior ERA strata and 0.78 (0.72; 0.84) in the tadalafil arm of the treatment-naïve and prior PDE-5i strata. The geometric mean ratio of M/T FDC vs monotherapy in treatment-naive and prior ERA strata (reflecting add-on tadalafil on top of macitentan) was 0.71 (95% CI: 0.61, 0.82; P<0.001) and the geometric mean ratio of M/T FDC vs monotherapy in treatment-naive and prior PDE5i strata (reflecting add-on macitentan on top of tadalafil) was 0.72 (95% CI: 0.64, 0.80; P<0.001). These results were consistent in subgroup analyses (including prior PAH therapy strata) and sensitivity analyses.

6-minute walking distance

The change in 6MWD was 52.9 ± 88.2 m in the M/T FDC arm of the treatment-naive and prior ERA strata and 43.3 ± 78.0 m in the M/T FDC arm of the treatment-naive and prior PDE5i strata, whereas the change in PVR was 38.5 ± 70.4 m in the macitentan arm of the treatment-naïve and prior ERA strata and 15.9 ± 45.0 m in the tadalafil arm of the treatment-naïve and prior PDE-5i strata.

The treatment effect of M/T FDC vs monotherapy in treatment-naive and prior ERA strata was 16.0 (95% CI: -17.0, 49.1; P=0.38) and the treatment effect of M/T FDC vs monotherapy in treatment-naive and prior PDE5i strata was 25.4 (95% CI: -0.93, 51.6; P=0.059).

3.3. Uncertainties and limitations about favourable effects

The study design was flawed in terms of the chosen primary outcome parameter and subsequent study duration and sample size. The primary endpoint of the study was change in PVR, which, as stated in the CHMP scientific advice (EMA/CHMP/SAWP/123302/2019) can only be considered acceptable for the substitution indication.

The 6MWD as the primary outcome with duration of 24 weeks and associated sample size calculation was previously recommended in support of the requested add-on and first line initial therapy indications. This was advice was not followed and instead 6MWD was included as a secondary outcome. As stated in outcome scientific advice (EMA/SA/0000074632), demonstration of a statistically significant and clinically relevant effect on PVR plus a clinically relevant positive trend (numerical difference of 20 meters with $P<0.10$) for the 6MWD could be accepted as a "gatekeeper" for the acceptance of further supportive data for justification of the add-on and initial indication.

For the "Prior PDE-5i + treatment naïve stratum" (reflecting add-on macitentan on top of tadalafil), the improvement in 6MWD in A DUE of M/T FDC over tadalafil was 25.4 meters with a 95% CI of -0.93, 51.6 (corresponding P=0.059), meeting the gatekeeping criteria. This effect was also consistent across prior PAH strata. The treatment effect of M/T FDC vs tadalafil was 33.0m (95% CI: -5.3; 71.4; P=0.09) in the treatment naïve strata and 25.9m (95% CI: 0.9; 50.9; P=0.04) in the prior PDE-5i strata. The post-hoc supportive analyses (supportive analyses B) using prior clinical trials (unanchored matched-adjusted indirect comparison) demonstrated a change from baseline to week 24 in 6MWD of 31.6m (95% CI 10.9, 52.4m) for M + T over tadalafil. However, it should be noted that this was found in an analysis which performed matching based on a clinically important subset of the original covariates (WHO FC, 6MWD and log[NT-proBNP]), since in the initial weighting a 65% reduction from the original sample size was observed, suggesting a low degree of similarity between the patient populations compared prior to matching. This emphasizes that these findings should be interpreted with caution, recognizing the limitations imposed by the unanchored matched-adjusted indirect comparison approach, making this at best supportive data.

For the "Prior ERA + treatment naïve stratum" (reflecting add-on tadalafil on top of macitentan), the improvement in 6MWD in A DUE of M/T FDC over macitentan was only 16 meters with a wide 95% CI of -17 to 49 (corresponding P=0.4). This effect was not consistent across prior PAH treatment. The treatment effect of M/T FDC vs macitentan was 20.4m (95% CI: -20.3; 61.1; P=0.32) in the treatment-naïve strata and 8.5m (95% CI: -40.0; 58.0; P=0.73) in the prior ERA strata. Furthermore, the effect of M/T FDC over macitentan was even lower in the rank-based linear model, where the treatment effect of M/T FDC over macitentan was 9.86m (95% CI: -19.2; 38.84; P=0.58). Supportive evidence (supportive analyses A) could therefore not be considered for the M/T FDC versus macitentan comparison as the gate-keeping criteria was not met. Importantly, in the A DUE study, no added benefit of M/T FDC over either monotherapy could be shown for other outcomes, including quality of life measures, absence in worsening in WHO FC or morbidity/mortality events. Furthermore, for the initial therapy combination, it is also unclear what the efficacy benefit is of initial combination therapy over sequential therapy (i.e. starting one monotherapy for one or two weeks and if tolerable switching to the FDC), given that this approach allows a gap to assess tolerability of the first treatment before starting the second treatment.

In response to these issues, the Applicant agreed to amend the wording of the indication and to remove the initially proposed add-on and first line initial treatment indications, thereby solving this issue.

An advantage of a FDC is that the pill load will be reduced from two or three (for 10/20 and 10/40, respectively) separate tablets once daily, to one FDC tablet once daily. However, there is no data presented supporting the fact that this leads to improved adherence or drug safety. Furthermore, in the A DUE trial, therapy adherence was equally high for all treatment regimens in the randomised trial.

3.4. Unfavourable effects

In the A DUE 16-week DB period, the proportion of participants who experienced at least 1 AE in the M/T FDC group (82.2%) was higher than in the macitentan group (71.4%) and similar to the tadalafil group (79.5%). SAEs were reported more frequently in the M/T FDC (14.0%) group than in the macitentan (8.6%) and tadalafil (9.1%) groups. Within the M/T FDC group, SAEs were reported by more treatment-naïve participants than those who have had prior treatment with an ERA or a PDE-5i (16.3% treatment-naïve, 14.3% prior ERA, and 10.8% prior PDE-5i).

Adverse events occurring more frequently in the M/T FDC group compared with macitentan and/or tadalafil monotherapy were myalgia, nausea and various adverse events of special interest:

The anaemia AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (18.7% vs 2.9% vs 2.3%). Within the M/T FDC group during the DB period, the incidence of anaemia AESIs was comparable between the treatment-naïve and prior PDE-5i strata (22.4% and 21.6%, respectively), and lower in the prior ERA stratum (4.8%).

The oedema AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (20.6% vs 14.3% vs 15.9%). Within the M/T FDC group during the DB period, oedema AESIs were reported more frequently in the treatment-naïve stratum (30.6% compared with 9.5% in prior ERA, 13.5% in prior PDE-5i).

The hypotension AESI were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (7.5% vs 0% vs 0%). Within the M/T FDC group during the DB period, a greater proportion of participants in the prior ERA stratum had hypotension AESIs (14.3%) compared with the 6.1% in treatment-naïve and 5.4% in prior PDE-5i.

Cardiac disorders were reported in 16 (15.0%) of participants in the M/T FDC group compared to 2 (5.7%) in the macitentan group and 4 (9.1%) in the tadalafil group. The difference was mainly driven by AEs denoting cardiac failure reported in 4 (3.7%) participants, left ventricular failure in 1 (0.9%) participant, and right ventricular failure in 1 (0.9%) participant in the M/T FDC group.

During the A DUE trial, AEs leading to discontinuation of study intervention were reported more frequently in the M/T FDC group as compared to the macitentan and tadalafil groups (8.4% vs 0% vs 4.5%). More than half of the 9 participants in the M/T FDC group who discontinued study intervention during the DB period were treatment-naïve (12.2% treatment-naïve, 4.8% prior ERA, and 5.4% prior PDE-5i). There was no trend based on individual PTs or SOCs.

3.5. Uncertainties and limitations about unfavourable effects

The major uncertainty regarding the unfavourable effects is the limited sample size and limited duration of the double-blind phase of 16 weeks. The open-label phase has a long duration, but without a control group no reliable conclusions on safety can be drawn for the long-term maintenance phase.

During the A DUE 16-week DB period, there were 3 deaths (2 treatment-emergent) in the M/T FDC group and none in the macitentan and tadalafil groups. None were assessed by the investigators as related to study treatment. However, due to the limited follow-up of the double-blind phase, it is unknown how M/T FDC affects long-term survival.

Regarding the observed disbalance in cardiac failure, it is unclear whether this is a chance finding or related to the M/T FDC, as cardiac failure was not deemed a AESI for either macitentan or tadalafil.

3.6. Effects Table

Table 63: Effects Table for YUVANCI (Macitentan/tadalafil FDC 10/40mg), based on A DUE DB-period.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
PVR	Change from baseline in pulmonary vascular resistance, ratio of week 16 to baseline				**SoE**: Consistent in subgroup analyses and sensitivity analyses
		Treatment-naive and prior ERA strata			
		Ratio	0.55 (0.50; 0.60)	0.77 (0.69; 0.87)	Geometric mean ratio of M/T FDC vs monotherapy 0.71 95% CI: 0.61, 0.82; P<0.001
		Treatment-naive and prior PDE5i strata			
		Ratio	0.56 (0.52; 0.60)	0.78 (0.72; 0.84)	Geometric mean ratio of M/T FDC vs monotherapy 0.72 95% CI: 0.64, 0.80; P<0.001
6MWD	Change from baseline in 6 minute walking distance	Treatment-naive and prior ERA strata:			
		meters	52.9 ± 88.2	38.5 ± 70.4	Treatment effect 16.0 95% CI: -17.0, 49.1; P=0.38
		Treatment-naive and prior PDE-5i strata			
		meters	43.3 ± 78.0	15.9 ± 45.0	Treatment effect 25.4 95% CI: -0.93, 51.6; P=0.059
Unfavourable Effects					
AESI	Anaemia	%	18.7%	2.9% (M) 2.3% (T)	Most participants with anaemia AESI were treatment-naïve. The events were generally mild or moderate.
AESI	Oedema	%	20.6%	14.3% (M) 15.9% (T)	Most participants with oedema AESI were treatment-naïve. The events were generally mild or moderate.
AESI	Hypotension	%	7.5%	0% (M) 0% (T)	All hypotension AESI were of mild or moderate intensity.
AE	Cardiac failure	%	3.7%	0% (M) 2.3% (T)	Occurred mostly in participants 65 years or older, treatment-naïve, and with comorbidities.

Abbreviations: PVR: Pulmonary vascular resistance; 6MWD: 6-minute walking distance; AESI: Adverse event of special interest.
Notes: The strata "Treatment effect in treatment-naive and prior ERA strata" can be considered as the comparison of Yuvanci versus macitentan, and thus the added value of tadalafil. The strata "Treatment effect in treatment-naive and prior PDE-5i strata" can be considered as the comparison of Yuvanci versus tadalafil, and thus the added value of macitentan.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

From a regulatory perspective, the importance of the favourable effects, i.e. reduction in **PVR**, depends on the indication. The A DUE trial primarily demonstrated a contribution of both components on PVR, which is considered sufficient for a substitution indication in the context of the *Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/158268/2017). However, this is not sufficient for an add-on or first-line initial therapy indication. Whilst PVR is a key diagnostic parameter and a prognostic risk estimator in PAH, a clinically relevant magnitude and timing of change in response to treatment is not defined and validated to be suitable for a pivotal study primary endpoint. For this reason, the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension (EMEA/CHMP/EWP/356954) does not support PVR as primary endpoint. However, it was considered acceptable to use PVR to support the substitution indication, also given the fact that both macitentan and tadalafil already are indicated for PAH treatment as monotherapy or in combination therapy.

For the add-on and first-line initial therapy indications, the **6MWD** results are of primary interest. Given the fact that both active substances of the fixed combination medicinal product are approved for a long time in this orphan disease, it was stated in the scientific advice (EMA/SA/0000074632), that demonstration of a statistically significant and clinically relevant effect on PVR plus a clinically relevant positive trend (numerical difference of 20 m with P<0.10) for the 6MWD could be accepted as a "gatekeeper" for the acceptance of further supportive data. This criterion has only been met for the "*PDE-5i + treatment naïve stratum*" of the A DUE trial. The post-hoc supportive analyses using prior clinical trials (unanchored matched-adjusted indirect comparison) demonstrated a change from baseline to week 24 in 6MWD of 31.6m (95% CI 10.9, 52.4 m) for M/T over tadalafil. Taken together, the results demonstrate clinical efficacy of add-on macitentan on top of tadalafil. Therefore, the add-on indication for macitentan on top of tadalafil is considered acceptable. However, for the "*ERA + treatment naïve stratum*", the gatekeeping criterion was not reached, precluding assessment of supportive data. After raising this issue, the Applicant agreed to remove the proposed add-on and first-line initial treatment indications, thereby solving these issues.

In general, the adverse events and general **safety** profile are in line with the mono-components although higher incidences were found for certain AE(SI). No new safety concerns were identified. Anaemia, oedema and hypotension each occurred more often in the M/T FDC arm as compared to the mono-therapy arms. Anaemia is a known adverse reaction of macitentan and this AESI was generally mild or moderate and clinically manageable but occurred most often in treatment-naïve patients. Oedema and fluid retention are known events associated with macitentan. The AESIs were generally mild to moderate, but also occurred more often in treatment-naïve patients. The hypotension AESI were generally mild or moderate and clinically manageable, and likely is the direct consequence of the concomitant introduction of two vasodilators to patients. Overall, while most unfavourable effects were mild to moderate in nature and generally well manageable, the unfavourable effects were more likely to occur in treatment-naïve patients. The importance of these unfavourable effect is thus highest for the treatment-naïve patients. However, given the removal of the proposed add-on and first-line initial treatment indications, this is no longer an issue.

3.7.2. Balance of benefits and risks

For the substitution indication, the balance of benefits and risks is positive, as the A DUE trial demonstrated a contribution of both mono-components on the pharmacodynamic marker PVR, while the higher incidence of adverse events (of special interest) is not applicable in this situation since patients will already have been

treated with both macitentan and tadalafil. The proposed add-on and first-line initial treatment indications have been removed from the product information.

3.7.3. Additional considerations on the benefit-risk balance

Of note, the Applicant on multiple locations refers to the ESC guideline recommendation to start treatment with initial combination therapy of macitentan and tadalafil. However, real world data, survey data and literature data all indicate that the ESC guideline recommendation to start with initial combination therapy is poorly taken up in clinical practice. Potential reasons are the low quality of evidence (based on Chin et al. 2021 and Sitbon et al. 2020, none of which had an appropriate comparator arm of monotherapy) or the preference for physicians to use stepwise therapy to assess tolerability per drug.

Lastly, the proposed indication refers to a general "treatment" indication, whereas the mono-component tadalafil is only registered to improve exercise capacity. However, since the combination therapy includes both tadalafil and macitentan, and macitentan has also demonstrated efficacy on morbidity and mortality events, it is considered appropriate to use a general treatment indication for the fixed dose combination, as this includes macitentan.

3.8. Conclusions

The overall benefit/risk balance of YUVANCI is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that YUVANCI is not similar to Opsumit and Winrevair within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of YUVANCI is favourable in the following indication(s):

> *Yuvanci is indicated as substitution therapy for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Yuvanci is marketed, all patients who are expected to use Yuvanci are provided with the following educational material:

- Patient Card.

These conditions fully reflect the advice received from the PRAC.