25 July 2024
EMA/389480/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on a group of an extension of marketing authorisation and an extension of indication variation

Opsumit

International non-proprietary name: Macitentan

Procedure No. EMEA/H/C/002697/X/0051/G

Note

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

Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Alu-PE	aluminum-Polyethylene
ASMF	active Substance Master File
API	active Pharmaceutical Ingredient
AUC0-24h,ss	area under the plasma concentration-time curve over a 24-hour dosing interval at steady state
AUCu,combo,ss	combined unbound exposure parameter computed as the sum of macitentan and aprocitentan AUC0-24h,ss weighted by their unbound fraction and by their proportion of in vitro potency
ALT	alanine transaminase
AST	aspartate aminotransferase
BSA	body surface area
BSC	biopharmaceutical Classification System
BSE	bovine Spongiform Encephalopathy
CCO	clinical cutoff for analysis
CEC	Clinical Event Committee
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	confidence limits
CQA	Critical Quality Attribute
CTD	connective tissue disorder
CSR	Clinical Study Report
DP	Disease progression
DP	Drug Product
DS	Drug Substance
EOCP	End of Core Period
EOS	end of study
EOT	end of treatment
ERA	endothelin receptor antagonist

ES	Eisenmenger syndrome
EU	European Union
FC	Functional class
FMI	final market image
FOIA	Freedom of Information Act
GLSM	geometric least squares mean
GMP	Good Manufacturing Practice
GMS	Global Medical Safety
HCE	hierarchical composite endpoint
hPAH	heritable pulmonary arterial hypertension
HPLC	High-Performance Liquid Chromatography
HR	hazard ratio
HPO	Hypothalamic pituitary ovarian
ICH	International Conference of Harmonization
iCSR	interim Clinical Study Report
iPAH	idiopathic pulmonary arterial hypertension
IV	intravenous
KBE	Key binding element
MedDRA	Medical dictionary for regulatory activities
LDPE	Low-Density Polyethylene
LSM	least square mean
LVEI	Left Ventricular Eccentricity Index
NE	not estimable
NMT	Not more than
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OSAE	Other Significant AE
PA-Alu-PVC-PE	Polyamide-Aluminum-Polyvinyl Chloride-Polyethylene
PAH	pulmonary arterial hypertension
PBRER	Periodic Benefit Risk Evaluation Report
PDE-5i	phosphodiesterase Type 5 inhibitor
Ph.Eur.	European Pharmacopoeia

PK	pharmacokinetics
PSUR	Periodic safety update report
PT	preferred term
PVOD	pulmonary edema associated with veno-occlusive disease
QC	Quality Control
QP	Qualified Person
QTTP	Quality Target Product Profile
RH	Relative Humidity
RMP	Risk Management Plan
SAE	serious adverse event
SC	subcutaneous
SCP	Summary of Clinical Pharmacology
SER	SERAPHIN
SCS	Summary of Clinical Safety
SoC	standard of care
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment-emergent adverse event
TOM	TOMMOROW
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary
WO	Win odds

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 6 October 2023 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with new strengths (1 and 2.5 mg dispersible tablet) grouped with an extension of indication (C.I.6.a) to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 1 month to less than 18 years of age of WHO Functional Class (FC) I to III for OPSUMIT, based on interim results from AC-055-312 study (TOMORROW). This is a multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC for film-coated tablets are updated. The Package Leaflet and Labelling are updated in accordance. Version 14.1 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0457/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0012/2023 was not yet completed as some measures were deferred. However, the PIP P/0457/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0457/2023.

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 MAH did submit a critical report addressing the possible similarity with orphan medicinal products for which a positive CHMP opinion was adopted in June 2024 and the European Commission Decision is pending.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 26 February 2015 (EMEA/H/SA/3002/1/2014/PA/PED/II), 24 June 2021 (EMA/SA/0000058737) and 19 May 2022 (EMA/SA/0000086611). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Antonio Gomez-Outes Co-Rapporteur: Patrick Vrijlandt

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	6 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	30 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 February 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	29 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	6 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2024
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	27 June 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	02 July 2024 17 July 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 July 2024

Upon request of the CHMP, the PDCO provided an opinion on the paediatric data with regard to safety and efficacy based on data collected in accordance with the agreed paediatric investigation plan.	25 July 2024
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 Opsumit on	25 July 2024
The CHMP adopted a report on similarity of Opsumit with name of the authorised orphan medicinal product(s) on (see Appendix on similarity)	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Macitentan is currently approved by the European Commission as 10 mg film-coated tablet for oral use for the following indication:

> *"Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.*
>
> *Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1)".*

This application for macitentan (Opsumit) is an extension of Marketing Authorisation to register a new pharmaceutical form (dispersible tablets) with one dose strength (2.5 mg), grouped with a Type II variation for adding a therapeutic indication in paediatric patients aged 2 years to less than 18 years with pulmonary arterial hypertension.

The proposed indication for macitentan is as follows. Additions are shown in red underlined text, deletions are shown in red with ~~strikethrough~~):

- ***10 film-coated tablets:***

Adults

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

~~Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease~~ (see section 5.1).

Paediatric population

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III (see section 5.1).

- ***2.5 mg dispersible tablets:***

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years of age of WHO Functional Class (FC) II to III (see Section 5.1).

Pulmonary arterial hypertension is a life-threatening and chronically debilitating condition, characterized by a progressive increase in pulmonary arterial pressure and in pulmonary vascular resistance, potentially leading to right heart failure and death, especially in children (Ploegstra 2023). Pulmonary hypertension in childhood shares many common features with PH in adulthood; however, there are differences, which concern epidemiology, aetiology, genetic background, age-dependent diagnostic and treatment approaches, and disease monitoring (Humbert 2023).

Historically, the definition of PH in children has been the same as in adults, i.e. mean pulmonary arterial pressure (mPAP) ≥25 mmHg. The definition for PH has now been redefined to mPAP >20 mmHg in adults as well as in children. The impact of an mPAP 21–24 mmHg on outcomes in children is unknown. The criterion of pulmonary vascular resistance index (PVRI) ≥3 WU·m2 in the definition for PAH in children remains unchanged [Rosenzweig et al, 2019].

The most common forms of paediatric PAH are idiopathic Pulmonary Arterial Hypertension (IPAH), hereditable (HPAH), and associated Pulmonary Arterial Hypertension (aPAH).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Current epidemiological data on paediatric PH are mainly derived from registry cohorts; as a result, they are affected by study design, logistics and the scope of clinical practice underlying patient selection for these registries. Accurate estimates of the prevalence and incidence of PAH in children do not exist (Widlitz 2003).

The reported annual incident rate for paediatric PH is 64/million children. The distribution of the various aetiologies of PH in childhood differs from PH in adulthood. Pulmonary arterial hypertension is the most frequent type of PH in children, with the vast majority (82%) of cases being infants with transient PAH (i.e. PPHN or repairable cardiac shunt defects). Of the remaining children with PAH, most have either IPAH, HPAH, or irreversible CHD-associated PAH. The reported incidences of IPAH/HPAH and (non-transient) CHD-associated PAH are 0.7 and 2.2/million children, respectively, with a prevalence of 4.4 and 15.6/million children, respectively. Another significant proportion (34–49%) of children with non-transient PH are neonates and infants with PH associated with respiratory disease, especially developmental lung diseases, including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), and congenital pulmonary vascular abnormalities. (Humbert 2023)

In the NIH registry, the median untreated survival for children after diagnosis of idiopathic PAH (IPAH) was reported to be 10 months as opposed to 2.8 years for adults (D'Alonzo et al. 1991).

Although treatments approved for PAH in adults have shown favorable effects in children, treatment remains unsatisfactory. The 1-, 3-, and 5-year adverse outcome free survival (including death, lung transplantation, atrial septostomy, or Potts shunt palliation) from time to diagnosis was 83.9%, 75.2%, and 71.8%, respectively (Ploegstra 2023). Especially early mortality remains substantially high and needs further improvement.

The key predictors of adverse outcome identified in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry (ClinicalTrials.gov Identifier: NCT02610660) include young age, etiology, WHO FC, and a set of hemodynamic predictors.

2.1.3. Biologic features, aetiology and pathogenesis

PH can present at any age from the neonatal period to adulthood. There are 5 different groups of pulmonary hypertension based upon different causes (Humbert et al, 2023). These groups are defined by the WHO and are referred to as pulmonary hypertension WHO Groups. Pulmonary arterial hypertension (PAH) refers to WHO Group 1.

PAH disease aetiologies are described in the following table (Humbert et al, 2023). The more frequent aetiologies in children are idiopathic, heritable, associated with connective tissue disease and associated with congenital heart disease (underlined in the following table). PPHN remains in the PAH group but has been moved to a subgroup (Subgroup 1'' within group 1), as it is considered to be a specific entity with a more transient course in most cases (Humbert et al, 2023).

GROUP 1. Pulmonary arterial hypertension
1.1. Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable (familial)
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.4.1. Eisenmenger's syndrome
Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
1.4.4.2. PAH associated with prevalent systemic-to-pulmonary shunts
• Correctable
• Non-correctable: Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
1.4.4.3. PAH with small/coincidental defects
Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.
1.4.4.4. PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.
1.4.5 Schistosomiasis
1.5. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1.6 Persistent pulmonary hypertension of the newborn

Source: Humbert et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618-3731. Erratum in: Eur Heart J. 2023 Apr 17;44(15):1312.

2.1.4. Clinical presentation, diagnosis

Although the clinical presentation of pPAH may vary according to the aetiology, the most frequent symptoms are dyspnoea, fatigue, chest pain, dizziness, syncope, cyanosis, palpitations and irritability (Berger et al. 2012). Syncope is more common in children. Clinical course of PAH may be characterized by progressive deterioration and occasional episodes of acute decompensation. Progression of the disease may lead to right cardiac failure, oedema, haemoptysis, cerebrovascular accidents from paradoxical emboli, and cardiac arrhythmias. (Humbert 2023). The WHO functional class system was implemented for disease evaluation of patients with PAH to define the disease severity of symptoms and disease impact on day-to-day activities.

Since the aetiology of paediatric PH is very diverse, a methodical and comprehensive diagnostic approach is crucial to reach an accurate diagnosis and treatment plan. As in adults, IPAH is a diagnosis 'per exclusion'. Right heart catheterization (RHC) is the gold standard for definitively diagnosing and establishing the nature of PH and provides important data for stratifying risk. However, RHC necessity should be balanced with associated risks. Major complications associated with RHC in children with PH have been reported to be 1–3% and are generally associated with clinical condition and young age (newborns and young infants). As a result, cardiac catheterisation in paediatric PAH is strongly recommended to be performed in experienced paediatric PH centres using strategies to prevent these potential complications and having the ability to manage complications (Rosenzweig et al, 2019; Humbert et al, 2023).

Indications for repeat cardiac catheterisation in children with PH are not well defined, but include assessment of treatment effect, clinical deterioration, detection of early disease progression and prediction of prognosis. It has, however, not been shown whether changes in haemodynamic parameters are associated with change in clinical outcome and therefore these parameters do not meet the requirements to serve as established treatment goals (Rosenzweig et al, 2019).

Paediatric PAH often is associated with comorbidities and developmental or genetic disorders. Given the frequent association of paediatric PAH with chromosomal, genetic, and syndromic anomalies, genetic testing may be considered for defining aetiologies and comorbidities, stratifying risk, and identifying family members at risk (Humbert et al, 2023).

It has been suggested that the clinical course of PAH is less predictable in children than in adults. If untreated, the condition may progress more rapidly in children leading to reduced survival in children compared to adults over time.

The key predictors of adverse outcome identified in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry (ClinicalTrials.gov Identifier: NCT02610660) include young age, etiology, WHO FC, and a set of hemodynamic predictors.

2.1.5. Management

Pharmacological approaches are divided into those regarded as supportive or background treatment (aimed at alleviating vasoconstriction, breathlessness, and thromboembolic complications) and those that target the underlying pathophysiology. Therapies that are currently approved for the treatment of PAH in adults include prostacyclin and its analogues (epoprostenol, treprostinil, iloprost and beraprost), endothelin receptor antagonists (ERAs; bosentan, macitentan and ambrisentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat) and selective prostacyclin receptor agonist (selexipag).

The ultimate goal of treatment in children should be to improve survival and facilitate normal childhood activities without limitations. The management of children remains challenging because treatments have long depended on evidence-based adult studies and the clinical experience of paediatric experts (Humbert 2023). In the absence of randomized clinical studies in pediatric PAH patients, recommended treatment algorithms are extrapolated from those in adults and enhanced with data from observational studies in children with PAH (Humbert 2023).

At the time the TOMORROW study was designed, there was no PAH-specific therapy approved globally for use in children. To date, only 5 of 10 drugs approved for treatment of PAH in adults have also been approved for pediatric use in the EU (Table 1). Although survival rates are now slightly improved when compared to historical cohorts, outcome in paediatric PAH in the current management is still poor (Ploegstra 2023).

Table 1. Drugs Approved for Treatment of Pediatric Patients with PAH

Therapy	Medicines	Administration/ Dosing Frequency	Approval in EU: Age category/Approval Date	Approval in US: Age category/Approval Date
Endothelin receptor blockers	Bosentan (Tracleer®)	Oral Twice daily	≥1 year of age and older (recommendation)/ 06 Feb 2015	≥3 years of age and older 05 Sep 2017
	Ambrisentan (Volibris®)	Oral Once daily	≥8 to less than 18 years of age/ 22 Sept 2021	NA
PDE-5i	Sildenafil (Revatio®/ Granpidam®)	Oral Three times a day	≥1 to <18 years of age/ 14 Nov 2016	≥1 to <18 years of age (WHO Group 1) 31 Jan 2023
	Tadalafil (Adcirca®)	Oral Once daily	≥2 years of age/ 24 Feb 2023	NA
Soluble guanylate cyclase stimulator	Riociguat (Adempas®)	Oral Three times a day	<18 years of age and ≥50 kg and in combination with ERAs/ 01 June 2023	NA

Sequential combination therapy is the most widely utilised strategy both in RCTs and in clinical practice: from monotherapy with a PDE5-i or ERA, there is an addition of a second (ERA+PDE5i) and then a third drug (normally a prostanoid) in cases of inadequate clinical results or in cases of deterioration [Humbert 2023].

Despite therapies approved, pediatric PAH is still a complex condition associated with significant morbidity and mortality [Hansmann 2016, Ploegstra 2023] and the unmet medical need in pediatric PAH remains high.

2.2. About the product

Macitentan (OPSUMIT®) is an orally active, nonpeptide, potent dual ERA (ETA and ETB). In PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

Macitentan belongs to the pharmacotherapeutic group of antihypertensives, antihypertensives for PAH. [ATC code: C02KX04].

Macitentan is currently approved in the EU as 10 mg film-coated tablet for oral use, as monotherapy or in combination, for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, based on data generated in a long-term Phase 3 study (AC-055-302/SERAPHIN). Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

The claimed extension of therapeutic indication in paediatric population is as monotherapy or in combination, for the long-term treatment PAH in paediatric patients aged 2 years to less than 18 years of age of WHO Functional Class (FC) II to III.

This extension of the marketing authorisation seeks the approval of a new pharmaceutical form (dispersible tablets) with one new strength (2.5 mg) intended to treat paediatric patients.

2.3. The development programme/compliance with guidance/scientific advice

The following clinical studies in paediatric participants as well as extrapolation, modelling, and simulation studies were planned to be conducted:

- Study AC-055-312/**TOMORROW** (hereafter referred to as 'TOMORROW'): PK, safety, and efficacy study in children with PAH from ≥1 month to <18 years of age. **[PIP Study 8]**
- Study 67896062**PAH1013** (hereafter referred to as 'PAH1013'): PK and safety study in children with PAH from ≥1 month to <2 years of age. **[PIP Study 11].** At time of the submission, no patients were enrolled.
- Study 67896062**PAH3001** (hereafter referred to as 'PAH3001'): PK and safety study in Japanese children with PAH from 3 months to <15 years of age.

Extrapolation, modelling, and simulation studies:

- Population PK modelling and simulation study: based on results from the pediatric TOMORROW and PAH1013 studies and the adult AC-055-302/SERAPHIN (hereafter referred to as 'SERAPHIN') study. **[PIP Study 9]**
- Pharmacodynamic similarity assessment of data from the adult SERAPHIN study and the paediatric TOMORROW study for extrapolation of efficacy. **[PIP Study 10]**

Part 1: including TOMORROW participants ≥2 years of age.

Part 2: including TOMORROW and PAH3001 participants ≥1 month to <2 years of age.

- Combined descriptive analysis of PK, safety, and efficacy of macitentan in children with PAH from 1 month to less than 2 years of age (Study TOMORROW, Study PAH1013, and Study PAH3001). **[PIP Study 12]**

The application submitted is based on:

- All PK, safety, and efficacy data collected during the completed Core Period of the **TOMORROW study** for participants ⩾**2 years** of age and older and for participants ⩾**1 month to <2 years** of age.
- The **interim** PK, safety and efficacy data of **study PAH3001** (up to Week 24 visit for the first 2 enrolled participants <2 years of age) for participants **≥3 months to <2 years of age in Japan**.
- **Population PK modelling and simulation study** based on results from the pediatric TOMORROW study (full data set of the completed Core Period), Study PAH3001 (up to the Week 24 visit for the first 2 enrolled participants <2 years of age) and the adult SERAPHIN study.
- **Pharmacodynamic similarity assessment of** data from the adult SERAPHIN study and the completed Core Period of the paediatric TOMORROW study **(≥2 years of age**) for extrapolation of efficacy data.
- **Pharmacodynamic similarity assessment** of macitentan treatment using combined data from participants ≥1 month to <2 years of age (from the completed Core Period of TOMORROW and up to the Week 24 visit of PAH3001), data from participants ≥2 to <18 years of age (from the completed Core Period of TOMORROW), and adult data from the SERAPHIN study.
- The **combined descriptive analysis** of PK, safety, and efficacy of macitentan in participants from **1 month to less than 2 years** of age based on data from the TOMORROW and PAH3001(up to the Week 24 visit) studies. Note that the PAH1013 study has been terminated and no participants have been enrolled.
- **Safety data of adolescent participants** (≥12 to <18 years of age at the time of enrolment) randomized to macitentan in the completed SERAPHIN, MAESTRO, and RUBATO studies are also presented for evaluation. **Safety** events collected **by pharmacovigilance during post-marketing** use of macitentan from the GMS Global Safety database and literature data were also used as supportive safety data.

To support the development of macitentan in the paediatric population, the Applicant requested EMA SA on multiple occasions.

- On 26 February 2015 the Applicant received SA on the following clinical and quality aspects (EMA/CHMP/SAWP/92854/2015):

- The adequacy of a new clinical study to assess the long-term efficacy and safety of macitentan in all subsets of the paediatric PAH.

The study design, proposed population, dosing strategies and endpoints were discussed. The Applicant emphasized their ambition to perform a large clinical mortality/morbidity study in paediatrics, which would be more informative regarding the benefit risk of macitentan in this population than the previous agreed PK/PD study. Although there were issues that deserved some discussion, the CHMP agreed with the proposed outcome study and acknowledged the value of a dedicated paediatric study, even with the known similarities between adult and paediatric PAH. Of noted, it was emphasized that minimising differences in assessed endpoints from the SERAPHIN

study would facilitate bridging of the adult data/indication during assessment of the paediatric indication. In addition, it was remarked that experience in paediatric patients included SERAPHIN study should be further evaluated and discussed, especially, the issue that a high dropout rate was encountered in this population.

- On 24 June 2021 the Applicant received SA on the following clinical and quality aspects (EMADOC-1700519818-693396):
  - Acceptability of proposed clinical formulation bridging strategy.

The CHMP concluded that the switch of the clinical Phase 3 formulation to the FMI formulation for all subjects on macitentan in the ongoing Phase 3 study could be acceptable, provided that the issues discussed during SA were addressed at the time of MAA. In addition, it was remarked that the bridging approach between the two paediatric formulations, discussed within the SA, would be acceptable assuming the efficacy in the paediatric population was demonstrated based on clinical data from the ongoing paediatric Phase 3 study. It was understood that the ongoing paediatric Phase 3 study (AC-055-312) was an efficacy study. If extrapolation of efficacy from the adult to the paediatric population is planned (based on safety, PK and PD data from the current paediatric study), bioequivalence of the to-be-marketed paediatric formulation and the adult formulation should be demonstrated.

- On 19 May 2022 the Applicant received SA on the following clinical aspects (EMADOC-360526170-1051035):

Acceptability of dissolution method proposed for quality control release and stability testing of dispersible tablet formulations 1 mg and 2.5 mg.

2.4. Quality aspects

2.4.1. Introduction

This line extension application for Opsumit is to register a new pharmaceutical form (dispersible tablets) to support extension of the therapeutic indication in paediatric patients aged 2 years to less than 18 years with pulmonary arterial hypertension.

The finished product is presented as an immediate-release dispersible tablet for oral administration containing 2.5 mg of macitentan as active substance.

Other ingredients are: mannitol (E421), isomalt (E953), croscarmellose sodium (E468) and magnesium stearate (E470b).

The product is available in an aluminium cold-form film blister with integrated desiccant and an aluminium push-through lidding foil.

2.4.2. Active Substance

No new information has been provided on the active substance (AS) with this line extension. The new presentation uses active substance of the same quality as used in the approved presentations film coated tablets and the active substance is manufactured by the approved manufacturing sites. Therefore, the information is not needed for the assessment of this line extension.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is an immediate-release dispersible tablet for oral administration The tablet appears as white to almost white, round tablet, approx. 9 mm diameter, debossed with a "2.5" on one side and with “Mn” on the other side. Macitentan is currently commercially available as an immediate release, film-coated tablet containing 10 mg of the active substance (under the trade name Opsumit).

An age-appropriate, uncoated, immediate-release, dispersible tablet formulation for oral administration of macitentan has been developed for the paediatric population. It contains the same active substance (AS) as the approved Opsumit. The AS is blended with the excipients, followed by compression to give the final proposed commercial formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. None of the excipients are of human or animal origin and there are no novel excipients used in the finished product. The choice, characteristics and function of the excipients have been discussed. Compatibility of the AS with the excipients has been demonstrated in formulation development studies and long-term stability studies.

Furthermore, in accordance with the *CHMP Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)*, these excipients have been evaluated and found suitable for paediatric use. All excipients are used at levels that result in an acceptable daily exposure for the paediatric population. The list of excipients is included in section 6.1 of the SmPC.

Key physicochemical characteristics were adequately evaluated and the potential effect on the relevant properties are considered according to the ICH Q8 Guideline. According to ICH M9 Biopharmaceutical Classification System (BCS), macitentan is classified as a BCS Class 2 compound with low aqueous solubility and high intestinal permeability, for a maximum dose of 10 mg per intake. The AS is manufactured in compliance with its approved specifications and the same thermodynamically stable solid form is used.

The FP manufacturing conditions have been proven not to induce polymorphic conversion of the AS as confirmed by solid state analysis of the FP batches. Also, no polymorph conversion is observed in the stability studies under ICH conditions when the product is stored in the commercial packaging.

The quality target product profile (QTPP) for the commercial paediatric formulation was defined as an immediate-release dispersible tablet, containing 1 or 2.5 mg of macitentan, dosing a maximum of 4 tablets a day, enabling a daily dose of 10 mg. It is clarified that the 1 mg strength is not intended for marketing in the EU.

Different formulation concepts were explored and evaluated in clinical studies before selecting the final commercial paediatric formulation, from initial phase 3 formulations to a final phase 3 for commercial paediatric formulations.

The robustness of the final commercial formulation towards excipient composition has been verified. The formulation composition and process were optimised, leading to the final phase 3/commercial formulation that was used in the final stages of the clinical study.

In support of the *in vivo* study, an *in vitro* comparison is performed between Opsumit film coated tablets and the final phase 3/commercial formulation dispersible tablets 2.5 mg. Since both

(reference Opsumit film coated tablets and commercial formulation dispersible tablets 2.5 mg) have a different QC method due to the difference in formulation and manufacturing process, the assessment of *in vitro* similarity was only performed in multi-pH media. The 2.5 mg paediatric formulation can be considered *in vitro* similar to the adult 10 mg Opsumit film coated tablets formulation in the 3 physiological pH dissolution media. No overages are used in the FP manufacture.

Dissolution is the quality attribute most likely to impact the bioavailability of the FP. A dissolution method has been developed for quality control (QC) during release and stability testing of the FP, and to ensure batch-to-batch consistency. The selection of dissolution parameters was adequately discussed.

In support of the *in vivo* study, an *in vitro* comparison is performed between Opsumit film coated tablets and the final phase 3/commercial formulation dispersible tablets 2.5 mg. Since both (reference Opsumit film coated tablets and commercial formulation dispersible tablets 2.5 mg) have a different QC method due to the difference in formulation and manufacturing process, the assessment of *in vitro* similarity was only performed in multi-pH media. The 2.5 mg paediatric formulation can be considered *in vitro* similar to the adult 10 mg Opsumit film coated tablets formulation in the 3 physiological pH dissolution media. No overages are used in the FP manufacture.

Dissolution is the quality attribute most likely to impact the bioavailability of the FP. A dissolution method has been developed for quality control (QC) during release and stability testing of the FP, and to ensure batch-to-batch consistency. The selection of dissolution parameters was adequately discussed. The discriminating capabilities of the proposed dissolution method was investigated testing different product batches manufactured with varied process parameters, with varied AS quality attributes and varied FP composition. The discriminative power of the dissolution method has been demonstrated when varying AS quality attributes and this was considered satisfactory.

The dispersible tablets are intended to be administered as a dispersion in drinking water. Studies were conducted to assess the suitability of water as a vehicle for the administration using the administration procedures proposed in the product information/labelling.

The dispersed tablets are tested after a defined timeframe when stored at room temperature to evaluate the chemical stability of the product. Furthermore, studies are conducted to evaluate the administration procedure via spoon and glass beaker with the dose accuracy test.

The compatibility of the selected vehicle with the FP was tested with a dedicated in-use study. The applicant states that after 2 hours of storage in the glass beaker all results are within the specified acceptance criteria and the results demonstrate that there is no or negligible impact of the preparation in water on the performance of the product, and that water is a suitable vehicle to disperse the FP when administered with a glass beaker or spoon.

The UPLC method used to test the intact tablets for assay and purity is the same used for the tablets dispersed in water. Complementary partial validation activities have been conducted for testing the tablets dispersed in water, whose specificity chromatograms, quantitation and detection limit, linearity plots and stability of solution information are also provided. Therefore, the complementary validation is acceptable.

The FP manufacturing process of Macitentan 2.5 mg dispersible tablets consists of a conventional direct compression process constituted of a premixing step, followed by blending and compression steps.

A science-based criticality analysis approach to determine the critical controls for FP manufacturing processes has been developed. This approach assigns criticality based on process parameter and material attribute impact on product Critical Quality Attributes (CQAs). The CQAs were derived from the Quality Target Product Profile (QTPP) and patient impact (safety, efficacy, and therapy compliance).

A criticality assessment of quality attributes was performed, during which the quality attributes were evaluated and ranked according to the severity of their impact on patient safety and efficacy, and the degree of knowledge uncertainty in the severity ranking. Nevertheless, a Design space has not been requested.

After process optimisation and characterisation, the primary stability batches were manufactured at commercial scale and are fully representative of the commercial batches.

The selected primary container closure system for commercial supply consists of an aluminium cold-form film blister with integrated desiccant and an aluminium push-through lidding foil. The compatibility of the primary packaging materials of the container closure system with the FP is demonstrated by the stability data. The composition of the desiccant was provided. There is no chemical interaction of the desiccant with the medicinal product.

The product contact layer of both materials meets the requirements of *EU regulation No 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food*.

2.4.3.2. Manufacture of the product and process controls

The FP manufacturing process of Macitentan 2.5 mg dispersible tablets consists of a 6 step conventional direct compression process including a premixing step, followed by blending and compression steps.

The bulk stability data for dispersible tablets packed support the claimed holding time for the bulk product. Compliance with the *NfG on Start of shelf-life of the finished dosage form* has been confirmed.

Process validation data from three commercial scale batches (covering also the 1 mg strength) has been presented. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

2.4.3.3. Product specification

The finished product release and shelf life specifications, include appropriate tests for this kind of dosage form: appearance (visual), tablet dimension, identification of macitentan (UHPLC, UHPLC/UV), assay (UHPLC), chromatographic purity (UHPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur., HPLC/UV), disintegration time (Ph. Eur.), water content (KF), fineness of dispersion (Ph. Eur.) and microbial purity (Ph. Eur.).
The specifications for release and stability testing of the FP have been established in accordance with *ICH Q6A*. The proposed test and limits are acceptable.

A risk assessment regarding the potential presence of elemental impurities in the FP has been conducted in accordance with the *ICH Q3D Guideline* considering potential contributions from the AS, excipients, manufacturing equipment, container closure system (primary packaging), and processing water. From this component-based risk assessment, supplemented with analytical screening, it can be concluded that none of the elemental impurities assessed are expected to exceed their corresponding control thresholds in the FP. The information on the control of

elemental impurities is satisfactory. The manufacturing process and analytical controls in place are considered adequate to assure that the levels of the elemental impurities in the finished product do not exceed the permitted levels. It is thus not necessary to include any elemental impurity controls in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual 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) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).A summary of the nitrosamine risk assessment is presented; the documentation has been provided and is considered adequate. The conclusion is that there is no combined presence of amine functionality and nitrites in the final FP, therefore, there is no safety risk. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

A The analytical methods used have been adequately described and not pharmacopoeial methods were appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch results for 15 commercial scale and 20 smaller batches were provided. Batch data from the 1 mg strength batches was also provided. All the results comply with the specifications, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification

2.4.3.4. Stability of the product

Stability data from 3 commercial-scale batches of FP stored for up to 12 months under long term conditions (25 °C / 60% RH), under intermediate conditions (30 °C/ 65% RH) for up to 12 months and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data were also provided for three full scale batches of the 1 mg strength (same blend) which is not intended for marketing in the EU. Results up to 12 months at long-term and intermediate conditions and up to 6 months at accelerated conditions are provided. Regarding shelf-life and storage conditions, all stability batches comply with the definitive specifications.

Samples were tested for appearance, assay, chromatographic purity, dissolution, disintegration time, fineness of dispersion and microbiological purity. The analytical procedures are the same used for release and were shown to be stability indicating.

Forced degradation studies under stress conditions were performed on placebo and one pilot FP batch. The results obtained indicate a varied degradation profile of the AS in the product depending on the tested stress conditions. Moreover, photostability was also studied in line with the ICH guideline. The FP also remains stable when exposed to light when stored in the primary packaging.

Based on available stability data, the proposed shelf-life of 2 years without special temperature storage conditions but with the condition "Store in original package to protect from moisture" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

No materials of human or animal origin are used in the manufacturing of the finished product

2.4.4. Discussion on chemical, pharmaceutical and biological 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.

2.4.5. Conclusions on the chemical, pharmaceutical and biological 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.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Macitentan was approved under the trade name Opsumit by the EMA in 2013 at a recommended dose of 10 mg once daily for the long-term treatment of adult PAH patients.

The marketing authorisation holder (MAH), Janssen Cilag International NV is requesting a variation in the terms of the authorisation of Opsumit. This application is for a pediatric line extension of macitentan, as monotherapy or in combination, for the long-term treatment of PAH in children aged 2 years to less than 18 years of age. The proposed dosing regimen for macitentan in pediatric patients achieves similar exposure as observed in adults receiving a 10 mg daily dose.

No non-clinical development programme to support the pediatric program included in this application has been provided. This extension application is supported by the nonclinical information that supported macitentan (Opsumit for adult use, which was previously provided under procedure number H0002697).

The nonclinical program consisted of studies on pharmacology (pharmacodynamics and safety pharmacology), pharmacokinetics and drug metabolism, single- and repeat-dose toxicity, carcinogenicity, genotoxicity, reproductive and developmental toxicity including juvenile toxicity, and phototoxicity.

2.5.2. Pharmacology

No additional nonclinical pharmacology studies have been submitted.

2.5.3. Pharmacokinetics

No additional nonclinical toxicity studies have been submitted.

2.5.4. Toxicology

No additional nonclinical toxicity studies have been submitted.

2.5.5. Ecotoxicity/environmental risk assessment

The MAH has submitted an ERA based on the EMEA 2006 guideline (EMEA/CHMP/SWP/4447/00 corr 2) that includes a screening assessment of the PBT of macitentan based on an experimentally determined n-octanol/water partition coefficient (log K_{OW}), the calculnitation of the predicted environmental concentration ($PEC_{SURFACEWATER}$) for the use of the product by the adult population (F_{PEN} from the most recent OD from the COMP), $PEC_{SURFACEWATER}$ for the use of the product by the paediatric population (F_{PEN} from Leber 2021) and total $PEC_{SURFACEWATER}$ (adult+paediatric) and a comparison to the threshold of 0.01 µg/L set by the EMA for further assessment.

In Phase I, the predicted environmental concentration (PEC) calculation is restricted to the aquatic compartment and it should be calculated using the following formula:

$$PEC_{surfacewater} = (DOSEai \times Fpen) / (WASTEW_{inhab} \times DILUTION)$$

*where, DOSE*ai = 10 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1}, default)

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (-)

Using the prevalence of 1.4/10,000 in the recommended OD, a refined F_{PEN} of 0.00014 can be determined for the adult population:

F_{PEN} Percentage of market penetration (= 0.00014).

Leading to the following PECsw for adults:

$$PEC_{SURFACE\ WATER} = 0.0007\ \mu g/L$$

The scope of this variation is extension of the indication for Opsumit as treatment of PAH in paediatric patients of age ≥ 1 month to ≥ 24 months.

Doses of 1 to 2.5 mg are proposed for the treatment of pediatrics ⩾ 1 and < 6 months and ⩾ 6 months to <24 months, respectively.

Doses of 3.5 mg, 5.0 mg and 7.5 mg are proposed for pediatrics in the body weight range ⩾ 10 kg and <15 kg: ⩾ 15 kg and <25 kg and ⩾ 25 kg and <50 kg, respectively.

The adult dose (10 mg/day) is proposed for pediatrics ⩾ 50 kg. Therefore, the use of Opsumit in paediatric population does not change the maximum daily dosage (10 mg for adults and children).

The prevalence of PAH in pediatric population is estimated to be in the range of 3.7 to 20 patient per million (ppm) (Leber et al. 2021). Consequently, a market penetration factor F_{pen} of 0.0001 can be calculated as follows:

$$F_{pen} = P_{REGION} (T_{TREATMENT} X \eta_{TREATMENT,P} / N_D)$$

Where:

F_{PEN}: Market penetration factor.

P_{REGION}: Prevalence in the region (worst-case 20/1000000).

$T_{TREATMENT}$: Duration of one treatment period (assumed to 365 days/year for a conservative estimate).

$\eta_{TREATMENT}$: Number of treatment periods per year (since the treatment is assumed to continue throughout the year, this is considered to be 1).

N_D: Number of days per year (365 days)

Hence,

$$F_{PEN} = 0.00002 \times [(365 \times 1) /365] = 0.00002$$

This refined F_{pen} value (0.00002) value, considering only the paediatric population, is used in the PEC calculation instead of the EMEA default value of 0.01.

$$\text{Thus, } PEC_{surfacewater} = 10 \times 0.00002 \times 10^3 / 200 \times 10 = 0.0001 \text{ µg/L}$$

Therefore, this value added to the $PEC_{surfacewater}$ for the adult population generates a total $PEC_{surfacewater}$ of 0.0008 µg/L (i.e., 0.0007 + 0.0001 µg/L). Although this represents an increase, the $PEC_{surfacewater}$ of 0.0008 µg/L is approximately one order of magnitude below the EMA action limit of 0.01 µg/L.

Summary of main study

Substance (INN/Invented Name): Macitentan			
CAS-number (if available): 441798-33-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	3.91	Potential PBT: N
PBT-statement :	Macitentan is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined	0.0008	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Upon request, the applicant has provided an updated ERA consisting of a phase I with a $PEC_{surfacewater}$ calculated using a refined Fpen of 0.00014 for adult population (>12 years) from the original application (EMEA/H/C/002697/0000) supplemented with a $PEC_{surfacewater}$ covering the current extension for paediatric patients. A PBT assessment that should be part of phase I was missing but the Applicant provided a study (Tarran, 2013) where the log K_{ow} was determined using the slow-stir method in accordance with OECD No.123. The molecule was brought into neutral form. The log K_{ow} (average of 3 values) was 3.91. As the value is below the trigger value of 4.5, it can be concluded that macitentan is not a PBT substance. The $PEC_{surfacewater}$ for the paediatric

patients has been refined using prevalence data, the reference for this refinement (Leber 2021 paper) has been provided by the Applicant (see References):

2.5.7. Conclusion on the non-clinical aspects

Macitentan is already used in existing marketed products and no significant increase in environmental exposure is anticipated as $PEC_{surfacewater}$ for macitentan is below the action limit of 0.01 µg/L and macitentan is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore macitentan is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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

Analytical methods

For the quantification of plasma concentrations of macitentan and its active metabolite aprocitentan, LC-MS/MS methods were developed at Swiss Bioanalytics AG (Birsfelden, Switzerland), Actelion (Allschwil, Switzerland), and ICON, formerly PRA Health Sciences, (Assen, The Netherlands). These methods were validated and used in different studies (see Table 2).

Table 2. Bioanalytical methods used for clinical studies with PK measurements.

Study ID (Location)	Matrix	Analyte	Concentration Range (lower end of the concentration range is the LLOQ)	Method	Method Validation Report (Location)	Bioanalytical Study Number
AC-055-121	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	BA-13.225 (Mod5.3.1.4/BA-13.225)	BA-15.019 (included in CSR)
67896062PAH1008	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	BA13063 (Mod5.3.1.4/BA13063)	JJP21256-21256X-A (included in CSR)
67896062PAH1010	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	BA13063 (Mod5.3.1.4/BA13063)	JJP22213-22213X-A (included in CSR)
AC-055-303 (SERAPHIN-OL-PK Substudy)	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	SBA_S_04081 (MAA OPSUMIT/Mod5.3.1.4/ SBA_S_04081)	SBA_S_11079 (included in CSR)
AC-055-312 (TOMORROW)	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	BA13063 (Mod5.3.1.4/BA13063)	Not yet available [a]
67896062PAH3001 (Japanese Study)	Plasma Plasma	Macitentan Aprocitentan	1.00-2,000 ng/mL	LC-MS/MS	BA13063 (Mod5.3.1.4/BA13063)	Not yet available [a]

[a] The study-specific bioanalytical reports will be part of the final CSRs of the respective studies and will be available upon request once these are completed. Source: Mod5.3.1.1/67896062PAH1008; Mod5.3.1.1/AC-055-121; Mod5.3.1.2/67896062PAH1010; Mod5.3.3.2/AC-055-303PKsub; Mod5.3.5.2/AC-055-312iCSR and iCSRAdd; and Mod5.3.5.2/67896062PAH3001iCSR.

Absorption

The absorption of macitentan in adults has been described in the initial MAA. According to the MAH, the absorption of macitentan in pediatric patients is comparable to the absorption of macitentan in adults.

The MAH stated that in pediatric participants with PAH aged ≥2 years who participated in the PK substudy of Study AC-055-312, the steady-state t_{max} of macitentan was similar to that of adults with PAH who received 10 mg QD across different pediatric age and weight groups. While C_{max} appeared to be slightly lower in pediatric participants compared with the historical adult PK data, there was no clear trend.

Bioequivalence

Macitentan is currently commercially available as an immediate release, film-coated tablet containing 10 mg of the active drug substance (OPSUMIT®). An age-appropriate, uncoated, immediate-release, dispersible tablet formulation for oral administration of macitentan was developed specifically for the use in the paediatric population.

Initially, a 5-mg dispersible tablet (G013) with comparable PK to the approved OPSUMIT® 10-mg film-coated tablet (G001) was developed. To support a full paediatric dose regimen during the Phase 3 study program (AC-055-312 [TOMORROW]), 2 additional strengths were developed, a 0.5 mg (G011) and a 2.5 mg (G012) strength. According to the MAH, all 3 strengths of this formulation (G011, G012, and G013) were identical in terms of qualitative composition and similar in vitro dissolution profiles. These tablets were initially supplied as Phase 3 clinical study material (also called "Clinical Service Formulation" or "CSF")

To anticipate the commercial launch of the paediatric formulations, 2 dose-proportional formulations in excipient composition were developed by the commercial manufacturing site, using the direct compression manufacturing process, a 1 mg (G018) and a 2.5 mg (G019) strength, allowing clear visual differentiation by size, shape, and debossing. These formulations were the final Phase 3/proposed commercial formulations (also called "Final Market Images" or "FMI").

Table 1: Overview of the Formulations Developed During Clinical Stages

Formulation	Clinical Stage	Dosage Form	Strength	Tablet Weight
Initial Phase 3 Formulation (CSF)				
G011	Phase 3	Dispersible tablet	0.5 mg	50 mg
G012	Phase 3	Dispersible tablet	2.5 mg	50 mg
G013	Phase 3	Dispersible tablet	5 mg	50 mg
Final Phase 3/Commercial Formulation (FMI)				
G018	Phase 3/Commercial	Dispersible tablet	1 mg	100 mg
G019	Phase 3/Commercial	Dispersible tablet	2.5 mg	250 mg

Source: Mod3.2.P.2.2.1/Tab1

Biowaiver for additional strength

The biopharmaceutic studies evaluating the biocomparability of the CSF and FMI formulations evaluated the higher 2.5 mg strength of the FMI only. An additional evaluation of the lower 1 mg strength was not considered necessary by the MAH, based on the following arguments:

- The PK of macitentan is dose-proportional in the dose range of 1 to 30 mg upon multiple dosing.
- The 2.5 mg (G019) and 1 mg (G018) FMIs are dose-proportional formulations.

- Both strengths are immediate-release tablets with systemic action produced according to the same conventional manufacturing process (direct compression).
- Both strengths were in-vitro similar in 3 different pH media, as well as based on the proposed QC method.

The sponsor requested a biowaiver for the 1 mg strength of the final Phase 3/commercial formulation (G018).

In summary, three clinical Phase 1 studies have been conducted in healthy adults to assess the biocomparability of the different formulations used:

- Study AC-055-121: an open-label, single-dose, randomized, 2-treatment crossover Phase 1 study to assess the biocomparability of the adult film-coated tablet (OPSUMIT®) and CSF paediatric dispersible tablet (G013) formulation of macitentan.
- Study PAH1008: an open-label, single-dose, randomized, 2-way crossover Phase 1 study to assess the relative oral bioavailability of the FMI (G019) and CSF paediatric formulations (G013).
- Study PAH1010: an open-label, single-dose, randomized, 2-way crossover Phase 1 study to assess the bioequivalence of the FMI macitentan tablet (G019) and the approved film-coated tablet (OPSUMIT®).

AC-055-121: Single-center, open-label, randomized, two-treatment, single-dose, crossover study in healthy subjects to investigate the biocomparison of the adult and pediatric formulation of macitentan.

Subjects were randomized to one of two possible treatment sequences A/B or B/A, where A was the adult formulation (single 10 mg dose of macitentan) and B was the paediatric formulation (2x5 mg dispersible tablets).

Further information is listed below:

Protocol approval date	4 May 2015
IEC approval of protocol	25 May 2015
Period clinical study	8 September 2015 - 19 October 2015
Principal Investigator	
Clinical facility	CEPHA s.r.o.,
Bioanalytical facility	Actelion Pharmaceuticals Ltd., Allschwil, Switzerland

Certificates of analysis were provided for both test and reference formulations.

Method of administration

The adult formulation film-coated tablet was given with 240 mL of water to subjects in the sitting position on an empty stomach.

The paediatric formulation was suspended in a tablespoon of water, approximately 10 to 15 mL taken from the 240 mL, for 1 min. The subject was administered the suspended study drug, followed by drinking the remaining water in the sitting position on an empty stomach.

Population studied

All 12 subjects completed the study according to protocol and were therefore included in the statistical analysis.

Pharmacokinetic variables

The plasma PK parameters of macitentan and its active metabolite ACT-132577 were derived by non-compartmental analysis of the plasma concentration-time profiles.

The measured individual plasma concentrations of macitentan and ACT-132577 were used to directly obtain Cmax and tmax. AUC was calculated according to the linear trapezoidal rule, using the measured concentration-time values above the LOQ. Values below LOQ were set to zero. $AUC_{0-\infty}$ was calculated by combining AUC_{0-t} and AUC_{extra}. The AUC_{extra} represents an extrapolated value obtained by Ct/λz, where Ct is the last concentration above the LOQ and λz represents the terminal elimination rate constant determined by log-linear regression analysis of the measured plasma concentrations in the terminal elimination phase.

Statistical analysis

SAS® software, version 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analysis and the reporting of clinical and PK data.

The paediatric and adult formulation treatments were compared via mixed-effects model using log-transformed values of the endpoint as dependent variable, treatment, treatment sequence, and period as fixed effect and subject nested within sequence as random effect. Geometric mean ratios (test/reference) and 90% CI were calculated from the corresponding back-transformed least-square means for period of the mixed-effects models.

Difference in Tmax between paediatric and adult formulation treatments was explored using the nonparametric Wilcoxon signed rank test and Hodges-Lehmann's estimates of the median differences (test-reference) and their 90% CIs.

The period and carry-over effects were investigated using the mixed model.

Results

All pre-dose concentrations were below the limit of quantification for both macitentan and ACT-132577.

Tmax was not observed in the first sampling point for neither macitentan nor ACT-132577.

The percentage of extrapolated AUC was below 20% for all subjects, for both macitentan and aprocitentan.

A summary of the main pharmacokinetic parameters of macitentan is shown in Table 11-1.

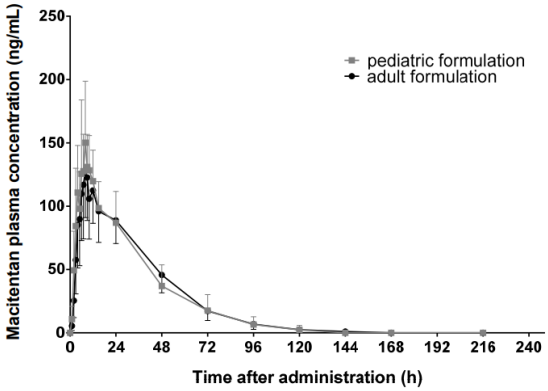
Table 11-1 Summary of the main pharmacokinetic parameters of macitentan by treatment

Parameter [unit]	Statistics	Treatment A	Treatment B
C_{max} [ng/mL]	N/missing	12/0	12/0
	Geometric mean	130.80	149.12
	95% CI of geometric mean	110.20,155.24	125.30,177.48
$t_{1/2}$ [h]	N/missing	12/0	12/0
	Geometric mean	16.711	16.357
	95% CI of geometric mean	14.737,18.948	14.402,18.579
AUC_{0-t} [ng·h/mL]	N/missing	12/0	12/0
	Geometric mean	4829.45	4705.52
	95% CI of geometric mean	4125.42,5653.62	3814.47,5804.72
$AUC_{0-\infty}$ [ng·h/mL]	N/missing	12/0	12/0
	Geometric mean	4873.86	4747.47
	95% CI of geometric mean	4168.05,5699.18	3852.50,5850.35
t_{max} [h]	N/missing	12/0	12/0
	Median	8.00	8.00
	Min,Max	7.0,12.0	6.1,12.0

Treatments: A = adult (reference) macitentan formulation, B = pediatric (test) macitentan formulation
Pharmacokinetic set. Source: Table PKS1 [Table 15-9]
Production date: 08DEC2015
AUC_{0-t} = area under plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification; $AUC_{0-\infty}$= area under plasma concentration-time curve from time zero to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration.

The mean plasma concentration-time curves for macitentan are shown in Figure 11-1.

Figure 11-1 Arithmetic mean (+SD) plasma concentration versus time profiles of macitentan (upper) and ACT-132577 (lower) after administration of the adult macitentan formulation (Treatment A) and after administration of the pediatric macitentan formulation (Treatment B)



Linear and semilogarithmic scale individual profiles were provided for both macitentan and its active metabolite.

Results of the statistical analysis for macitentan is shown in Table 11-3 below.

Table 11-3 Comparison of the main PK parameters for macitentan

Parameter	Statistics	
C_{max}	N/missing	12/0
	Ratio of geometric means (B/A)	1.140
	90% CI of the ratio	1.0420,1.2475
	p-value	0.025
AUC_{0-t}	N/missing	12/0
	Ratio of geometric means (B/A)	0.974
	90% CI of the ratio	0.9009,1.0537
	p-value	0.561
$AUC_{0-\infty}$	N/missing	12/0
	Ratio of geometric means (B/A)	0.974
	90% CI of the ratio	0.9018,1.0522
	p-value	0.551
$t_{1/2}$	N/missing	12/0
	Ratio of geometric means (B/A)	0.979
	90% CI of the ratio	0.9186,1.0431
	p-value	0.556
t_{max} [h]	N/missing	12/0
	Median (B-A)	0.000
	90% CI of the ratio	-0.5000,0.5000
	p-value	1.000

Treatments: A = adult (reference) macitentan formulation, B = pediatric (test) macitentan formulation
Pharmacokinetic set. Source: Table PK_TEST1 [Table 15-11]
Production date: 08DEC2015
AUC_{0-t} = area under plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification; $AUC_{0-\infty}$= area under plasma concentration-time curve from time zero to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration.

Concomitant medication

No concomitant medications were taken by subjects during the study.

PAH1008: **Single-center, open-label, single-dose, randomized, 2-way crossover phase 1 study in healthy adult participants to assess the relative oral bioavailability of two macitentan pediatric formulations.**

Subjects were randomized to one of two possible treatment sequences A-B or B-A according to a 2-sequence, 2-period design. For each participant, 2 treatments (A and B) were planned, 1 in each treatment period. In Treatment A (test), participants were administered a single oral dose of 10 mg macitentan formulated as FMI. In Treatment B (reference), participants received a single oral dose of 10 mg macitentan as the CSF.

Further information is listed below:

Protocol approval date: 21 September 2021

IEC approval protocol: 2 March 2022

Period clinical study: 8th July 2021 – 5th October 2021

Principal investigator:

Clinical facility: Belgium (not specified)

Bio-analysis: PRA Health Sciences

Statistics: SGS Belgium

Certificates of analysis were provided for both test and reference formulations.

Method of administration

The formulation of study interventions (FMI and CSF) was suspended in a tablespoon of water, approximately 10 to 15 mL taken from 240 mL, for 5 min. The participants were administered the suspended study intervention, followed by drinking the remaining water in sitting position. Intake took place after at least 10 hours of fasting. Intake of water was not allowed from approximately 1 hour before until approximately 1 hour after study intervention intake (except for the water used for study intervention intake). No food was allowed for at least 4 hours postdose.

Population studied

A total of 16 healthy, male and female subjects were enrolled. Two participants, randomized to treatment sequence A-B, terminated study participation prematurely discontinued due to physician decision (1 participant; positive cocaine screening test) and withdrawal by participant (1 participant; personal reasons). As only paired observations for test and reference were to be included in the statistical analysis for this study, the 2 participants with missing Treatment B data were excluded from the inferential statistical analysis.

Pharmacokinetic variables

For each treatment, descriptive statistics were calculated for plasma concentrations of macitentan and its metabolite ACT-132577 at each applicable timepoint specified, and for the derived plasma PK parameters.

Statistics included sample size (n), mean, standard deviation (SD), CV, geometric mean, median, minimum, and maximum, except for the actual sampling time to reach the maximum observed plasma analyte concentration (t_{max}) and the actual sampling time of last measurable plasma analyte concentration (t_{last}) for which only n, median, minimum and maximum values were presented.

The inferential statistical analysis was done on log-transformed PK parameters of interest. The primary PK parameters of interest for bioavailability testing were Cmax, AUClast, and AUC∞ of macitentan and its metabolite ACT-132577.

No information was provided on the method of AUC calculation.

Statistical analysis

The mixed-effects model was used only to obtain the estimated least squares (LS) means, variances, and confidence intervals (CIs) for the difference between the 2 treatments. Thus, the purpose of the model was to obtain model-based CIs. Only paired observations for test and reference were included in the statistical analysis.

The LS means of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed-effects analysis of variance (ANOVA) model, with treatment, treatment sequence, and period as fixed effects, and participant as a random effect. A 90% CI was constructed for the difference between the LS means of Treatment A (test) and Treatment B (reference). Both the difference between the LS means and the 90% CIs were retransformed to the original scale to provide relative bioavailability estimates, ie, obtain an estimated ratio of geometric means and corresponding 90% CIs.

Results

Macitentan pre-dose concentrations for both treatments were below the limit of quantification (BLQ), however, predose ACT-132577 (aprocitentan) concentrations in period 2 of both treatments were quantifiable in 13 of 14 participants, and 4 of them had predose concentrations higher than 5% of the corresponding Cmax.

The percentage of extrapolated AUC was below 20% for all subjects, for both macitentan and aprocitentan.

Table 3. Pharmacokinetic Results of Macitentan After Single Oral Dose of 10 mg of Macitentan Formulated as Final Market Image (FMI) (Treatment A, Test) and of Macitentan as the Clinical Service Formulation (CSF) (Treatment B, Reference) in Fasted Conditions; PK Population (Study 67896062PAH1008)

Pharmacokinetics of Macitentan mean (SD), t_{max}: median (range)	Treatment A (Test)	Treatment B (Reference)
n	16	14
C_{max} (ng/mL)	160 (37.6)	179 (36.7)
t_{max} (h)	8.50 (5.00 - 15.00)	8.50 (7.00 - 15.00)
C_{last} (ng/mL)	3.63 (2.88)	4.28 (2.90)
AUC_{72h} (ng.h/mL)	4,755 (948)	4,756 (829)
AUC_{last} (ng.h/mL)	5,033 (1,156)	4,987 (1,045)
AUC_{∞} (ng.h/mL)	5,111 (1,131)	5,083 (1,051)
$t_{1/2}$ (h)	14.9 (3.1)	15.2 (3.5)
CL/F (L/h)	2.06 (0.518)	2.05 (0.451)
Vd_z/F (L)	43.3 (10.2)	43.7 (7.98)

Treatment A: A single oral dose of 10 mg macitentan formulated as Final Market Image (FMI) (dispersible tablets, 2.5 mg per tablet [G019]) in fasted conditions
Treatment B: A single oral dose of 10 mg macitentan as the Clinical Service Formulation (CSF) (dispersible tablets, 5 mg per tablet [G013]) in fasted conditions
Cross reference: Attachment TABPK06

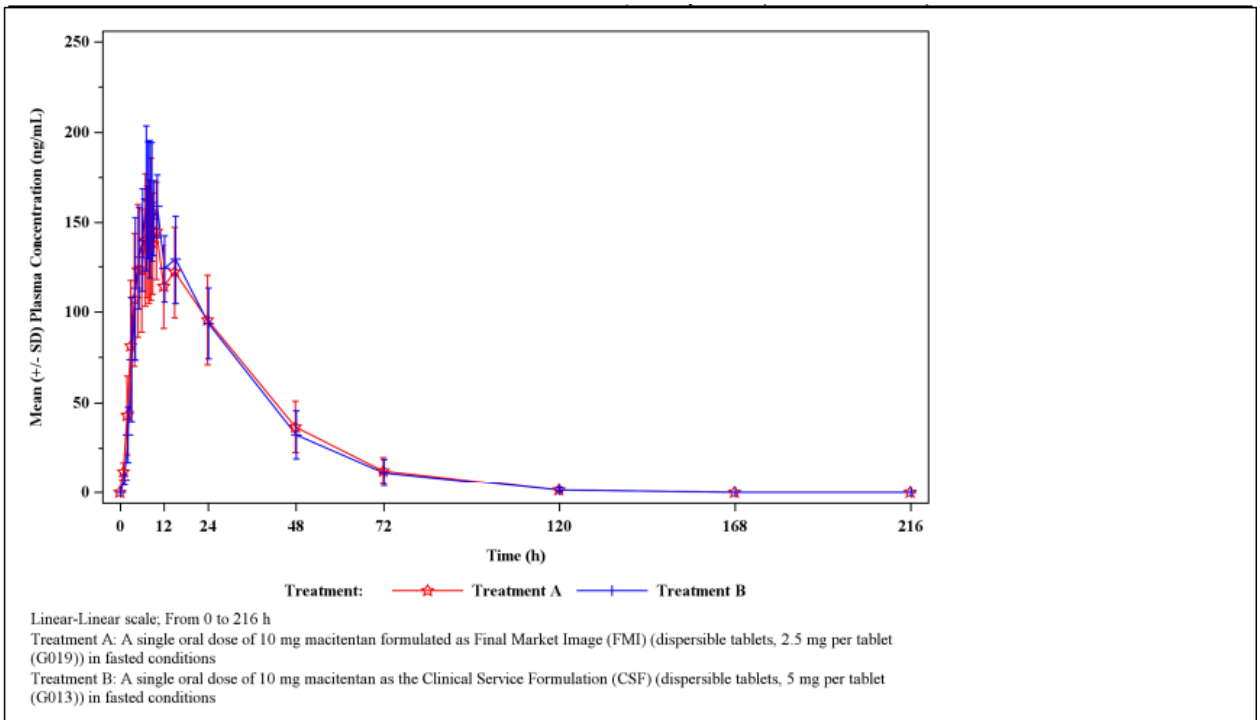
Table 4. Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Macitentan After Single Oral Dose of 10 mg of Macitentan Formulated as Final Market Image (FMI) (Treatment A, Test) and of Macitentan as the Clinical Service Formulation (CSF) (Treatment B, Reference) in Fasted Conditions; PK Population (Study 67896062PAH1008)

		Geometric LS Means		Geometric Mean Ratio (Test/Reference)				
PK Parameter (Macitentan)	N	Treatment A (Test)	Treatment B (Reference)	Ratio (%)	90% CI (%)	Intra-participant CV (%)	Inter-participant CV (%)	Post-hoc Power (%)
C_{max} (ng/mL)	14	155	176	87.76	83.58 - 92.16	7.2	19.3	94.3
AUC_{last} (ng.h/mL)	14	4,997	4,936	101.24	97.59 - 105.02	5.4	20.7	100.0
AUC_{∞} (ng.h/mL)	14	5,086	5,038	100.95	97.59 - 104.42	5.0	20.0	100.0

CI: Confidence Interval; CV: Coefficient of variation
N: number of paired observations
Test= Treatment A: A single oral dose of 10 mg macitentan formulated as Final Market Image (FMI) (dispersible tablets, 2.5 mg per tablet [G019]) in fasted conditions
Reference= Treatment B: A single oral dose of 10 mg macitentan as the Clinical Service Formulation (CSF) (dispersible tablets, 5 mg per tablet [G013]) in fasted conditions
Cross reference: Attachment TABPK12

The mean plasma concentration-time curves for macitentan are shown in Figure 5 below.

Figure 1. Mean Plasma Concentrations of Macitentan Versus Time; PK Population (67896062PAH1008)



Linear-Linear scale; From 0 to 216 h
Treatment A: A single oral dose of 10 mg macitentan formulated as Final Market Image (FMI) (dispersible tablets, 2.5 mg per tablet (G019)) in fasted conditions
Treatment B: A single oral dose of 10 mg macitentan as the Clinical Service Formulation (CSF) (dispersible tablets, 5 mg per tablet (G013)) in fasted conditions

Concomitant medication

Overall, 9 (56.3%) participants reported one or more concomitant therapies during the treatment phase. The most frequently reported concomitant medications were levonorgestrel (intrauterine contraceptive) and tozinameran (COVID-19 vaccine), each used by 3 (18.8%) participants. All other concomitant medications were not used for more than 1 participant per treatment.

Concomitant therapies due to AEs consisted of a single intake of 500 mg paracetamol for the AE headache (mild severity), on the day after a participant (randomized to Treatment Sequence A-B) received Treatment A.

PAH1010: A Single-center, Open-label, Single-dose, Randomized, 2-way Crossover Phase 1 Study in Healthy Adult Participants to Assess the Bioequivalence of the Dispersible Final Market Image (FMI) Macitentan Tablet (4 x 2.5 mg) and the Opsumit Tablet (10 mg) in Fasted Condition

This study was designed to demonstrate bioequivalence of the to-be-marketed paediatric formulation (FMI macitentan formulation [4 x 2.5 mg]) with the marketed Opsumit® tablet (10 mg) in fasted conditions.

Further information is listed below:

Protocol approval date	28 March 2022
IEC approval of protocol	11th May 2022
Period clinical study	23 June 2022 – 03 October 2022
Principal Investigator	(end date 12th July); (start date 13th July)
Clinical facility	Belgium
Bio-analysis and statistics	ICON Bioanalytical Laboratories

Certificates of analysis were provided for both test and reference formulations.

Method of administration

The adult formulation was taken orally, with approximately 240 mL of noncarbonated water.

For the paediatric formulation, the CSR indicates the following: "Refer to the pharmacy manual for guidance on the administration of study intervention". However, this document has not been found.

Population studied

A total of 28 participants was enrolled and randomly assigned to 1 of 2 treatment sequences. All 28 participants received at least 1 dose of any study intervention and all of them completed the study.

One participant was excluded from the Pharmacokinetics Data Analysis Set and the Pharmacokinetics Data Statistical Analysis Set due to a major protocol deviation (prohibited medication). Therefore, 27 participants were included in the main PK analyses. A PK sensitivity analysis was additionally done including all 28 participants.

Protocol deviations

Major protocol deviations were reported for 2 participants overall (both treatment sequence A-B):

- For 1 participant, the scheduled visits on Days 6, 8, and 10 of Period 1 were not performed on the required day as per protocol, because the participant could not attend these visits due to unexpected personal circumstances. Consequently, the 120, 168, and 216 hours post-dose PK samples were missing for this participant and treatment.
- For 1 participant, the use of prohibited medication (i.e.,) within 10 days before first study intervention administration was reported. The participant continued to use throughout the study except for when the participant was admitted to the study site during Period 1 and Period 2. The participant did not disclose the use of during the entire study period. This protocol deviation was identified upon further questioning by the investigator to review potential causes of the participant's markedly lower plasma concentrations of both macitentan and aprocitentan in Period 1 (Treatment A).

Pharmacokinetic variables

The primary parameters of interest for the statistical analysis were the log-transformed estimated AUC_{last}, AUC_{∞}, and C_{max} of macitentan.

No information was provided on the method used for AUC calculation.

Statistical analysis

The LS means of the log-transformed primary PK parameters of macitentan for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant as a random effect. A 90% CI was constructed for the difference between the LS means of Treatment A and Treatment B. Both the difference between the LS means and the 90% CIs were retransformed to the original scale to obtain an estimated ratio of geometric means and corresponding 90% CIs.

During the sensitivity analysis including a participant with a major protocol deviation (prohibited medication) and outlying PK measurements (see Section 4.2 and Section 5.1.3), the mixed model for C_{max} had convergence issues. Therefore, a one-sample t-test was conducted on the null

hypothesis that the mean difference in log C_{max} and AUCs for paired observations was equal to zero at a significance level of 0.1. The calculated mean difference and 90% CIs were converted back to the original scale by taking the anti-log, to give the GMR and 90% CIs. The one-sample t-test was performed on both data sets (with and without the participant with major protocol deviation [prohibited medication]).

Results

All participants except 1 showed quantifiable pre-dose concentrations of aprocitentan in Period 2. For 3 participants following administration of Treatment B and 1 participant following administration of Treatment A, the quantifiable pre-dose concentration of aprocitentan was greater than 5% of the corresponding C_{max}. For those 4 profiles, all PK concentrations and PK parameters of aprocitentan were excluded from the descriptive statistics. For the other profiles with quantifiable pre-dose concentrations of aprocitentan lower than 5% of the corresponding C_{max}, the data were kept in all analyses.

The extrapolated part of AUC_∞ was lower than 20% among all profiles with an estimable half-life, except for 1 profile for aprocitentan in Treatment A. Aprocitentan AUC_∞ in Treatment A as well as the treatment ratio for AUC_∞ were reported but excluded from the descriptive statistics for this participant.

For the participant with the missing 3 last samples (i.e., 120, 168, and 216 hours post-dose) in Treatment A, the following macitentan and aprocitentan PK parameters were considered unreliable due to missing concentrations: Clast, AUC_{last}, AUC_∞ (where estimable), treatment ratios for AUCs (where estimable), CL/F, and Vdz/F (both for macitentan only). Those parameters were excluded from the descriptive statistics. In addition, macitentan AUC_{last} and AUC_∞ for this participant were excluded from the inferential statistical analyses as only paired observations were included.

PK results for macitentan are shown in Table 4 and 5 below.

Table 4: Pharmacokinetic Results of Macitentan After Administration of a Single Oral Dose of 10 mg (4 x 2.5 mg) Macitentan Formulated as FMI (Treatment A) and as a Single Oral Film-coated 10 mg Opsumit® Tablet (Treatment B) in Fasted Conditions; Pharmacokinetics Data Analysis Set (67896062PAH1010)

Pharmacokinetics of Macitentan mean (SD), t_{max}: median (range)	Treatment A (test)	Treatment B (reference)
n	27[a]	27
C_{max} (ng/mL)	178 (41.7)	186 (31.3)
t_{max} (h)	9.01 (7.50 - 12.00)	8.51 (5.00 - 15.00)
AUC_{72h} (ng.h/mL)	5,435 (1,044)	5,196 (880)
C_{last} (ng/mL)	4.80 (4.04)	3.84 (2.95)
AUC_{last} (ng.h/mL)	5,839 (1,299)	5,580 (1,116)
AUC_∞ (ng.h/mL)	5,948 (1,271)	5,666 (1,111)
$t_{1/2}$ (h)	16.1 (2.7)	15.7 (3.0)
CL/F (L/h)	1.77 (0.446)	1.84 (0.391)
Vd_z/F (L)	41.0 (8.43)	40.8 (8.19)

[a]: n=26 for C_{last}, AUC_{last}, AUC_∞, CL/F, and Vd_z/F.
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)
Cross-reference: Attachment TABPK06.

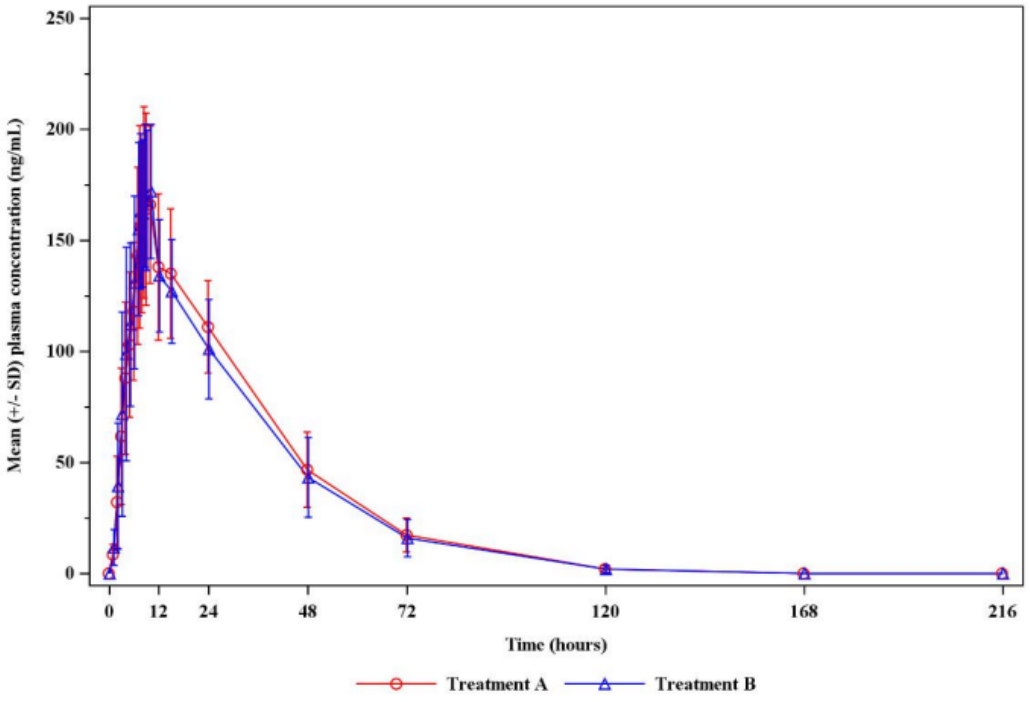
Table 5: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Macitentan After Administration of Single Oral Dose of 10 mg (4 x 2.5 mg) Macitentan Formulated as FMI (Treatment A) and as a Single Oral Film-coated 10 mg Opsumit® Tablet (Treatment B) in Fasted Conditions; Pharmacokinetics Data Statistical Analysis Set (67896062PAH1010)

	Geometric Mean			Treatment A vs Treatment B		Source of Variability	
PK Parameter	n	Treatment A (test)	Treatment B (reference)	GMR (%)	90% CI (%)	Intraparticipant CV (%)	Interparticipant CV (%)
C_{max} (ng/mL)	27	174	184	94.56	87.94-101.69	15.7	12.3
AUC_{last} (ng.h/mL)	26	5,704	5,508	103.54	99.49-107.77	8.4	20.9
AUC_{∞} (ng.h/mL)	26	5,818	5,594	104.01	100.07-108.11	8.1	20.5

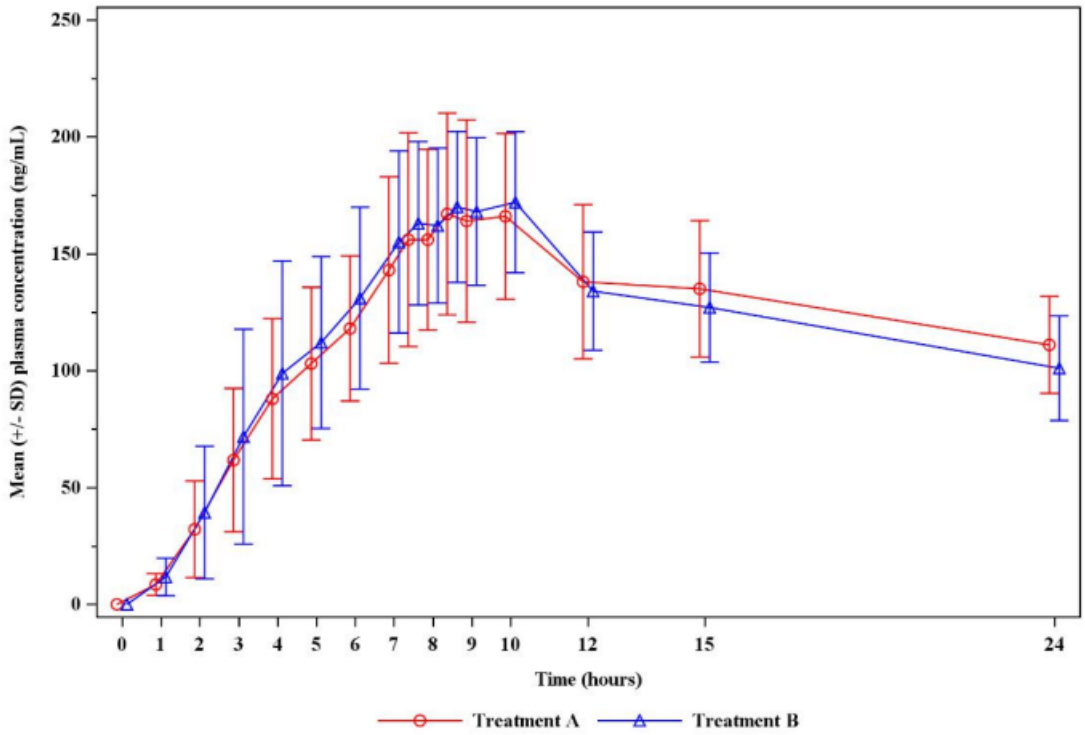
n: Number of paired observations; GMR: Geometric mean ratio; CI: Confidence interval; CV: Coefficient of variation
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)
Cross-reference: Attachment TABPK13.

The mean plasma concentration-time curves for macitentan are shown in Figure 2 below.

Figure 2: Mean Plasma Concentrations of Macitentan Versus Time; Pharmacokinetics Data Analysis Set (67896062PAH1010)

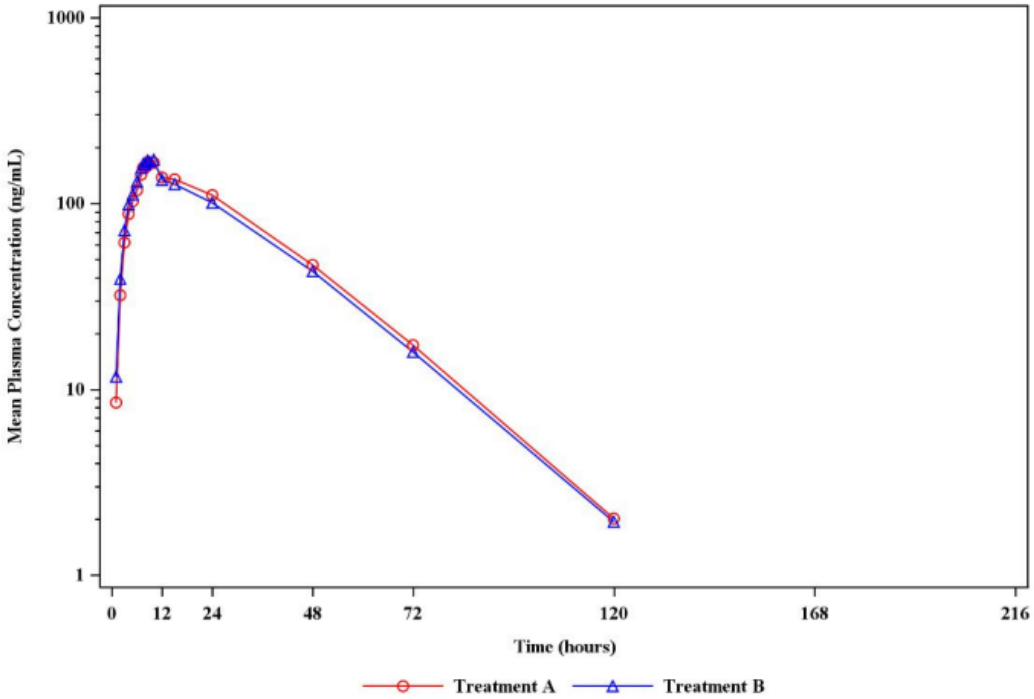


Linear-Linear scale; From 0 to 216 hours
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)



Linear-Linear scale; From 0 to 24 hours
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Figure 2: Mean Plasma Concentrations of Macitentan Versus Time; Pharmacokinetics Data Analysi (67896062PAH1010)



Semi-log scale; From 0 to 216 hours
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Sensitivity analysis

Additionally, a PK sensitivity analysis was done including all 28 participants.

Of note, sensitivity analysis provided different results compared with main analysis: the 90% CIs for the GMRs of the AUCs were contained within the predefined 80.00% to 125.00% bioequivalence limits while the lower bound of the 90% CI for the GMR of Cmax was below the 80.00%

TABPK13: Summary Table of Statistical Results of Macitentan; Pharmacokinetics Data Statistical Analysis Set (67896062PAH1010) Sensitivity analysis (Inclusion of participant S048 with major protocol deviation (disallowed comedication))

	Geometric Means			Treatment A vs Treatment B		P-values			Source of Variability (%)	
PK Parameter	n	Treatment A (test)	Treatment B (reference)	GMR (%)	90% CI (%)	Treat.	Period	Sequence	Intrasubject CV	Intersubject CV
C_{max} (ng/mL)	28	163	186	87.60	75.66-101.42	0.1353	0.7438	0.8714	33.0	0.0
AUC_{last} (ng.h/mL)	27	5272	5549	95.02	82.09-109.99	0.5563	0.2136	0.9670	32.2	16.4
AUC_{∞} (ng.h/mL)	27	5383	5635	95.54	82.68-110.39	0.5942	0.2224	0.8873	31.8	16.0

PK parameters were log-transformed and submitted to a linear mixed effects model including treatment, period and sequence as fixed effects and subject as a random effect.
n: Number of paired observations; GMR: Geometric mean ratio; CI: Confidence interval; CV: Coefficient of variation
Treatment A: single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Pharmacokinetics in the target population

The data for the current analysis were obtained from Study AC-055-312 and Study PAH3001 for pediatric participants with PAH and from Study AC-055-303_PK for adult participants with PAH (see overview in Table 2).

Table 2: Overview of Pediatric and Adult Data Included in the Population PK Analysis

Study (NCT number)	Population	Dosing Regimen	PK Sampling
Study AC-055-312 (NCT02932410) N=55	Male and female participants with symptomatic PAH between ≥2 and <18 years of age	Dispersible tablets (CSF or FMI) (pediatric formulation) Oral macitentan at multiple doses of 3.5, 5, 7.5, or 10 mg based on weight, once daily	PK samples at steady state: (predose, 1, 2, 4, 8, 12, 24 h) in a subset of up to 40 participants Trough concentration at Week 12
	Male and female participants with symptomatic PAH between ≥1 month and <2 years of age	Dispersible tablets (CSF or FMI) (pediatric formulation) Oral macitentan at multiple doses of 1 or 2.5 mg based on age, once daily	PK samples at Day 1: (2, 5, and 24 h) Trough concentration at Week 4 and Week 8
PAH3001 (NCT05167825) N=2	Male and female Japanese participants with symptomatic PAH between ≥3 months and <2 years of age	Dispersible tablets (FMI) (pediatric formulation) Oral macitentan at multiple doses of 1 or 2.5 mg based on age, once daily	PK samples at Day 1: (2, 5 and 24 h) Trough concentration at Week 4 and Week 8
AC-055-303_PK (NCT00667823) N=20	Male and female participants with symptomatic PAH	Film-coated tablets (adult formulation) Oral macitentan at multiple doses of 10 mg once daily	PK samples at steady state: (predose, 1, 3, 5, 6, 7, 8, 9, 10, 12, 14, 24 h)

CSF=clinical service formulation; FMI=final market image; N=number of participants; PAH=pulmonary arterial hypertension; PK=pharmacokinetics;
Source: Mod5.3.5.2/AC-055-312EOCP, Mod5.3.5.2/67896062PAH3001iCSR, and Mod5.3.3.2/AC-055-303PKSub.

The preliminary final analysis dataset (macitentan_pool_21Jul2023_mod_TSLD2.csv) included 20 adult participants and 57 pediatric participants, of which 9 were <2 years (N=7 from Study AC-055-312 and N=2 from Study PAH3001). The final analysis dataset is summarized in Table 3.

Table 3: Summary of Participants and PK Observations Included in the Analysis Dataset, Stratified by Study and Age and Weight Categories

Study	Age and Weight Categories	Number of Participants With Available Observations	Number of Macitentan Observations	Number of Aprocitentan Observations
Total		77	520	520
AC-055-303_PK		20	240	240
AC-055-312	Overall	57	280	280
Participants included in the PK substudy	≥6 months and <2 years	9	37	37
	≥2 years, ≥10 kg and <15 kg	3	24	24
	≥2 years, ≥15 kg and <25 kg	6	48	48
	≥2 years, ≥25 kg and <50 kg	11	80	80
	≥2 years, ≥50 kg	9	72	72
Participants included only in the main study	≥2 years, ≥10 kg and <15 kg	2	2	2
	≥2 years, ≥15 kg and <25 kg	4	4	4
	≥2 years, ≥25 kg and <50 kg	8	8	8
	≥2 years, ≥50 kg	5	5	5

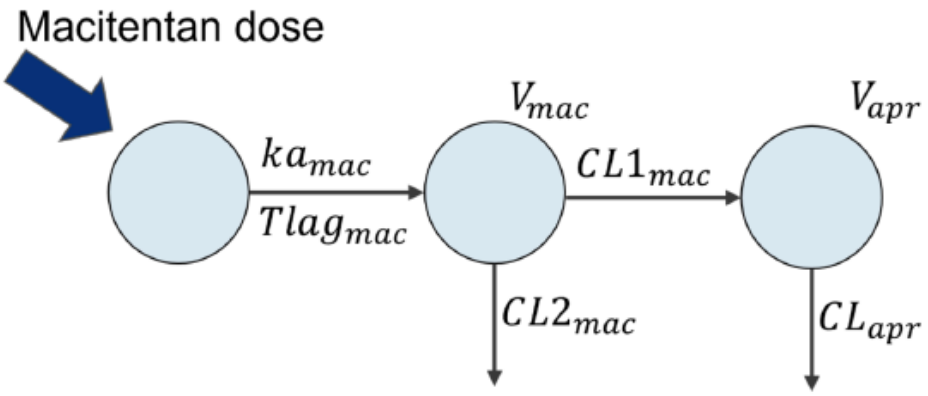
PK=pharmacokinetics.

Combined Population PK Model

To take into account that 3 enzymes (CYP3A4, CYP2C8, CYP2C19) involved in the metabolism of

To take into account that 3 enzymes (CYP3A4, CYP2C8, CYP2C19) involved in the metabolism of macitentan contribute to the formation of aprocitentan, a combined model of macitentan and aprocitentan was developed. In this model, the formation of aprocitentan and its appearance in plasma depends only on the maturation of macitentan (ie, the absorption compartment for aprocitentan was removed), and it was assumed equal to 72.8% of the total clearance of macitentan, which corresponds to the sum of the metabolizing fractions of CYP3A4, CYP2C8, and CYP2C19. The other aspects related to macitentan absorption and elimination and aprocitentan elimination were retained as in the previous models. The combined model provided an OFV of -1,685.134, comparable to the sum of OFV of the macitentan and aprocitentan models developed separately (-539.878 and -1,110.543, respectively), and the parameter estimates for both macitentan and aprocitentan were comparable to the parameter estimates of the 2 separated models. Summary tables of the model development and the comparison of model estimates between the combined model and the macitentan and aprocitentan models are presented in Appendix 5. The combined model adequately described the observed data of both macitentan and aprocitentan, and it was therefore retained as the final model. A graphical representation of the model structure is presented in Figure 3, where CL1mac and CL2mac correspond to 72.8% and 27.2% of total CLmac.

Figure 3: Graphical Representation of the Combined Model Structure



CL_{apr} [L/h]= apparent clearance of aprocitentan; CL_{1mac} and CL_{2mac} [L/h]=72.8% and 28.2% of total macitentan apparent clearance, respectively; ka_{mac} [h^-1]=absorption rate constant for macitentan; $Tlag_{mac}$ [h]=lag time of macitentan absorption; V_{apr} [L]=apparent volume of distribution for aprocitentan; V_{mac} [L]=apparent volume of distribution for macitentan.

Final model

Table 8: Parameter Estimates of the Final Combined Population PK Model

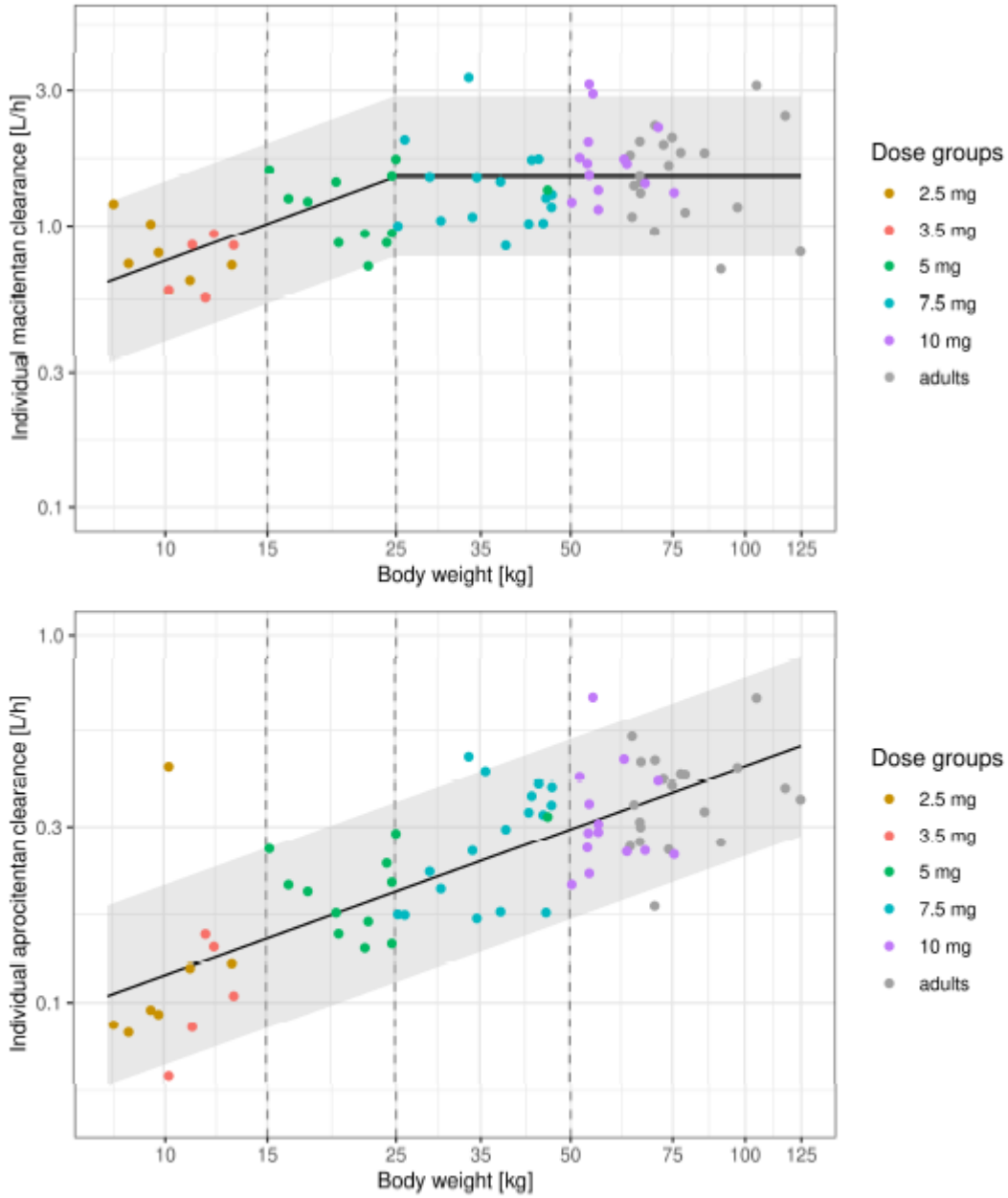
Parameter	Macitentan		Aprocitentan	
	Estimates	RSE%	Estimates	RSE%
ka	0.241	34.1	---	---
Tlag	0.541	44.2	---	---
CL_{ref}	1.49	6.11	0.357	4.96
V_{ref}	39.3	20.2	48.3	27.5
IIV CL (CV%)[a] [shrinkage%]	0.158 (41.4%) [5.96%]	20.1	0.117 (35.2%) [3.18%]	26.0
IIV V (CV%)[a] [shrinkage%]	0.179 (44.3%) [33.9%]	29.7	0.25 (53.3%) [55.2%]	44.4
WT on CL	0.758	20.3	0.568	11.0
WT on V	0.449	16.4	1.19	13.1
RUV (CV%)[a]	0.0858 (29.9%)	24.4	0.0223 (15.0%)	22.8

CL=apparent clearance; CL_{ref}=apparent clearance for reference weight of 25 kg (macitentan) or 70 kg (aprocitentan); CV=coefficient of variation; IIV=inter individual variability; ka= micro rate constant of absorption / absorption rate constant; PK=pharmacokinetics; RSE=relative standard error; RUV=residual unexplained variability; Tlag=time delay in absorption; V=apparent volume of distribution; V_{ref}=apparent central volume of distribution for reference weight of 70 kg; WT=individual body weight.
[a]CV% are computed using sqrt(exp(ω2)-1)×100.

Overall, all the parameter estimates showed high precision, with RSE% being <30% for structural parameters (except for macitentan ka and Tlag, which were 34.1% and 44.2%, respectively) and <40% for IIV (except for IIV on aprocitentan V, which was 44.4%). The parameter estimates with RSE% obtained on 500 bootstrap replicates are reported in Appendix 6. Bootstrap RSE% were generally higher than the RSE% from the final model, especially for IIV on V for macitentan, and for V and IIV on V for aprocitentan. However, these results have to be interpreted with caution given the small sample size. Both macitentan and aprocitentan CL, important for the determination of AUC0-24h,ss were well captured, with low RSE%. The correlation between the random effects of

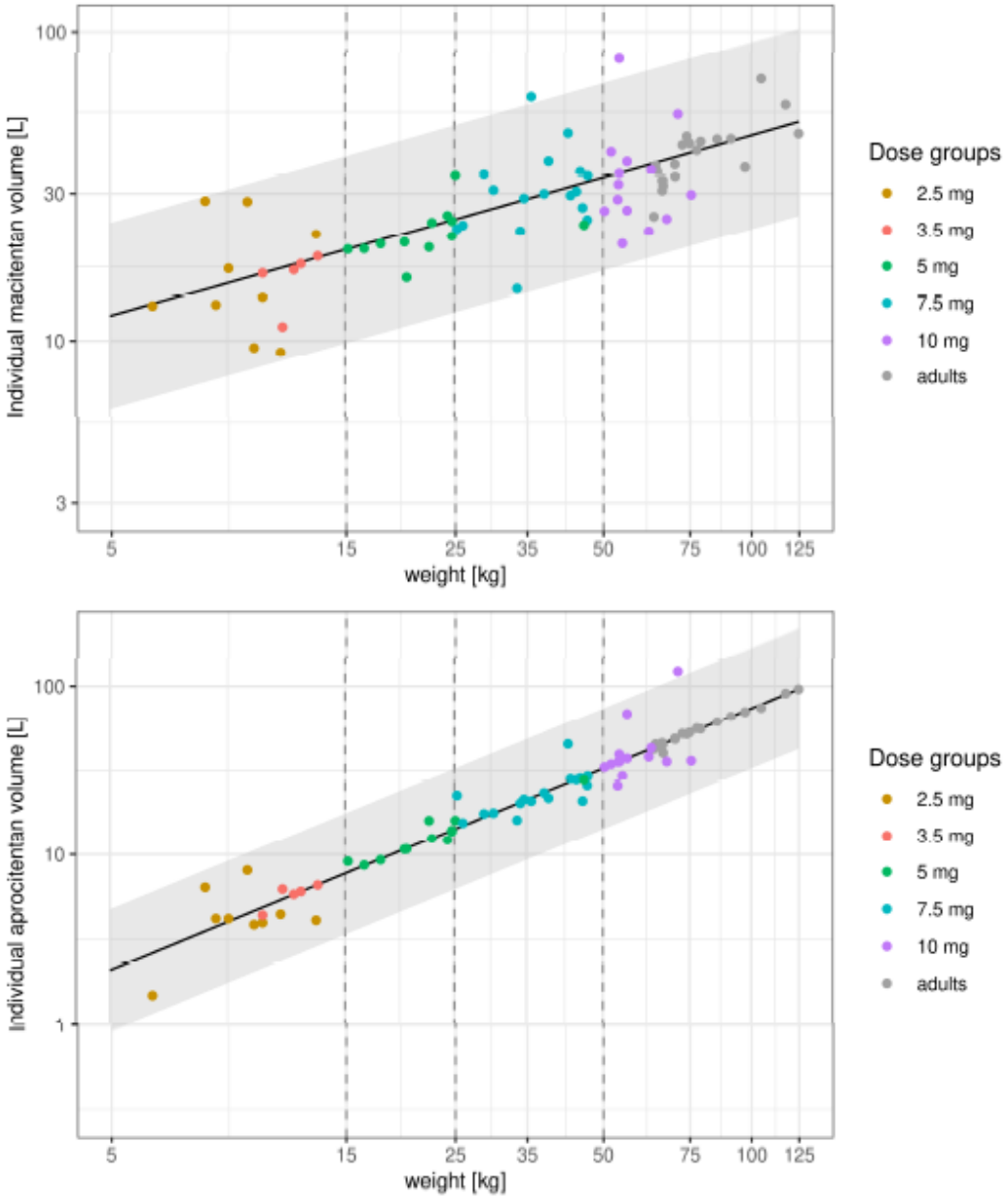
CL and V was negligible for all macitentan and aprocitentan parameters (see Appendix 7). Overall, the effect of body weight on macitentan clearance was lower than what was described by a power model with standard allometric coefficient, with CLmac being described as a constant value for participants ⩾25 kg and a power model with estimated coefficient (0.758) for participants <25 kg. For aprocitentan, body weight effect on clearance was estimated lower compared with the standard value (0.568) and was slightly higher for volume (1.19).

Appendix 12: Relationship Between Individual Estimated Macitentan and Aprocitentan Clearance Versus Body Weight for the Final Combined Population PK Model



CL=apparent clearance; PK=pharmacokinetics.
Colored dots: Individual estimated macitentan (top) and aprocitentan (bottom) CL [L/h], colored by dose groups.
Black line: estimated typical value of CL versus body weight.
Shaded area: 90% prediction interval of CL.
Vertical dashed lines: reference body weight values of the 4 pediatric weight categories.
Individual estimated CL for pediatrics <2 years (gold dots) are adjusted by age-dependent maturation.

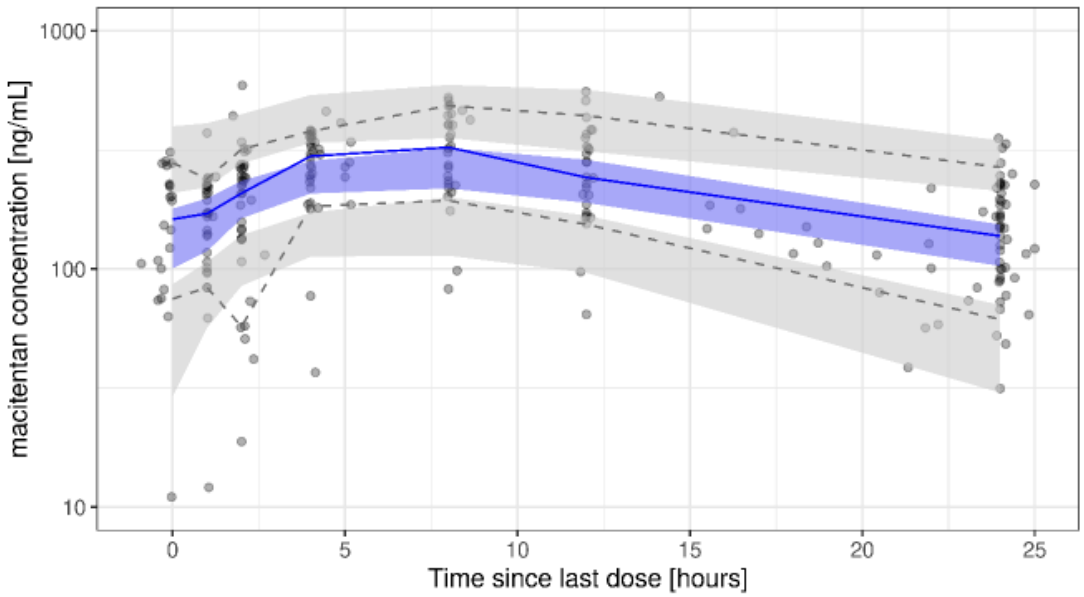
Appendix 13: Relationship Between Individual Estimated Macitentan and Aprocitentan Volume of Distribution Versus Body Weight for the Final Combined Population PK Model



PK=pharmacokinetics; V=apparent volume of distribution.
Colored dots: Individual estimated macitentan (top) and aprocitentan (bottom) V [L], colored by dose groups.
Black line: estimated typical value of V versus body weight.
Shaded area: 90% prediction interval of V.
Vertical dashed lines: reference body weight values of the 4 pediatric weight categories.

Results of the pcVPC for both pediatric participants and adult participants are shown in Figure 4 and Figure 5 for macitentan and in Figure 6 and Figure 7 for aprocitentan. Both final population PK models appeared to adequately capture the central tendency and the variability of the data for both adult and pediatric participants, as attested by the agreement between the observed 10th, 50th, and 90th percentiles of the data and the respective 95% CIs obtained from the simulations.

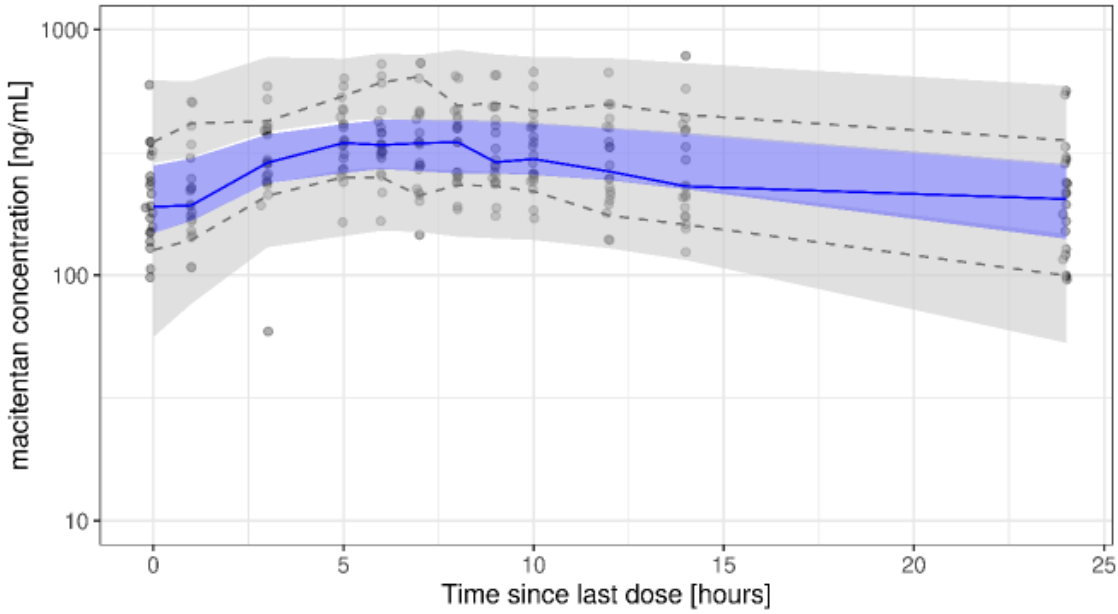
Figure 4: pcVPC of the Final Macitentan Population PK Model for Pediatric Participants



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; TSLD=time since last dose.

Continuous blue line: 50th percentile of macitentan observed data. Dashed gray lines: 10th and 90th percentiles of macitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: macitentan observed data plotted at the TSLD up to 25 hours. Through data after 25 hours (70 samples) were not displayed for readability. Both observed and simulated data were binned with breaks at times (hours): 0.5, 1.5, 3, 6, 10, 16.

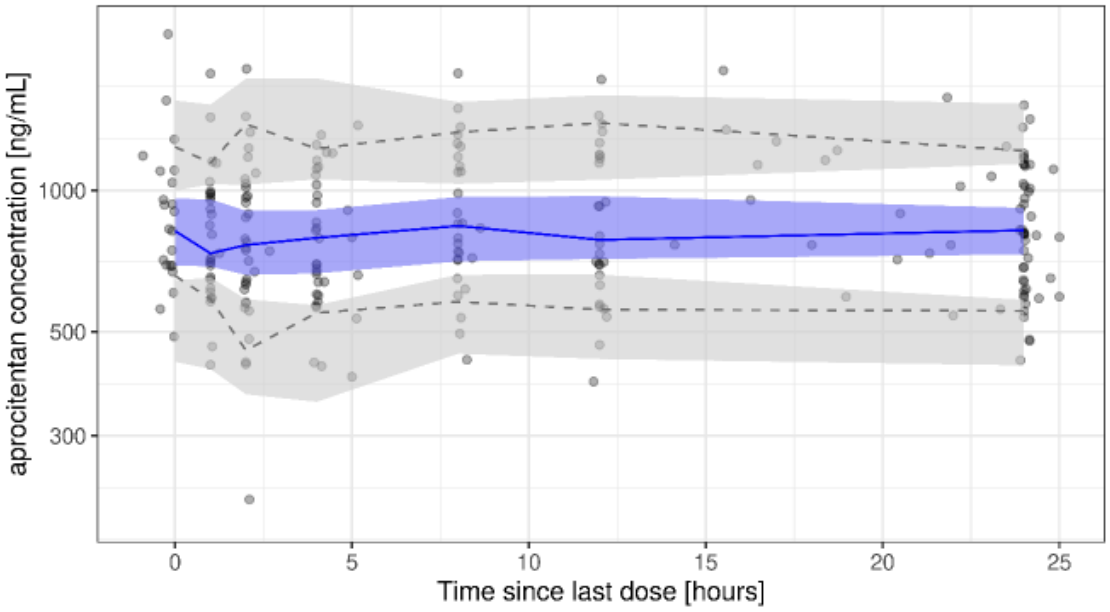
Figure 5: pcVPC of the Final Macitentan Population PK Model for Adult Participants



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; TSLD=time since last dose.

Continuous blue line: 50th percentile of macitentan observed data. Dashed gray lines: 10th and 90th percentiles of macitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: macitentan observed data plotted at the TSLD up to 25 hours. Both observed and simulated data were binned with breaks at times (hours): 0.5, 2, 4, 5.5, 6.5, 7.5, 8.5, 9.5, 11, 13, 19.

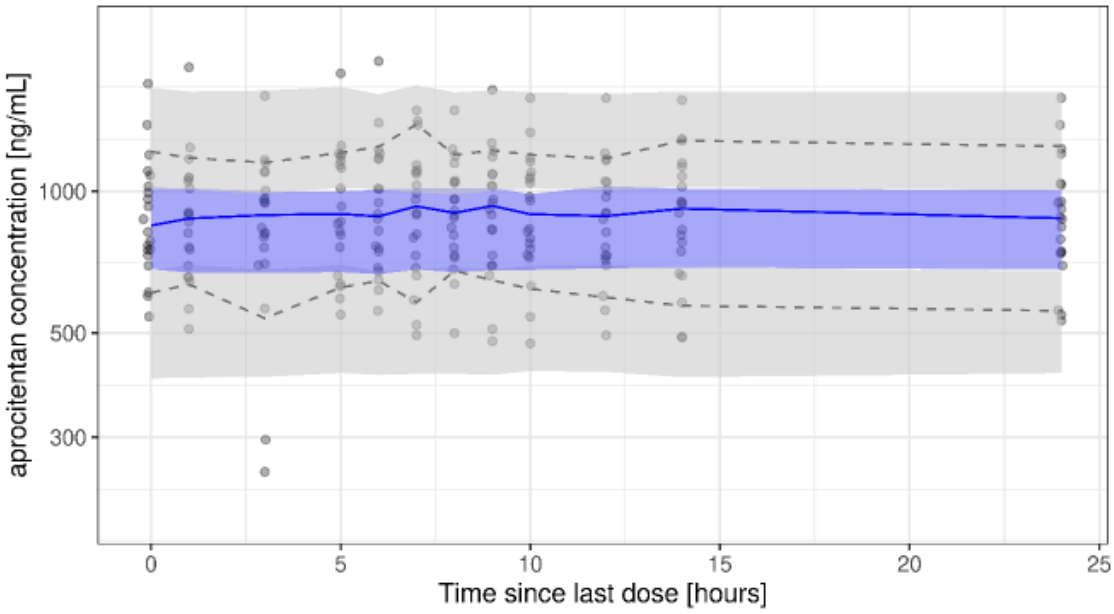
Figure 6: pcVPC of the Final Aprocitentan Population PK Model for Pediatric Participants



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; TSLD=time since last dose.

Continuous blue line: 50th percentile of aprocitentan observed data. Dashed gray lines: 10th and 90th percentiles of aprocitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: aprocitentan observed data plotted at the TSLD up to 25 hours. Through data after 25 hours (70 samples) were not displayed for readability. Both observed and simulated data were binned with breaks at times (hours): 0.5, 1.5, 3, 6, 10, 16.

Figure 7: pcVPC of the Final Aprocitentan Population PK Model for Adult Participants



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; TSLD=time since last dose.

Continuous blue line: 50th percentile of aprocitentan observed data. Dashed gray lines: 10th and 90th percentiles of aprocitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: aprocitentan observed data plotted at the TSLD up to 25 hours. Both observed and simulated data were binned with breaks at times (hours): 0.5, 2, 4, 5.5, 6.5, 7.5, 8.5, 9.5, 11, 13, 19.

The final analysis dataset included 20 adult participants and 62 pediatric participants, of which 11 were <2 years (N=9 from Study AC-055-312 and N=2 from Study PAH3001). Five new participants were included compared to the previous CCO date of 09 June 2023. Their age at baseline ranged from > 1 to 16 years old. The final analysis dataset is summarized in Table A2.

Table A2: Summary of Participants and PK Observations Included in the Analysis Dataset, Stratified by Study and Age and Weight Categories

Study	Age and Weight Categories	Number of Participants With Available Observations	Number of Macitentan Observations	Number of Aprocitentan Observations
Total		82	532	532
Adults (AC-055-303_PK)		20	240	240
Pediatrics (AC-055-312 and PAH3001)	Overall	62	292	292
Participants included in the PK substudy	≥6 months and <2 years	11	47	47
	≥2 years, ≥10 kg, and <15 kg	3	24	24
	≥2 years, ≥15 kg, and <25 kg	6	48	48
	≥2 years, ≥25 kg, and <50 kg	11	79	79
	≥2 years, ≥50 kg	9	72	72
Participants included only in the main study	≥2 years, ≥10 kg, and <15 kg	3	3	3
	≥2 years, ≥15 kg, and <25 kg	5	5	5
	≥2 years, ≥25 kg, and <50 kg	8	8	8
	≥2 years, ≥50 kg	6	6	6

PK=pharmacokinetics.

Table A3 shows the parameter estimates with the final population PK model based on data collected at CCO date of 09 June 2023 and up to EOCP. Overall, the impact of the additional data on the parameter estimates was minor, ie, percent differences between the 2 estimates were below 10% except for inter individual variability (IIV) on apparent volume of distribution (V) and individual body weight (WT) on V of macitentan (22.9% and 17.4%, respectively) and IIV on V and WT on V of aprocitentan (56.4% and -11.8%, respectively). These differences were considered minor and not clinically relevant.

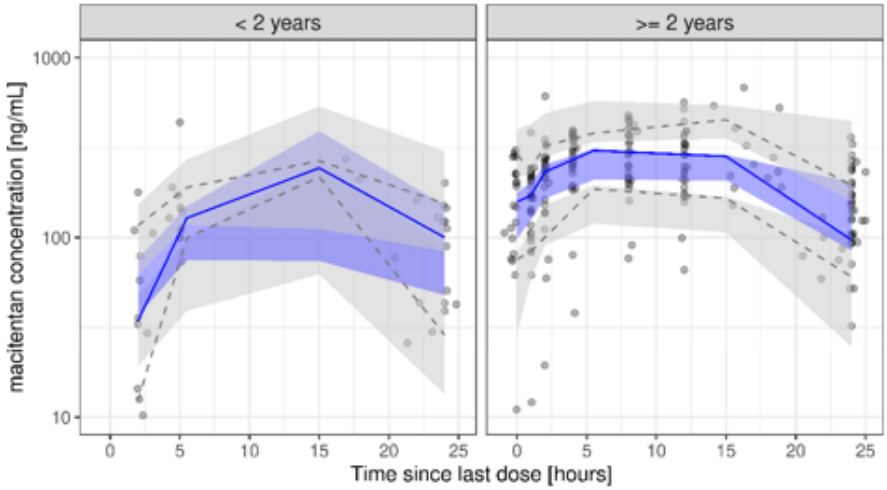
Table A3: Parameter Estimates of the Final Combined Population PK Model Based on CCO of 09 June 2023 and End of Core Period Data

Parameter	Macitentan Estimates			Aprocitentan Estimates		
	CCO 09 June 2023	End of Core Period	Difference (%)	CCO 09 June 2023	End of Core Period	Difference (%)
ka	0.241	0.224	-7.0	---	---	---
Tlag	0.541	0.500	-7.6	---	---	---
CL_{ref}	1.49	1.47	-1.3	0.357	0.355	-0.6
V_{ref}	39.3	39.0	-0.8	48.3	43.7	-9.5
IIV CL (CV%)[a] [shrinkage%]	0.158 (41.4%) [5.96%]	0.157 (41.2%) [13.0%]	-0.6	0.117 (35.2%) [3.18%]	0.113 (34.6%) [7.22%]	-3.4
IIV V (CV%)[a] [shrinkage%]	0.179 (44.3%) [33.9%]	0.22 (49.6%) [54.5%]	22.9	0.25 (53.3%) [55.2%]	0.391 (69.2%) [76.0%]	56.4
WT on CL	0.758	0.752	-0.8	0.568	0.585	3.0
WT on V	0.449	0.527	17.4	1.19	1.05	-11.8
RUV (CV%)[a]	0.0858 (29.9%)	0.0884 (30.4%)	3.0	0.0223 (15.0%)	0.0241 (15.6%)	8.1

CCO=clinical cutoff; CL=apparent clearance; CL_{ref}=apparent clearance for reference weight of 25 kg (macitentan) or 70 kg (aprocitentan) [L/h]; CV=coefficient of variation; IIV=interindividual variability; ka=absorption rate constant [h-1];; PK=pharmacokinetics; RUV=residual unexplained variability; Tlag=time delay in absorption [h]; V=volume of distribution; V_{ref}=apparent central volume of distribution for reference weight of 70 kg [L]; WT=individual body weight.

[a]CV% are computed using sqrt(exp(ω2)-1)×100.

Figure 10: Prediction-corrected Visual Predictive Check of Macitentan with the Final Combined Population PK Model for Pediatric Participants stratified by Age



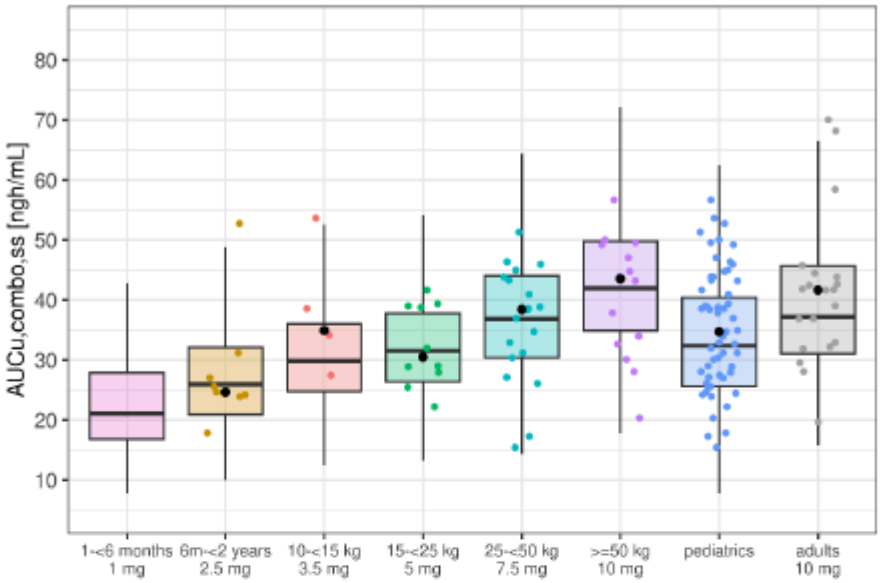
Continuous blue line: Median of observed macitentan data. Dashed gray lines: 10th and 90th percentiles of macitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: macitentan observed data plotted up to 25 hours since last dose. Through data after 25 hours (33 samples) were not displayed for readability.

Model-based simulations of AUCu,combo,ss are presented based on the final model obtain in the main analysis for the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age), for all pediatric groups combined, and in adults, with the individual estimates of AUCu,combo,ss overlaid. Model simulations were in line with individual exposure parameters and showed a comparable distribution of AUCu,combo,ss across pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age) and

adults, with slightly lower exposures for the ≥1 month and <6 months and the ≥6 months and <2 years groups.

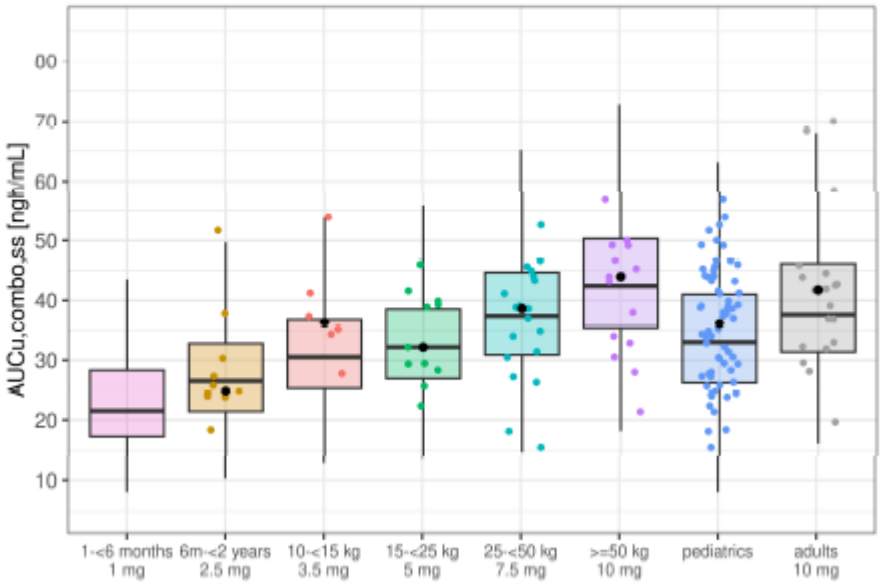
Figure A4: Comparison of Simulated and Predicted AUCu,combo,ss Overall and Stratified by Dose Group

A. CCO 09 June 2023



CCO=clinical cutoff.

B. End of Core Period

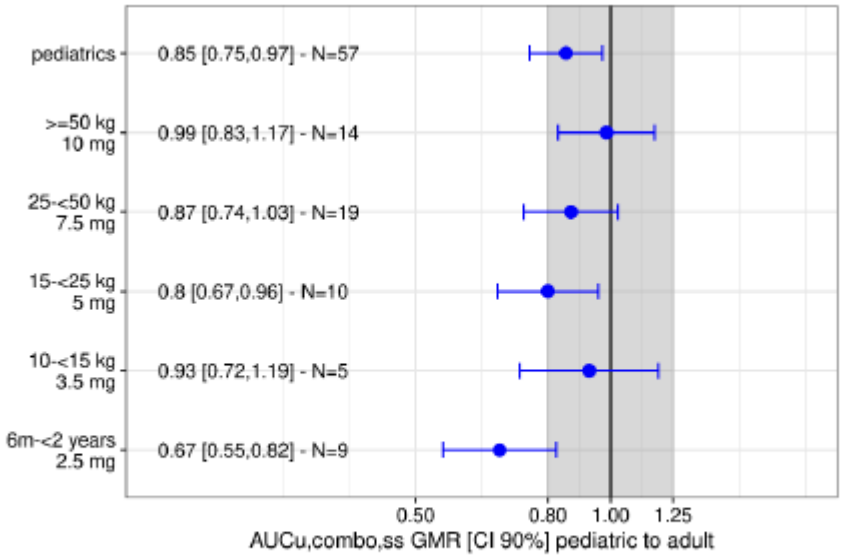


$AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady state;
$AUC_{u,combo,ss}$=combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency.
In the plot, "pediatrics" represents all pediatric participants combined and the other 5 groups refer to the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age).

Figure A5 shows the GMR and the associated 90% CI of AUCu,combo,ss for each pediatric weight group (participants ≥2 years of age) and age group (participants <2 years of age) versus adults. The GMR point estimates were within the 0.8 to 1.25 reference range for all pediatric groups, except the ≥6 months and <2 years group, where the GMR point estimate (0.67) was lower than the reference range based on the preliminar final dataset. These differences were considered minor and not clinically relevant, because 78% of the participants in the ≥6 months and <2 years group were already older than 20 months at the first day of treatment, and 44% of them reached 2 years of age during treatment. This may explain the relatively lower exposures observed in this group. The geometric mean ratio (GMR) point estimate in the different dose groups were slightly higher compared to the GMRs based on the final model obtained in the main analysis.

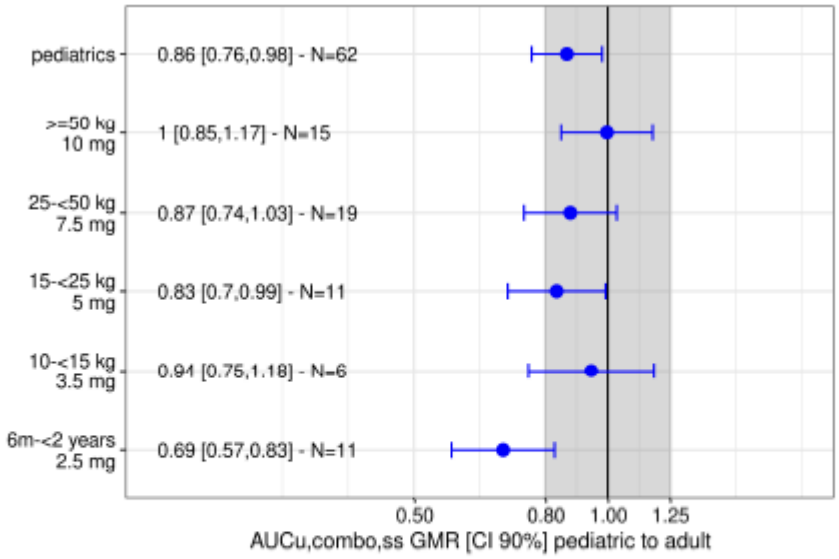
Figure A5: Forest Plot of the GMR and 90% CI of Predicted AUCu,combo,ss of Pediatrics (Stratified by Age and Weight Categories) Versus Adult Participants

A. CCO 09 June 2023



CCO=clinical cutoff; N=number of participants.

B. End of Core Period



$AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady state; $AUC_{u,combo,ss}$=combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency; GMR [CI 90%]=geometric mean ratio and 90% confidence interval of pediatric versus adult $AUC_{u,combo,ss}$; N=number of participants.

In the plot, "pediatrics" represents all pediatric participants combined and the other 5 groups refer to the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age).

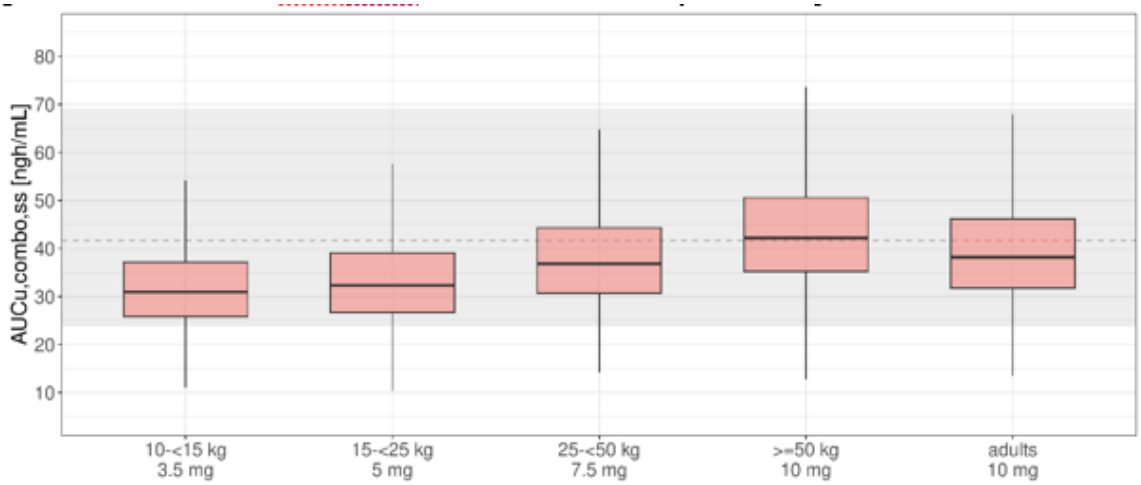
Pharmacokinetic interaction studies

Macitentan is mainly metabolized by the CYP P450 isozyme CYP3A4 (OPSUMIT SmPC 2022). Several DDI studies in healthy participants (with warfarin, cyclosporine A, sildenafil, rifampicin, and ketoconazole) were included in the initial MAA submitted in 2012 (MAA OPSUMIT/Mod2.7.2/Sec2.1.6) and subsequent years (3 DDI addenda to Mod2.7.2 submitted in 2015, 2018, and 2020); no additional DDI studies were conducted for the current submission.

Dose justification

Populations of pediatric subjects in each body-weight cohort (N = 10000 virtual subjects per cohort) were simulated following the CDC weight-for-age statistical tables (CDC 2000) and applying the LMS method (Cole 1992). The simulated individual parameters were used to derive AUCu,combo,ss. The simulations are shown in Figure 17.

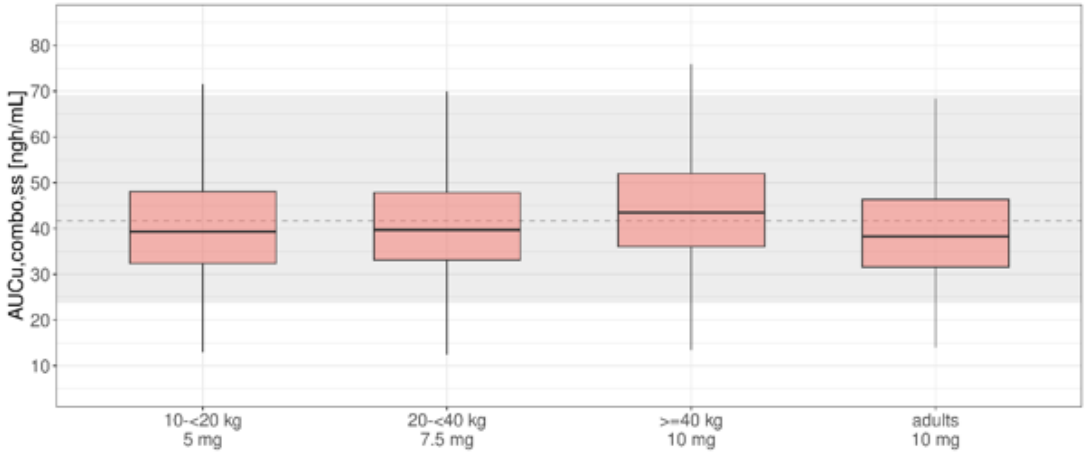
Figure 17: Simulated AUCu,combo,ss Overall and Stratified by Dose Group



$AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady-state; $AUC_{u,combo,ss}$=combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency.
Dark and light grey shaded area are the 1st to 3rd quartile interval and the 2.5th to 97.5th percentile interval of adult $AUC_{u,combo,ss}$ based on posthoc clearance parameters from the final popPK model with Salem ontogeny, respectively.
The horizontal dashed grey line is the median of adult $AUC_{u,combo,ss}$.

The ≥50 kg body-weight cohort is the only cohort for which the AUCu,combo,ss distribution matches the adult one. The other body-weight cohorts have slightly lower exposure. Alternative body-weight cohorts were simulated and are available in Figure 18.

Figure 18: Simulated AUCu,combo,ss Overall and Stratified by Dose Group at Alternative Body-Weight Cohorts



$AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady-state; $AUC_{u,combo,ss}$=combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency.
Dark and light grey shaded area are the 1st to 3rd quartile interval and the 2.5th to 97.5th percentile interval of adult $AUC_{u,combo,ss}$ based on posthoc clearance parameters from the final popPK model with Salem ontogeny, respectively. The horizontal dashed grey line is the median of adult $AUC_{u,combo,ss}$.

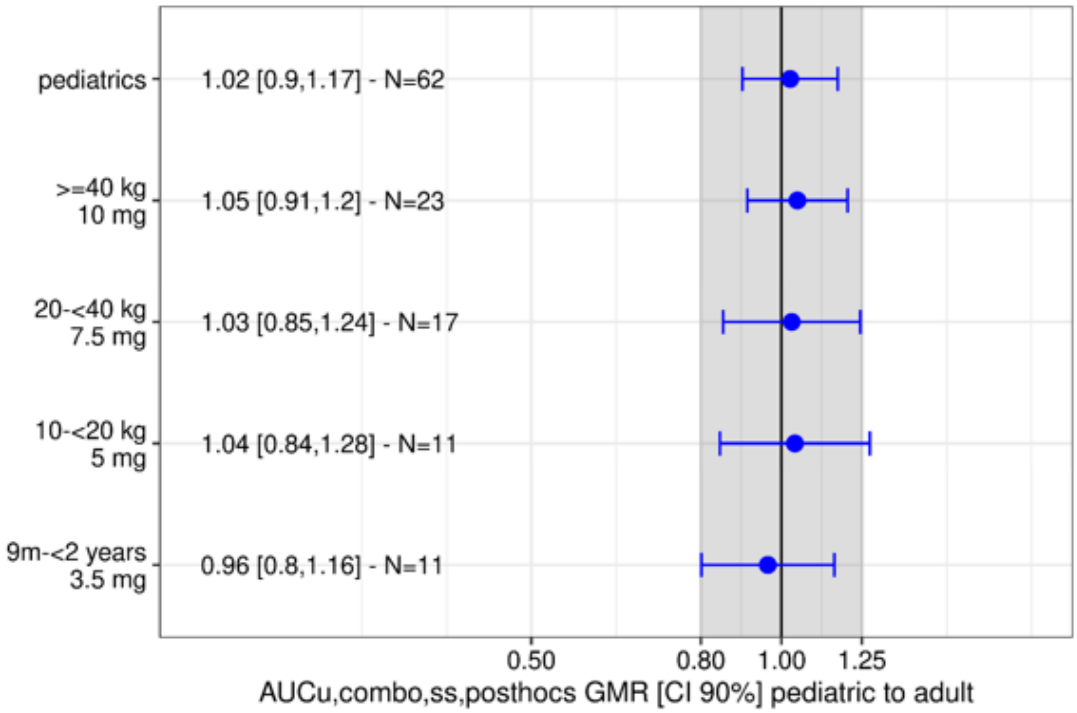
The alternative body-weight cohorts are:

- 5 mg once daily in subjects between 10 and less than 20 kg
- 7.5 mg once daily in subjects between 20 to less than 40 kg
- 10 mg once daily in subject from 40 kg

The AUCu,combo,ss distribution is overlaid with the adult one. Figure 19 presents the forest plot analysis of this new body-weight cohorts. All the GMRs are centered around 1.

Although the exposures based on the alternative dosing from the simulations provide a closer match to the adult exposures, the current dosing regimen proposed in the SmPC is still considered clinically appropriate based on the clinically available data on PK, pharmacodynamics, efficacy, and safety in younger patients who are 2 years of age or younger.

Figure 19: Forest Plot of the GMR and 90% CI of Predicted AUCu,combo,ss of Pediatrics (Stratified by Age and Weight Categories) Versus Adult Participants: New Body-Weight Cohorts



$AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady-state;
$AUC_{u,combo,ss}$= combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency;
GMR [CI 90%]=geometric mean ratio and 90% confidence interval of pediatric versus adult $AUC_{u,combo,ss}$;
N=number of pediatric participants in the group.
In the plot, "pediatrics" represents all pediatric participants combined and the other 5 groups refer to the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age).

2.6.3. Discussion on clinical pharmacology

Analytical methods

For the quantification of macitentan and aprocitentan, three different methods were used: SBA_S_04081, METH-042 (BA-13.225) and PRA-NL-SML-2097 (BA13063).

Biowaiver

The MAH has provided enough documentation to accept the biowaiver of the FMI 1 mg strength as well as to demonstrate that macitentan is dose-proportional also after single-dose administration up to and including 5 mg strength.

In TOMORROW study, 0.5 mg, 2.5 mg and 5 mg of the CSF were used. However, biocomparability studies have been only conducted with the CSF of 5 mg. The MAH has provided dissolution profiles to demonstrate in vitro similarity behaviour between 0.5 mg and 2.5 mg strengths versus 5 mg strengths. Therefore, it is acceptable that the biocomparability studies were carried out only with the CSF of 5 mg strength.

Bioequivalence

Three clinical Phase 1 studies were conducted to assess the biocomparability of the different formulations used during the development of the macitentan paediatric formulation. All studies

were open-label, single-dose, randomized, 2-way crossover and were conducted in fasting conditions.

The test and reference products were administered with water. For studies AC-055-121, PAH1008 and PAH1010a total of 240 mL of water were used. The MAH was asked to justify how the bioequivalence shown can be ensured if the quantity of water administered in those studies differs from the instructions for administration in the proposed SmPC, which recommends a maximum intake of 100 mL of water as paediatric patients are not expected to swallow 240 mL of water with the dispersible tablet. The explanations that the MAH has provided are not fully convincing. However, they may be considered supportive data suggesting lack of difference in exposure due to differences in water volume used in the clinical trial TOMORROW and this issue is not further pursued.

Opsumit film-coated tablets may be taken with or without food. All three studies evaluated bioequivalence in fasting conditions, which is usually considered the most sensitive study to detect potential differences. The bioavailability when the dispersible tablet is dispersed in soft food (e.g., apple pure) has not been investigated. According to Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2, "The effect of mixing the product with common food or drinks as specified by the applicant should be discussed for every oral paediatric medicinal product. Different food or drinks may have different properties and differ in their effect on the paediatric preparation. The SmPC and PIL should give clear instructions on what food and/or drinks, if any, have been demonstrated to be appropriate for mixing with the paediatric preparation". The applicant was invited to investigate and discuss the effect of dispersing the tablet with common food or drinks, in line with requirements of the above-mentioned Guideline. The MAH has provided the results of a compatibility study with liquids (orange juice, apple juice and skimmed milk) and soft food (apple sauce and yogurt). Validation results of the UHPLC method used have been also submitted.

For study AC-055-121 (CSF vs adult tablets), 12 subjects were enrolled and included in the PK analysis. Even though the 90% confidence intervals calculated by the MAH for AUC0-t and Cmax were inside the normal range of acceptability (80.00 – 125.00%) for both macitentan and its active metabolite ACT-132577, no definitive conclusions on the bioequivalence of both formulations can be drawn, since study samples were reanalysed for PK reasons, and this is not acceptable according to the EMA Guideline on the Investigation of Bioequivalence. Therefore, the MAH was asked to provide the PK data and the 90% CI T/R for Cmax and AUC using the initial results of batch 4. The updated results also confirm bioequivalence and are therefore considered acceptable

For study PAH1008 in principle, the FMI paediatric formulation is considered bioequivalent to the CSF paediatric formulation, as the 90% confidence intervals calculated for AUC0-last and Cmax were inside the normal range of acceptability (80.00 – 125.00%).

For study PAH1010 (FMI vs adult tablet), 28 patients were enrolled and completed the study, however 27 participants were included in the main PK analysis. One subject was excluded due to prohibited medication (use of senna leaves) which was identified upon further questioning by the investigator, once lower plasma concentrations of macitentan had been observed. The fact that this patient was excluded after the bioanalysis had taken place raises concerns and the MAH was asked to further clarify this exclusion. When this patient was excluded, the 90% confidence intervals calculated for AUC0-last and Cmax were inside the normal range of 80.00 – 125.00% for macitentan, however, the analysis that included all patients revealed that the lower bound of the 90% CI for the GMR of Cmax was below the 80.00%, and the MAH was asked to discuss the clinical relevance of a lower Cmax as observed. The explanations provided by the MAH do not

clarify this issue, therefore it is not suitable to exclude this patient from the PK analysis. In conclusion, bioequivalence cannot be concluded between the FMI and adult formulations in study PAH1010.

Pharmacokinetics in the target population

The clinical pharmacology properties of macitentan and aprocitentan in paediatric patients with PAH from 1 month to less than 18 years old have been characterized using a non-linear mixed effects modelling approach from Study AC-055-312 and Study PAH3001 together with adult patients with PAH (Study AC-055-303). The modelling strategy included a previously developed population PK model of macitentan in adult PAH patients, which has been updated for paediatric patients with the simultaneous characterization aprocitentan longitudinal PK data in paediatric patients with PAH from 6 months to less than 18 years old. Overall, the modelling strategy is endorsed.

The final population PK model includes a one-compartment model with first-order absorption. Linear disposition processes were assumed for macitentan and aprocitentan. The structural definition of the population PK model was able to characterize the longitudinal PK profiles of both macitentan and aprocitentan adequately. An allometric relationship (power relationship) on CL (0.758) and V (0.449) of macitentan was estimated. Although the allometric exponent on CL is consistent with the standard allometric exponent (0.75), it only affects to paediatric patients with PAH with <25 kg (Appendix 12). A constant CL was assumed for paediatric patients with ≥25 kg. Therefore, no body weight effect on CL in paediatric patients ≥25 kg was assumed. The allometric exponents of aprocitentan were also estimated (0.568 for CL and 1.19 for V), assuming a power function across the whole range of body weight values and were close to the standard allometric values. Despite of the difference between the standard value of V for macitentan (1 vs 0.449), the Applicant has justified the use of estimated allometric exponents for macitentan based on the important decrease of the objective function value seen during macitentan model development when the estimated exponents were incorporated. However, a slight underprediction of Cmax was detected for macitentan, therefore, the Applicant has performed a sensitivity analysis on Cmax to evaluate its contribution on macitentan exposure. The final model was rerun with fixed exponents of macitentan and aprocitentan. A Forest Plot of the GMR and 90% CI of Predicted Cmaxu,combo,ss of Pediatrics (Stratified by Age and Weight Categories) Versus Adult Participants using Model with Fixed or Estimated Allometric Exponents was performed. The combined unbound maximal concentration was calculated as the sum of macitentan and aprocitentan C_{max} at steady state weighted by their unbound fraction. The results showed no significant differences on Cmaxu combo,ss for all pediatric groups. Furthermore, a comparison of the distribution of AUC and Cmax parameters of macitentan and aprocitentan and their combination from a model with fixed or estimated exponents resulted in negligible differences, showing a slightly more variable distribution of PK exposure metrics with fixed vs estimated values.

In order to evaluate the impact of body weight effect of PK parameters, the Applicant has provided pcVPC stratified by age <2 and ⩾2 years of age and body weight <25 and ⩾25 kg for macitentan and aprocitentan. pcVPC of aprocitentan show relatively good model performance across the whole body weight range, however, pcVPC of macitentan show adequate model performance in patients with body weight <25 kg, >25 kg and ⩾2 years of age. It is observed that the pcVPC slightly under-estimates the median tendency in pediatric patients <25 kg between 5 and 20h after dose administration, which could be explained by a lack of sufficient PK samples around this period since the extreme percentiles 10th and 90th are well capture. On the other hand, pcVPC showed that model predictions are not reliable on patients <2 years of age.

An ontogeny function for CYP3A4 enzymes published by Salem et al. was assumed, but not experimentally confirmed with the current experimental data. An alternative hepatic ontogeny function published more recently is also available (Upreti, V.V. & Wahlstrom, J.L. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of paediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J. Clin. Pharmacol. 56, 266–283 (2016)). The Applicant claims that the selection of the Salem et al ontogeny functions is a more conservative approach from a safety point of view. Based on the Salem et al ontogeny functions, the macitentan metabolism in paediatric subjects is lower than in adults resulting in higher exposures in paediatrics for a given body-weight dose. However, with the Upreti ontogeny functions, the metabolism of macitentan is larger than in adults resulting in lower exposures in paediatrics compared to adults. Differences on the impact on model prediction between both functions have not been experimentally assessed. Furthermore, the results from the Salem et al function achieved 100% CYP maturation around 2 years of age, whereas with the Upreti et al function, 100% CYP maturation is achieved >6 years of age in all CYP's tested and higher metabolism than the adult population is predicted.

Model-based simulations were conducted to evaluate the proposed dosing regimen across the paediatric body weight cohorts vs the reference exposure in adults (Figure A4). For that purpose, unbound AUC combined (macitentan + aprocitentan) was computed taking into account their unbound fraction and their in vitro potency, which is accepted. A forest-plot analysis (Figure A5) was conducted to assess whether the predicted exposure stratified by age and weight categories provides similar exposure (within 0.8-1.25 range) as in adults using the same patient characteristics experimentally recruited. The median point estimate for each category lies within the 0.8-1.25 range, except for the 6m-<2 years of age (0.67) with the proposed dose level of 2.5 mg (N =7). Although it is acknowledged that most of the participants were in the upper end of the age interval (>18 months), the assumption of similar exposure as adult patients is not achieved.

The Applicant has provided a stochastic simulation considering a random distribution for virtual paediatric patients for every month from 1 to 24 months using both the Salem et al and Upreti et al ontogeny functions. The comparison between ontogeny functions revealed higher predicted exposures with Salem's function (19% higher in subjects below 6 months of age) compared to Upreti's function. No ontogeny information was available for UGT1A1, and ontogeny was assumed to be the same as for CYP3A4, which is uncertain. Further, the development of enzymatic activity in time follows a different patterns for the different enzymes involved (CYP3A4, 2C8, 2C9, 2C19 and UGT1A1), however, the relative importance of the different enzymes was assumed to be the same in all the different sub-age classes < 2 years of age. Importantly, the appropriateness of these assumptions cannot be verified, since no actual PK data are available to validate the model (limited data close to 2 years of age, no data in the 1 month-6 months subgroup. Simulated exposure in patients >9 months of age are highly comparable between both functions. Despite the differences in simulated exposure, >75% of the simulated exposure in paediatric patients from 1 to 24 months is within the 95% CI of the adult population with both ontogeny functions. Therefore, alternative dosing regimen are proposed, 1 mg from 1 month to less than 3 months, 2.5 mg from 3 months to less than 9 months and 3.5 mg from 9 months to less than 2 years of age. Although the alternative dosing regimen provided simulations better match the adult exposure, the Applicant considered the initial proposal in patients below 2 years of age (2.5 mg). Based on the evidence provided, the inconsistency of the initial proposal to achieve exposure levels matching the adult exposure in patients from 6 months to less than 2 years of age, the lack of recruited patients below 1 year of age, the non-reliable model predictions in children < 2 years of age, it was not possible to accept any macitentan dosing recommendation in patients below 2 years of age. Thus, the therapeutic indication has been restricted to patients ⩾2 years.

The forest-plot analysis also demonstrated that roughly 50% of paediatric patients from 15 to less than 25 kg would show a >20% lower exposure compared to adults with the proposed 5 mg dosing regimen. The Applicant provided the forest-plot analysis considering a body-weight cohort from 15 to less than 20 kg with 5 mg and 20 to less than 50 kg with 7.5 mg. The results showed that the GMR of the 15 to <20 Kg paediatric group is out of the reference range. Alternative dosing regimens (1 mg from 1 month to less than 3 months, 2.5 mg from 3 months to less than 9 months and 3.5 mg from 9 months to less than 2 years of age) provided simulations closer to match to the adult exposures in patients from 6 months to 2 years of age.

On the other hand, a stochastic simulation considering a random distribution of virtual paediatric patients from 2 years of age for each body-weight cohort were performed to derivate the exposure parameter (AUCu,combo,ss) following the current proposed dosing regimen. The results showed a slight lower exposure in paediatric patients compared to adult patients for all body-weight cohorts except for the ⩾50 kg body-weight cohort. Then, an update in body-weight cohorts was conducted to better match the adult exposure range. The alternative cohorts in patients >2 years of age (10-20kg, 20-40kg, >40kg) provided more similar exposure compared to the adult population, therefore, the dose recommendation in the SmPC was updated.

Pharmacokinetic interactions studies

The potential drug-drug interaction profile of macitentan was previously characterized in adult subjects. No DDI studies have been conducted in paediatric patients. Clinically relevant changes in macitentan exposure were observed with the co-administration of CYP3A4 inducers or inhibitors. It is expected that the DDI profile remains similar as in adults in paediatric patients from 2 to less than 18 years of age. The lack of in vivo DDI evaluation in paediatric population is endorsed.

Pharmacodynamics

This application is based on the extrapolation of efficacy and safety in adults to the paediatric population based on comparable exposure, since the study design of the pivotal study TOMORROW is considered inappropriate to draw firm conclusions on the efficacy (see efficacy discussion).

Preferred PD parameters such as haemodynamic parameters obtained by right heart catheterisation (RHC)(e.g. pulmonary vascular resistance (PVR), or cardiac index) have not been assessed in the TOMORROW study. As indicated in the concept paper on the need for revision of the paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010), due to the inherent procedural related risks, RHC cannot be requested for study purposes only. Instead, NT-proBNP could be considered an appropriate PD parameter. However, no PK/PD analyses for NT-proBNP both in terms of the paediatric and the adult population have been provided.

The Applicant has discussed about the possible similarity of the relationship between exposure, pharmacodynamic effects and efficacy in children and adults to expand the extrapolation concept based on literature data and pharmacological principles to justify the extrapolation of efficacy based on similar exposure.

The provided literature on the safe and efficacious use of macitentan in children supports the extrapolation of data from the adult population to the paediatric population aged ≥ 2 years, which is therefore considered acceptable. However, considering that in the provided publications the median age was ≥ 8.5 years or above, that the paediatric patients aged < 2 years in the TOMORROW study did not provide additional relevant information on efficacy and that the PK of

children aged < 2 has still not been established which precludes a recommendation for an appropriated dose for these patients, there is still insufficient evidence for children aged < 2 that similar exposures results in similar pharmacodynamic effects. Consequently, the indication has been limited to children aged ≥ 2 years.

2.6.4. Conclusions on clinical pharmacology

In conclusion, the objective of the three relative bioavailability studies was to show comparable systemic exposure with the adult film-coated tablet and the two dispersible tablets that were used on the clinical development.

The clinical pharmacology properties of macitentan and aprocitentan in paediatric patients with PAH from 1 month to less than 18 years old have been characterized using a non-linear mixed effects modelling approach from Study AC-055-312 and Study PAH3001 together with adult patients with PAH (Study AC-055-303). Overall, the modelling strategy is endorsed.

Based on the evidence provided, the inconsistency of the initial proposal to achieve exposure levels matching the adult exposure in patients from 6 months to less than 2 years of age, the lack of recruited patients below 1 year of age, the non-reliable model predictions in children < 2 years of age, it is not possible to accept any macitentan dosing recommendation in patients below 2 years of age. Thus, the therapeutic indication was restricted to patients ≥ 2 years.

2.6.5. Clinical efficacy

The Applicant followed a **2-step staggered approach** to present the pediatric efficacy data.

In the **first step**, a calendar driven interim analysis was performed for the participants ⩾2 years of age including also all currently available data of participants <2 years of age.

In a second step, follow-up analysis were provided.

Submitted efficacy data for treatment of PAH in pediatric **participants ≥2 to <18 years** of age were based on:

- All PK, safety, and efficacy data collected during the completed Core Period of the **TOMORROW study** for participants ⩾**2 years** of age and older and for participants **≥1 month to <2 years** of age.
- The **interim** PK, safety and efficacy data of **study PAH3001** (up to Week 24 visit for the first 2 enrolled participants <2 years of age) for participants **≥3 months to <2 years of age in Japan**.
- **Population PK modelling and simulation study** based on results from the paediatric TOMORROW study (full data set of the completed Core Period), Study PAH3001 (up to the Week 24 visit for the first 2 enrolled participants <2 years of age) and the adult SERAPHIN study.
- **Pharmacodynamic similarity assessment of** data from the adult SERAPHIN study and the completed Core Period of the paediatric TOMORROW study **(≥2 years of age)** for extrapolation of efficacy data.
- **Pharmacodynamic similarity assessment** of macitentan treatment using combined data from participants ≥1 month to <2 years of age (from the completed Core Period of TOMORROW and up to the Week 24 visit of PAH3001), data from participants ≥2 to <18 years of age (from the completed Core Period of TOMORROW), and adult data from the SERAPHIN study.
- The **combined descriptive analysis** of PK, safety, and efficacy of macitentan in participants from **1 month to less than 2 years** of age based on data from the TOMORROW and PAH3001(up to the Week 24 visit) studies. Note that the PAH1013 study has been terminated and no participants have been enrolled.

The summary of the clinical studies supporting this submission is shown in the tables below.

Table E-01: Overview of the main macitentan study included in the efficacy analysis

Study ID (Protocol Number)	**Countries/ Territories** **Number of Centers**	**Design/** **Study Population** **Primary Objective(s)** **Secondary Objective (s)**	**Total Number of Subjects**	**Study Drug(s): Formulation** **(Route of Administration)** **Dose Regimen** **Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Primary endpoint**
AC-055-312 **(TOMORROW)** Ongoing **[PIP study 8]**	This study was conducted at 51 study centers in: AUS, BRA, CHN, COL, ESP, FRA, HUN, ISR, MEX, MYS, PHE, POL, PRT, KOR, RUS, THA, UKR, USA, VNM	Phase 3 Prospective, open-label, randomized, controlled, parallel group, multicenter study Enrolled subjects were pediatric participants with PAH who were ⩾1 month to <18 years [1]. To evaluate the PK of macitentan in children with PAH. To evaluate safety and efficacy of macitentan in PAH children.	Planned: 200 to 300 Randomized :(⩾2 years of age): 148 Enrolled (<2 years of age): 9 Treated: 156 Recruitment has been closed.	Macitentan: 0.5, 2.5, and 5.0 mg dispersible tablet FMI: 1.0 mg and 2.5 mg dispersible tablet (Oral) Children less than (<) 2 years old will be assigned as a cohort to the macitentan group without randomization. The dose will be adjusted to the participant's age (for those <2 year old) or to the participant's body weight (for those greater than or equal to ⩾2 years old). SAEP will start at end of core period visit and ends at end of study visit. Up to 5 years[2]	**Age ≥2 to <18 Years [3,4]** Macitentan: 72 SoC: 75 **Age ≥1 month to <2 years:** Macitentan: 9	Trough (pre-dose) plasma concentrations of macitentan and its active metabolite aprocitentan at Week 12 (steady-state)

[1] Enrolment of participants 1 month to <2-years of age was enabled with protocol version 9.0.

[2] Study duration for each individual participant was varying and was based on their time of enrolment. At the EOCP, the Core Period of the study had been ongoing up to 7 years.

Table E-02. Overview of supportive studies contributing to the efficacy and safety for the Paediatric PAH Indication.

Study ID (Protocol Number)	**Countries/ Territories** **Number of Centers**	**Design/** **Study Population** **Primary Objective(s)** **Secondary Objective (s)**	**Total Number of Subjects**	**Study Drug(s): Formulation** **(Route of Administration)** **Dose Regimen** **Duration of Treatment**	**Number of Subjects Treated (by Treatment Group)**	**Primary endpoint**

PAH1013 **[PIP study 11]**	DEU, POL	Phase 1 Open-label, single-arm, Multicenter Children aged 1 month to <2 years with PAH To evaluate the pharmacokinetics of macitentan and its active metabolite (aprocitentan) in children aged 1 month to <2 years Safety and efficacy of macitentan in PAH children.	Planned: 10 **Enrolled: 0** **Treated: 0.** Study has been terminated. No patients were enrolled.	NA	Macitentan: 1 mg and 2.5 mg dispersible tablets (Oral) Participants will receive macitentan as a monotherapy or add-on to an existing therapy daily for 24 weeks during core treatment period. Optional treatment extension period of up to 1 year (with Macitentan: 3.5 mg and 5 mg) for those participants who completed the core treatment period. 24 weeks (optional up to 1.5 years)	Trough (pre-dose) plasma concentrations of macitentan and its active metabolite aprocitentan at Week 12 (steady-state)
PAH3001 *Ongoing*	This study is conducted in Japan.	Phase 3. Open-label, single-arm, multicenter study Japanese pediatric participants (aged between ⩾ 3 months and < 15 years) with PAH To evaluate the effect of macitentan on hemodynamic measures at Week 24. Safety and efficacy of macitentan in PAH children	<u>Planned:</u> 6 <u>Randomized :</u> 4 **<u>Treated: 2</u>**	NA	Macitentan: 1mg and 2.5 mg dispersible table (Oral) Participants will receive oral dose of macitentan based on age and body weight through Week 52. 52 weeks	Fold change at Week 24 in pulmonary vascular resistance index (PVRI)
Extrapolation, Modelling and simulation Population PK model	NR	To support extrapolation and the use of macitentan in children from 1 month to less than 18 years of age with PAH.				To compare the exposure to macitentan between paediatric subjects and adults using the logtransformed daily steady-state AUC.

AC-055-302 (**SERAPHIN)** *Completed*	This study was conducted at 158 study centers in: ARG, AUS, AUT, BEL, BGR, BLR, CAN, CHE, CHN, COL, DEU, DNK, ESP, FRA, GBR, HKG, HRV, HUN, IND, ILS, ITA, MYS, MXN, NLD, PER, POL, NOR, ROU, RUS, SGP, SRB, SVK, SWE, TUR, TWN, THA, UKR, USA, ZAF	Phase 3 Randomized, double-blind, placebo-controlled, parallel group, multicenter study Men or women of **at least 12 years of age with symptomatic PAH** (WHO Group 1.1-1.3 of the Venice classification) in modified WHO FC II to IV To demonstrate that macitentan prolongs time to the first morbidity or mortality event and to evaluate the benefit/risk profile of macitentan in the treatment of patients with symptomatic PAH	<u>Randomized:</u> 742 <u>Treated:</u> 742 <u>Completed:</u> 590	Macitentan 3 mg: 250 Macitentan 10 mg: 242 Placebo: 250 **Pediatric Participants (<18 years)**: 6 Macitentan 10 mg : 6	Macitentan: 3 mg and 10 mg (film coated tablet) Placebo: Matching Group 1: Macitentan 3 mg qd Group 2: Macitentan 3 mg qd Group 3: matching placebo qd 36 months	Time to first morbidity-mortality event.

AC-055-303 PK (Seraphin OL)	This study was conducted at 8 study centers in BLR, MEX RUS, SRB, SWE,	Phase 3 Prospective, single-arm, open-label, multicenter, PK substudy. To assess the PK of macitentan and its active metabolite ACT-132577 in patients with PAH.	Enrolled: 20 Treated: 20 Completed: 20	Macitentan: 10 mg film coated tablet (Oral) On Day 1, the study drug, one 10 mg tablet of macitentan, was taken immediately after the morning pre-dose blood sample at the clinic. Following this, the patient was considered enrolled into the SERAPHIN_PK substudy. Blood samples for PK were then drawn at specified time points after study drug administration over a 24-hour time period 2 days	20	

AC-055-305 **(MAESTRO)** *Completed*	AUT, BGR, CHE, CHN, CZE, ESP, FRA, DEU, GBR, GRC, HUN, ISR, ITA MYS, MEX, NLD, PHL, POL, PRT, ROU, RUS, SRB, TUR, USA, VNM, ZAF 71	Phase 3 Prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter study Men and women of at least 12 years of age with a confirmed diagnosis of Eisenmenger Syndrome, including subjects with Down's Syndrome 3 in WHO FC II, III or IV4. To demonstrate that macitentan improves exercise capacity in comparison to placebo in subjects with Eisenmenger Syndrome	<u>Randomized:</u> 226 <u>Treated:</u> 226 <u>Completed:</u> 223	Macitentan: 10 mg film coated tablet Placebo: Matching placebo (Oral) Eligible subjects were randomized in a 1:1 ratio to receive either macitentan 10 mg or placebo. 16 weeks	Macitentan: 114 Placebo: 112 **Pediatric participants (12 to <17 years):** Macitentan: 13 Placebo: 2	Change from baseline to Week 16 in exercise capacity, as measured by the 6-minute walk distance (6MWD)
AC-055H301 **(RUBATO)** *Completed*	AUS, CAN, CHN, CZE, DNK, FRA, NZL, POL, TWN, GBR, USA 27	Phase 3 Prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter study Men or women of **at least 12 years of age** To assess the effect of macitentan on exercise capacity (measured by peak VO2) in comparison with placebo in Fontan-palliated participants.	<u>Completed:</u> 130	Placebo: Matching placebo (Oral) Participants were randomized to 1:1 ratio in macitentan 10 mg or placebo 52 weeks	Macitentan: 68 Placebo: 69 **Pediatric participants (12 to <18 years):** Macitentan: 8	Change in peak VO2 (mL/kg/min) from baseline (randomization/Visit 2) to Week 16 (Visit 4).

2.6.5.1. Dose-response studies

The proposed dose for children is age and body weight dependent, with a dose range from 5 to 10 mg. A dispersible tablet formulation has been developed to accommodate the lower dose in the paediatric population. For paediatric use, macitentan will be provided as dispersible tablets for oral administration at dose strengths of 2.5 mg (FMI), and the 10 mg film-coated tablet approved for adults will also be available for paediatric use in patients ≥40 kg.

Table E-03: Recommended paediatric dosing regimen based on body weight

Body weight (kg)	Daily dose	Recommended number of tablets to be dispersed
≥ 10 and < 20	5 mg	2 x 2.5 mg
≥ 20 and < 40	7.5 mg	3 x 2.5 mg
≥ 40	10 mg	4 x 2.5 mg*

*Opsumit is also available as a 10 mg film-coated tablet. Opsumit administered in the form of one 10 mg film-coated tablet is bioequivalent to four 2.5 mg dispersible tablets. Therefore, one film-coated tablet may be used as a direct replacement for paediatric patients who weigh at least 40 kg and are aged 2 years and older.

No dedicated dose-finding study was conducted in paediatric patients with PAH. Dose recommendation proposed in SmPC is supported by clinical pharmacology [Please see Section 2. Clinical pharmacology].

Selected doses to the target paediatric population (i.e., aged 2 years to 17 years old with PAH classified as WHO functional class II and III) proposed are intended to reflect exposures comparable to the approved daily 10 mg dose of macitentan in adults (Procedure No EMEA/H/C/002697/0000;

To compare the exposure to macitentan between paediatric and adult PAH participants, population PK analyses were employed. The PK analyses were based on the pooled population of paediatric and adult participants from Study TOMORROW, Study PAH3001, and Study AC-055-303_PK (SERAPHIN-OL) where the target adult exposure was based on the PK substudy of SERAPHIN-OL.

Table E04. Clinical pharmacology studies in participants with PAH

Study ID	Objective(s)	Participants	Dose	Route	Formulation	Included in Population PK
AC-055-312 (TOMORROW), PK substudy	To evaluate the PK of macitentan in children with PAH	N=26 [a] (patients with PAH, aged ≥2 years to <18 years)	3.5, 5, 7.5, or 10 mg per day, depending on body weight	oral	Dispersible tablet (CSF or FMI) [b]	Yes
AC-055-312 (TOMORROW), Addendum	To evaluate the PK of macitentan in children with PAH	N=7 (patients with PAH, aged <2 years)	1 or 2.5 mg per day, depending on age	oral	Dispersible tablet (CSF or FMI) [b]	Yes
PAH3001	To evaluate the effect of macitentan on hemodynamic measures at Week 24	N=2 (Japanese patients with PAH, aged <2 years)	2.5 or 3.5 mg per day, depending on age	oral	Dispersible tablet (FMI)	Yes
AC-055-303_PK	To assess the PK of macitentan and its active metabolite in	N=20 (adults with PAH, 25 to 72 years	10 mg per day	oral	Film-coated tablet	Yes

[a] In total, 29 participants aged ≥2 years were enrolled and 26 had evaluable PK profiles.
[b] Initially, the macitentan CSF (0.5, 2.5, and 5.0 mg dispersible tablets) was used as study drug. The CSF was replaced by the pediatric FMI formulation (1.0 mg and 2.5 mg dispersible tablets) during the study.

2.6.5.2. Main study(ies)

Main study in this application was the pivotal clinical trial is **AC-055-312 (TOMORROW Study).**

Study AC-055-312 (TOMORROW): pediaTric use Of Macitentan tO delay disease pRogRessiOn in PAH Worldwide.

TOMORROW study is an ongoing prospective, multicentre, open label, randomized, controlled, parallel group, Phase 3 study with an open-label, single-arm extension period to assess pharmacokinetics, safety, and efficacy of macitentan versus SoC in paediatric participants with PAH ≥1 month to <18 years of age.

The initial submission provided by the MAH was based on Analysis 1:

- **Analysis 1**: (interim analysis of Core Period).
  The PK, safety, and efficacy data reported for Analysis 1 were based on the following clinical data cutoffs (participants who have not discontinued from the study were followed beyond these CCOs):
    - **CCO1 (30 November 2022)** analyses were performed for the **population ≥2 years.**
    - **CCO3 (21 July 2023)** analyses were performed for the **population <2 years.**

As part of the response to D120 List of Questions, data was provided based on Analysis 2:

- **Analysis 2** (final analysis of Core Period).

Since the study is still ongoing, Analysis 3 data is not available

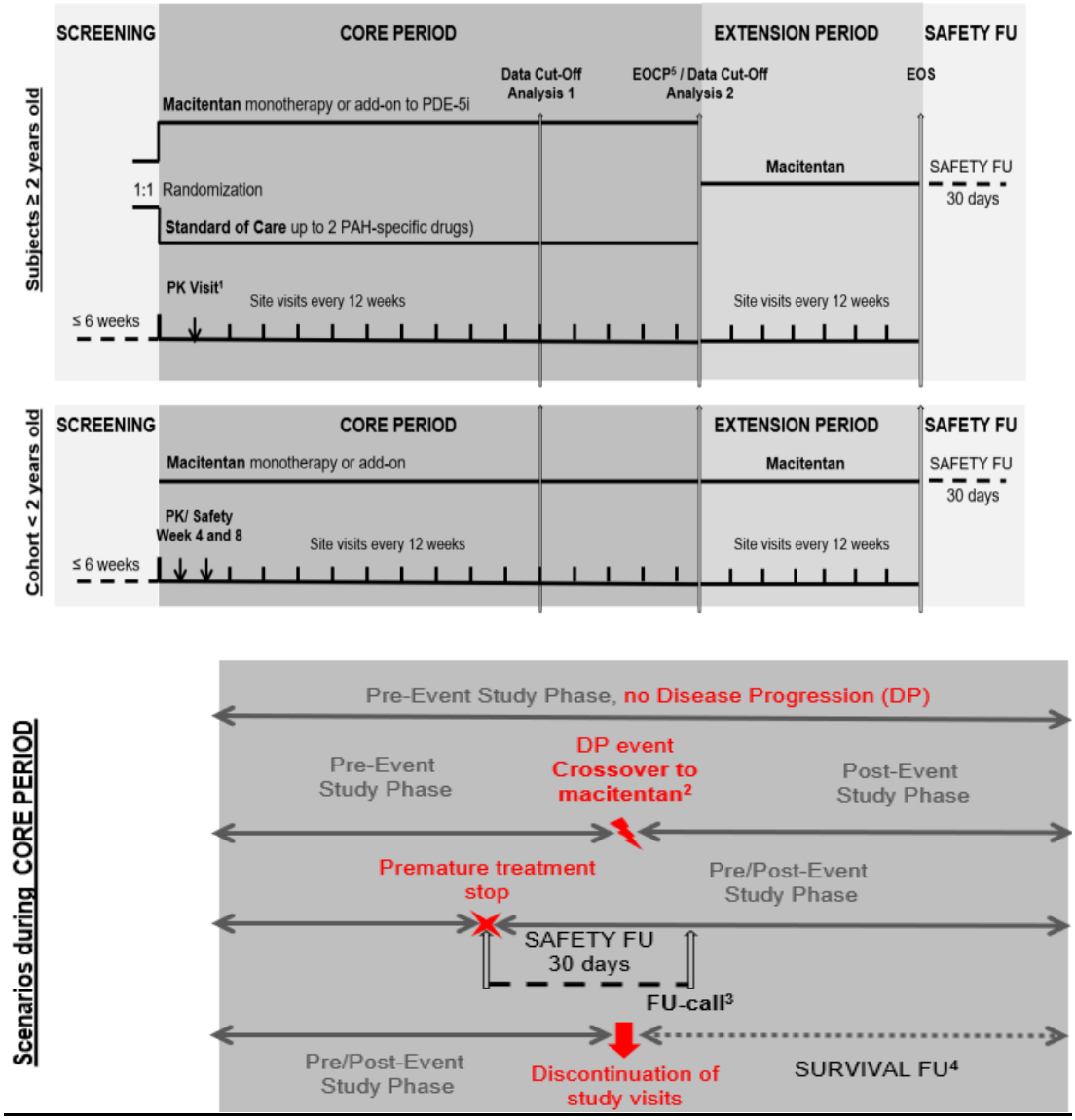
- **Analysis 3** (final analyses including the Core Period and the SAEP).

This is a calendar-driven study and time points of analysis depend on dates to meet regulatory commitment. As such, the number of participants enrolled in the study at the current cut-off date does not reflect the planned study participant numbers which were initially driven by an event-driven study design. Study duration for each participant is based on their time of enrolment.

At the Analysis 1 timepoint: the Core Period of the study was ongoing for at least 5 years. All participants were planned to remain in the study until the cut-off date for Analysis 2 in 2024. Study participation in the core period at timepoint of Analysis 2 was up to 7 years. Thereafter, if it is considered in the best interest of the participant, continuation in the open-label single-arm extension period with macitentan will be offered.

Enrolment of children <2 years of age was only initiated once sufficient PK data for macitentan were obtained in older children in the TOMORROW study. Therefore, the recruitment period for children <2 years of age is shorter as compared to the recruitment period of the older age groups.

Figure E-01: TOMORROW study design



EOS = end of study; FU = follow-up; IV = intravenous; PAH = pulmonary arterial hypertension; PDE-5i =phosphodiesterase Type 5 inhibitor; PK = pharmacokinetics; SC = subcutaneous.
1 The PK Visit will occur under steady-state conditions (i.e., ≥ 10 days of same macitentan dose)
2 After disease progression confirmed by the CEC, the subject enters the Post-Event Study Phase. In the macitentan group, the study treatment will continue during this Post-Event Study Phase until EOS. Subjects in the SoC group will be offered cross-over to macitentan, if this is considered in the best interests of the subject per their investigator' s judgement.
3 Subjects discontinuing macitentan or SoC treatment prematurely have a Safety FU call 30 days (+ 1 week) after the treatment stop. End of standard of care will be declared, if a planned PAH-specific drug class is discontinued, or if any additional PAH-specific drug class is added, or if subjects cross-over to macitentan after CEC-confirmed disease progression.
4 Subjects discontinuing site visits during the Core Period will have Survival FU contacts at least yearly to collect vital status.
5 Subjects still in the 12-weekly visit schedule at Analysis 2 will come for the EOCP Visit before the cutoff date announced by the Sponsor, and will be offered to enter the single-arm extension period. The eligibility to continue/start macitentan in the single-arm extension period (SAEP) must be confirmed as described in Section 8.13.
For subjects who continue macitentan or SoC treatment until EOCP but do not enter the SAEP, the EOCP will constitute their EOS Visit and they will have a Safety FU call 30 days (+ 1 week) after EOS. Note: For subjects who after EOS in the SAEP cannot access macitentan continued access program will be put in place (e.g., post-trial access [PTA] or long-term extension [LTE] study) to allow treatment continuation as per local regulations. For subjects who complete the study treatment and who are eligible for a continued access program (PTA or LTE study), enrollment into the continued access program should occur on the same day as the EOS Visit to avoidmacitentan treatment interruption and the Safety FU period will be waived.

Methods

Study Participants

- Key inclusion/exclusion criteria for TOMORROW study:

Eligibility for enrolment was based on the results of screening for the following inclusion and exclusion criteria:

Inclusion criteria

- Males or females between ≥ 1 month and < 18 years of age.
- Subjects with body weight ≥3.5 kg at randomization.
- PAH diagnosis confirmed by historical RHC (mPAP ≥ 25 mm Hg, and PAWP ≤ 15 mm Hg, and PVRi > 3 WU x m2), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by LAP or LVEDP (in absence of mitral stenosis) assessed by heart catheterization.
- PAH belonging to the Nice 2013 Updated Classification Group 1 (including subjects with Down Syndrome) and of following etiologies:
    - iPAH
    - hPAH
    - PAH associated with CHD:
        – PAH with co-incidental CHD (confirmed by BCAC)
        – Post-operative PAH (persisting/recurring/developing ≥ 6 months after repair of CHD)
    - Drug or toxin-induced PAH
    - PAH associated with HIV
    - PAH-aCTD
- WHO FC I to III.
- PAH-specific treatment-naïve subjects or subjects on PAH-specific treatment (mono-therapy or combination of two therapies) *.

    **Treatments other than PDE-5 inhibitors, such as prostanoids, cannot be continued in the macitentan arm, and therefore will have to be stopped if the patient is randomized into the macitentan arm. The appropriateness of stopping such treatment must be assessed by the investigator before screening the patient for the study and should not be done for the sole objective of selecting a patient for the study.*

- Females of childbearing potential must have a negative pregnancy test at Screening and at Baseline, and must agree to undertake monthly pregnancy tests, and to use a reliable method of contraception (if sexually active) up to EOS.

Exclusion criteria

- Subjects with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.
- Subjects with PAH associated with open shunts, as specified below:
    a. Eisenmenger syndrome
    b. Moderate to large left-to-right shunts.
- Subjects with the following congenital cardiac abnormalities:
    a. Cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, pulmonary atresia with ventricular septal defect, unless operatively repaired and with no residual shunt
    b. Univentricular heart and/or subjects with Fontan-palliation.
- Subjects with pulmonary hypertension due to lung disease (e.g., bronchopulmonary dysplasia).

- Subjects with known diagnosis of bronchopulmonary dysplasia
- Subjects receiving a combination of > 2 PAH-specific treatments at randomization.
- Treatment with IV or SC prostanoids within 4 weeks before randomization, unless given for vasoreactivity testing.
- In children ≥ 2 y.o.: Previous treatment with macitentan at any time.
- Treatment with another investigational drug within 4 weeks prior to randomization.
- Any PAH-related surgical intervention planned, or subjects listed for organ transplantation related to PAH.
- Treatment with strong inducers of CYP3A4 such as rifabutin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort (hypericum perforatum), within 4 weeks prior to randomization.
- Systemic treatment with strong inhibitors of CYP3A4 such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone elfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole within 4 weeks prior to randomization.
- Systemic treatment with moderate dual CYP3A4/ CYP2C9 inhibitor (e.g., fluconazole and amiodarone), or administration of a combination of a moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole, piperine) within 4 weeks prior to randomization.
- Subjects with pulmonary vein stenosis.
- Known concomitant life-threatening disease with a life expectancy < 12 months.
- Hemoglobin or hematocrit < 75% of the lower limit of normal range (LLN).
- Serum AST and/or ALT > 3 ×ULN.
- Severe hepatic impairment, e.g., Child-Pugh Class C
- Clinical signs of hypotension which in the investigator's judgment would preclude initiation of a PAH-specific therapy.
- Severe renal insufficiency (estimated creatinine clearance 221 µmol/L)
- Pregnancy (including family planning) or breastfeeding.
- Known hypersensitivity to ERAs, or any of the excipients.
- Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study treatment

Treatments

Participants ≥2 years who were confirmed eligible at Visit 2 were randomized in a 1:1 ratio to either receive macitentan or initiate/continue standard of care (SoC).

Children <2 years of age are assigned as a cohort to the macitentan group without randomization.

- Macitentan

Macitentan, open-label, was administered once daily via oral route in dispersed form in water (including participants who can swallow tablets) to children randomized to the macitentan arm of the study.

- Participants with no PAH-specific therapy at randomization received macitentan monotherapy.
- Participants on a PDE-5i monotherapy at randomization received macitentan as add-on therapy.
- Participants on an ERA or oral/inhaled prostanoids monotherapy at randomization received macitentan monotherapy instead.
- Participants on a PDE-5i in combination with another PAH-specific therapy at randomization
  received the combination of macitentan and the PDE-5i.

- SoC

The study protocol did not impose any predefined comparator drug. SoC (including PAH non-specific treatment and/or up to 2 PAH-specific medications as per local practice) was administered to the children ⩾2 years who were randomized to the control arm.

Participants treated with a phosphodiesterase type 5 inhibitor (PDE-5i) and/or other PAH-specific treatment (such as an ERA or inhaled/oral prostanoids) at baseline continued their medications. Additional PAH-specific therapy (excluding macitentan and IV/SC prostanoids) prescribed as SoC in IRT prior to Visit 2 could be initiated.

Participants randomized to the SoC arm were treated as follows:

- Participants on only PAH non-specific medications at randomization continued on their medications.
- Participants on a PDE-5i and/or on other PAH-specific treatment (such as ERA, or inhaled/oral prostanoids) at randomization continued on their medications.
- For all participants, additional PAH-specific therapy (excluding macitentan and IV/SC prostanoids), if prescribed during the screening period, could be initiated.

During the Pre-event study phase, participants ≥ 2 y.o. were randomized to receive either macitentan once daily or SoC. During the post-event study phase, background treatment may have been escalated in both treatment arms as per local practice. Any additional treatment, including IV or SC prostanoids, was allowed in both treatment arms. Participants in the macitentan arm could continue to receive macitentan. Participants in the SoC arm were offered to cross over to macitentan treatment if Clinical Event Committee (CEC) had confirmed the disease progression and this was in their best interests per their investigator's judgment.

Study duration for each individual participant was based on their time of enrolment.

Concomitant and rescue therapies

PAH non-specific therapies (e.g., diuretics, anticoagulants, oxygen, calcium channel blockers) and changes to such medications are allowed during all study periods in both treatment arms.

- *Screening Period*
  Any PAH-specific therapy (excluding macitentan and IV/SC prostanoids) can be given or initiated as mono- or combination therapy with a maximum of two treatments.

- *Core Period*

  - *Macitentan group:* In subjects ≥ 2 years, a PDE-5 inhibitor was the only allowed PAH-specific background medication until disease progression in the macitentan arm. All other PAH-specific medications must be stopped.

    After randomization and in the presence of PAH worsening, any PAH-specific treatment and/or continuous oxygen and/or IV diuretics, except ERA, could be initiated per investigator's judgment.

    Participants in the macitentan arm continued receiving macitentan after a CEC-confirmed disease progression event.

  - *SOC arm:* Any PAH-specific treatment (other than macitentan and IV/SC prostanoids) as either mono- or double combination therapy prescribed as SoC before randomization could be administered.
    Participants in the SoC arm were offered macitentan if the CEC confirmed disease progression and if this was considered in the best interests of the participant per their investigator's judgment.

- *Single-arm Extension Period*

Any PAH-specific medication except an ERA could be administered in addition to macitentan.

- Cohort of children **<2 years:**

  allowed to use macitentan during Screening period. Participants <2 y.o. that were on off-label macitentan at the time of Screening were eligible for enrolment.
  Oral/ inhaled prostanoid treatment were also allowed as PAH-specific background therapy in all study periods.

Objectives

- Primary objective:

  - To evaluate the PK of macitentan in children with PAH.

- Secondary objectives:

  - To assess safety and tolerability of macitentan in children with PAH.
  - To assess efficacy of macitentan in children with PAH

Outcomes/endpoints

- *Primary PK endpoint*

  In participants ≥2 years in the macitentan arm: Trough (predose) plasma concentrations of macitentan and its active metabolite aprocitentan at Week 12 (steady-state)

  In participants <2 y.o. on macitentan: Trough concentrations of macitentan and its active metabolite aprocitentan at Week 4 (steady-state).

  PK data was listed by subject number and PK endpoints were analyzed descriptively by body weight and age group in subjects ≥ 2 y.o. and < 2 y.o., respectively.

- *Secondary efficacy endpoint (key efficacy endpoint)*

  Time to first CEC-confirmed disease progression: Time to the first of the following CEC-confirmed disease progression events occurring between randomization/Visit 2 and EOCP:
  - Death (all causes)
  - Atrial septostomy or Potts' anastomosis, or registration on lung transplant list
  - Hospitalization due to worsening PAH[§]
  - Clinical worsening* of PAH defined as:
    - Need for, or initiation of new PAH-specific therapy[#] or IV diuretics or continuous oxygen use AND at least 1 of the following:
      - Worsening in WHO FC, or
      - New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or
      - New occurrence or worsening of at least 2 PAH symptoms (ie, shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue), or
      - New occurrence or worsening of signs of right heart failure not responding to oral diuretics.
    - [§] Excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (e.g., pneumonia).
  - Worsening from Baseline.
    - # E.g., ERA, PDE-5 inhibitor, prostanoid, IP receptor agonist, soluble guanylate cyclase stimulator

- *Other secondary efficacy endpoints* include:

  - time to first CEC-confirmed hospitalization for PAH between randomization and EOCP

- time to CEC-confirmed death due to PAH between randomization and EOCP;
- time to death (all-causes) between randomization and EOCP,
- WHO FC status (I or II vs III or IV) at Week 24,
- percent baseline plasma NT-proBNP at Week 24,
- a post hoc endpoint was added assessing the time to first NT-proBNP worsening (>35.4 pmol/L) in participants with normal NT-proBNP values at baseline (≤35.4 pmol/L),
- change from baseline to Week 48 in mean daily time spent in moderate to vigorous physical activity as measured by accelerometry,
- change from baseline to Week 24 in tricuspid annular plane systolic excursion (TAPSE), and left ventricular eccentricity index measured by echocardiography (centrally assessed),
- change from baseline to Week 24 in Quality of Life as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15).

- *Exploratory efficacy endpoints*

- Panama FC status (I or II vs III or IV) at Week 24
- Change from Baseline up to Weeks 12, 24, and 48 in exercise capacity as measured by the 6MWT in children ≥6 years of age who were developmentally able to understand and perform the test.

- *Other exploratory Efficacy Endpoint Analyses*

Complementary to the planned analyses, 4 hierarchical composite endpoints (HCEs) have been defined and added as new exploratory efficacy endpoints to maximize the information for decision making while giving priority to the most clinically important event.

The first HCE is defined as per the following components and hierarchy:

1. Time to death or registration for lung transplantation (CEC-confirmed). For participant who died after they were registered for lung transplantation, the date of registration will be considered in the analysis.
2. Time to first CEC-confirmed hospitalization for PAH.
3. Time for first CEC-confirmed clinical worsening.
4. Change in WHO FC from baseline to Week 24.

The second HCE is defined as per the following components and hierarchy:

1. Time to death or registration for lung transplantation (CEC-confirmed). For participant who died after they were registered for lung transplantation, the date of registration will be considered in the analysis.
2. Number of CEC-confirmed hospitalization for PAH.
3. Number of CEC-confirmed clinical worsening.
4. Change in WHO FC from baseline to Week 24.

The third HCE is defined as per the following components and hierarchy:

1. Time to death or registration for lung transplantation (CEC-confirmed). For participant who died after they were registered for lung transplantation, the date of registration will be considered in the analysis.
2. Time to first CEC-confirmed hospitalization for PAH.
3. Time for first CEC-confirmed clinical worsening.
4. Change in WHO FC from baseline to Week 24.
5. Change in PedsQL™ 4.0 SF15 Short Form generic core physical functioning score from baseline to Week 24. The parent's form will be used.

The fourth HCE is defined as per the following components and hierarchy:

1. Time to death or registration for lung transplantation (CEC-confirmed). For participant who died after they were registered for lung transplantation, the date of registration will be considered in the analysis.
2. Time to first CEC-confirmed hospitalization for PAH.
3. Time for first CEC-confirmed clinical worsening.
4. Change in WHO FC from baseline to Week 24.

5. Percent change in NT-proBNP from baseline to Week 24.

Difference in proportion of winners, as well as Win ratio and Win odds, were provided to quantify clinical benefit of macitentan in the paediatric population, along with Finkelstein and Shoenfeld test.

In addition, a multicomponent clinical response definition based on WHO FC, NT-proBNP and BSA-normalized TAPSE at baseline and at Week 24 has been specified (Table E05). A participant must be a responder in all 3 endpoints to be counted as clinical responder in the analysis. If for a given participant, the response cannot be determined and is missing for at least one endpoint, the participant will be counted as non-clinical responder. The differences in proportions of responders between treatment groups has been quantified.

Table E-05: Response criteria for each endpoint included in the multicomponent clinical response

Endpoint	Baseline	Week 24	Responder
WHO FC	I/II	I/II	Yes
		III/IV	No
	III*	I/II	Yes
		III/IV	No
NT-proBNP (pmol/L)	< 35.4# pmol/L	< 35.4# pmol/L	Yes
		≥ 35.4# pmol/L	No
	≥ 35.4# pmol/L and <76.7# pmol/L	< 35.4# pmol/L	Yes
		≥ 35.4# pmol/L and <76.7# pmol/L	Yes
		≥ 76.7# pmol/L	No
	≥76.7# pmol/L and ≤129.8# pmol/L	< 76.7# pmol/L	Yes
		≥76.7# pmol/L and ≤ 129.8# pmol/L	Yes
		>129.8# pmol/L	No
	>129.8# pmol/L	≤ 129.8# pmol/L	Yes
		>129.8# pmol/L **and** percent change from baseline < -10%	Yes
		>129.8# pmol/L **and** percent change from baseline ≥ -10%	No
BSA-normalized TAPSE (mm/m^2)	≥ 15/BSA mm/m^2	≥ 15/BSA mm/m^2	Yes
		< 15/BSA mm/m^2	No
	< 15/BSA mm/m^2	≥ 15/BSA mm/m^2	Yes
		< 15/BSA mm/m^2 and percent change from baseline > 10%	Yes
		< 15/BSA mm/m^2 and percent change from baseline ≤ 10%	No

Sample size

The sample size of approximately 200 participants and not more than 300 participants was driven by feasibility, and no formal sample size calculations are provided. The study recruitment is to be closed by the fourth quarter of 2023 to allow at least 12 weeks study follow-up for Analysis 2 in the first quarter of 2024. Analysis 1 and 2 cutoff dates were driven by the regulatory timelines.

Randomisation and blinding (masking)

Screening Period: from signed informed consent and ends with randomization or confirmation of screening failure (up to 6 weeks after signed informed consent).

Subjects ⩾2 years who were confirmed eligible at Visit 2 were centrally assigned/randomized via an IRT system in a 1:1 ratio to either receive macitentan or initiate/continue standard of care (SoC).

Randomization was stratified by ongoing/planned endothelin receptor antagonist (ERA) treatment (yes vs no) and by World Health Organization functional class (WHO FC) (FC I/II vs FC III) at

randomization. The proportion of participants with ERA treatment, as a component of the planned SoC, was limited to a maximum of 40% of the overall number of randomized participants.

Subjects <2 years of age**:** the stratification variables at randomization do not apply to this cohort. This cohort is only enrolled into the macitentan arm. The ERA cap did not apply to this cohort.

Blinding: None (Open label). A CEC, consisting of independent paediatric PAH experts, was appointed to review and adjudicate in a blinded fashion the secondary endpoints related to disease progression.

Statistical methods

The study was originally designed to enrol a sufficient number of children to observe at least 187 primary disease progression events. Given recruitment challenges and number of events observed by 2021, the study design was changed from an event-driven study to a PK, safety, and efficacy study with a fixed study duration (calendar-driven analysis timepoints).

Time points of analysis depend on dates to meet regulatory commitment. As such, the number of participants enrolled in the study at the current cutoff date does not reflect the planned study participant numbers which were initially driven by an event-driven study design. Study duration for each participant is based on their time of enrolment.

The planned analyses timepoints for the study overall are:

- **Analysis 1**: (interim analysis of Core Period).
  The PK, safety, and efficacy data reported for Analysis 1 were based on the following clinical data cutoffs (participants who have not discontinued from the study were followed beyond these CCOs):
    - CCO1 (30 November 2022) analyses were performed for the population ≥2 years.
    - CCO3 (21 July 2023) analyses were performed for the population <2 years.
- **Analysis 2** (final analysis of Core Period).
- **Analysis 3** (final analyses including the Core Period and the SAEP).

Analysis Sets

The Final Analysis of Core Period CSR includes all data from participants ⩾2 y.o. and <2 y.o. from the Core Period of the study.

Data analysis sets were parsed by age for pharmacokinetics (PK Set), safety (safety analysis set [SAS]), and efficacy (full analysis set [FAS]) and included PK Set 1 and PK Set 2 (⩾2 y.o.); SAS1 (⩾2 y.o.), SAS 2 (<2 y.o.) and SAS3 (⩾2 y.o. and <2 y.o.); and FAS1 (⩾2 y.o.), FAS 2 ((⩾2 y.o.) and FAS3 (⩾2 y.o. and <2 y.o.).

Overall testing strategy: The analysis of the primary PK variable was presented by descriptive summaries, and no hypothesis testing was performed. The analysis of secondary and exploratory endpoints was presented using p-values compared to the nominal 0.05 2-sided alternative (where applicable) as this was not a formal significance conclusion. There was no multiplicity control for secondary endpoints.

- PK

Primary PK analysis: Primary analysis was performed on PK Set 1. Trough plasma concentrations of macitentan and aprocitentan at Week 12 (participants ⩾2 y.o.) were summarized by body weight, age group, and overall, respectively, using arithmetic mean, geometric mean, minimum,

median, maximum, SD, SE,CV, and 2-sided 95% confidence interval (CI) of the mean. For PK Set 3, trough plasma concentrations of macitentan and aprocitentan at steady state (Week 4) were summarized. If the Week 4 PK sample was not evaluable, the Week 8 PK sample was used. PK endpoints were analyzed descriptively by age group in participants <2 y.o. (agegroups <6 months and ⩾6 months based on age at Screening).

- Safety

Analysis of the safety variables was performed as per SAP from randomization (or Visit 2 for participants <2 y.o.) until EOCP. Adverse events (AEs), serious adverse events (SAEs), AEs leading to premature treatment discontinuation were summarized for 3 different periods of interest:

-*Overall core period* (the randomization date (or Visit 2 for participants <2 y.o.) up to end of Core Period).

-*Main treatment period* (for participants ≥2 y.o., from the randomization date up to end of randomized macitentan or SoC + 30 days (or end of Core period whichever comes first), or for crossover participants up to start of macitentan or end of SoC + 30 days, whichever comes first. For participants <2 y.o., from Visit 2 up to end of macitentan + 30 days (or end of Core period whichever comes first).

-*Post-crossover to macitentan period for crossover participants only*. From the start of macitentan (initiated at crossover) up to end of macitentan + 30 days or the end of the Core Period, whichever comes first. For crossover participants, baseline is the last non- missing value recorded before or on the start of macitentan (initiated at crossover).

Summary tables were produced for safety sets SAS1 for participants >2 y.o. and SAS2 for participants <2 y.o. Summary tables were also produced by age category, gender, and race. Mostly all AEs were summarized for the "Overall core period" and "Main treatment period" for all subjects and for the"Post-crossover to macitentan period" only for crossover subjectsLaboratory tests were summarized in the Main treatment period and the Post-crossover to macitentan period for crossover participants. Other safety variables (vital signs, growth and sexual maturation) were summarized only on the Main treatment period.

- Efficacy:

The analysis of the time-to-event secondary efficacy variables were performed according to the intent-to-treat principle. Treatment effect estimates, 95% CIs, and p-values are provided for exploratory purposes only. No multiplicity adjustment was applied for the multiple analysis timepoints.

The analysis of the time-to-event efficacy variables was performed using a 2-sided stratified log-rank test with the stratification factors as ongoing/planned ERA treatment (yes vs no) and WHO FC (FC I/II vs FC III) performed at randomization as documented in the IRT. The treatment effect was estimated based on a Cox proportional hazards model adjusting for the same randomization stratification factors. Estimates of each HR and the associated 95% CIs were displayed. Kaplan-Meier estimates were calculated with 2-sided 95% CIs at relevant timepoints for each treatment arm and displayed in both a graphical (where the number of participants at risk was at least 10% of the total number of participants in the analysis set) and a tabular form. In addition, the number of participants at risk, the number of participants censored, and the number of participants with event were computed at each timepoint and for each treatment arm.

Subjects with no CEC-confirmed disease progression had their time to disease progression right-censored at the time of EOCP, or cutoff date for the respective analysis, whichever comes first. No additional imputation method was used.

- The analysis of other efficacy variables (WHO FC status, NT-pro BNP levels, change in moderate to vigorous physical activity, echocardiographic parameters) considered values collected up to the end of randomized macitentan or SoC + 7 days (or up to the clinical cutoff date, whichever occurred first), or up to start of macitentan for crossover participants.

- Health Outcomes

QoL as measured by the PedsQL™ 4.0 SF15 Short Form Generic Core Scales: Total scores across all ages and by age groups, separately for parent/caregiver reports and for subject reports. As the answers to each question are reverse scored, a higher score indicates better health. Values were collected up to the end of randomized macitentan or SoC + 7 days (or up to the clinical cutoff date, whichever occurred first), or up to start of macitentan for crossover participants. Quality of life was not collected in the cohort of subjects < 2 y.o.

Analysis 2 cutoff date was the primary analyses for these endpoints; p-values will be provided in addition to the treatment effect estimates and 95% CLs. No multiplicity adjustment will be applied.

- Subgroups analysis

Subgroup analyses, based on the FAS1 were performed for key efficacy endpoint (first CEC-confirmed disease progression events), with a separate analysis for each subgroup variable using an un-stratified proportional hazards regression:

- WHO FC at randomization (I/II vs III)
- Ongoing/planned ERA at randomization (Yes vs No)
- Ongoing/planned PDE-5i treatment at randomization (Yes vs No)
- PAH etiology ([iPAH, hPAH, HIV, drug or toxin induced,] vs. [PAH with coincidental
- CHD, CHD post-operative] vs [PAH-aCTD])
- Geographical region (North America vs Europe/Israel vs Asia/Australia vs Other)
    - Europe/Israel is considered reference category because it is the largest region
- Age for participants ≥2 y.o. (≥2 to <6 years / ≥6 to <12 years / ≥12 to <18 years)
    - -The oldest age group is considered reference category because it is closest to adult
    - population
- Age for participants <2 y.o. (<6 months/ ≥6 months).
- Sex (male vs female)
- Race (white vs black or African American vs. Asian vs. Other [includes Other, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Applicable)

Results

Participant flow

Disposition of participants at EOCP is presented in Table E-06. Out of the 157 participants, 1 participant in the macitentan arm did not receive treatment.

Table RSI E-06. Participants Disposition; FAS3 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care	Macitentan (< 2 Years Old)	Total
Analysis set: FAS3	73	75	9	157
Subjects enrolled < 2 years old	-	-	9 (100.0%)	9 (5.7%)
Subjects randomized ≥ 2 years old	73 (100.0%)	75 (100.0%)	-	148 (94.3%)
Subjects treated	72 (98.6%)	75 (100.0%)	9 (100.0%)	156 (99.4%)
Subjects ≥ 2 years old who prematurely discontinued randomized macitentan or SoC during the Core Period	17 (23.3%)	31 (41.3%)	-	48 (30.6%)
Subjects < 2 years old who prematurely discontinued macitentan during the Core Period	-	-	1 (11.1%)	1 (0.6%)
Crossover subjects	-	8 (10.7%)	-	8 (5.1%)
Subjects who prematurely withdrew from regular study visits during the Core Period	17 (23.3%)	21 (28.0%)	1 (11.1%)	39 (24.8%)
Subjects who prematurely withdrew from study	14 (19.2%)	15 (20.0%)	1 (11.1%)	30 (19.1%)
Subjects who are lost to follow-up in the Core Period	1 (1.4%)	2 (2.7%)	0	3 (1.9%)
Subjects who completed the Core Period	59 (80.8%)	60 (80.0%)	8 (88.9%)	127 (80.9%)
Subjects who enroll in single-arm extension study	48 (65.8%)	40 (53.3%)	8 (88.9%)	96 (61.1%)
Subjects who completed the study	9 (12.3%)	21 (28.0%)	0	30 (19.1%)

Children ≥ 2 years

At EOCP a total of 148 participants ≥2 y.o. were randomized to receive either macitentan or SoC.

Of the 48 participants ≥2 y.o. who prematurely discontinued study treatment (32.7% of participants ≥2 y.o.), the main reasons for discontinuation were physician's decision (25 [17.0%], of which 15 participants [10.2%] discontinued for lack of efficacy/treatment failure, 1 in the macitentan arm and 14 in the SoC arm), parent/participant's decision (14 participants [9.5%], 7 in each arm), and death (8 participants [5.4%], 6 in the macitentan arm and 2 in the SoC arm). No participants discontinued treatment due to the COVID-19 pandemic nor due to the regional crisis in Ukraine and Russia.

For participants ≥2 y.o., percentage of discontinuations was comparable between age groups, with a trend for an increase of discontinuations in the older age groups. The difference in the percentage of discontinuations between the SoC arm and the macitentan arm was higher in the ≥12 to <18 years age group:

- ≥2 to <6 years age group: 4 participants (30.8%) discontinued in the macitentan arm and 10 (45.5%) in the SoC arm. Reasons for discontinuation were death (2 participants [15.4%] in the macitentan arm and 2 participants [9.1%] in the SoC arm), physician's decision (1 participant [7.7%] in the macitentan arm and 7 participants [31.8%] in the SoC arm), and parent/subject's decision (1 participant [7.7%] in the macitentan arm).

- ≥6 to <12 years age group: 6 participants (20.7%) discontinued in the macitentan arm and 9 (28.1%) in the SoC arm. Reasons for discontinuation were death (1 participant [3.4%] in the
macitentan arm), physician's decision (3 participants [10.3%] in the macitentan arm and 8 participants [25.0%] in the SoC arm), and parent/subject's decision (2 participants [6.9%] in
the macitentan arm and 1 participant [3.1%] in the SoC arm).

- ≥12 to <18 years age group: 7 participants (23.3%) discontinued in the macitentan arm and 12 (57.1%) in the SoC arm. Reasons for discontinuation were death (3 participants [10.0%] in the macitentan arm), physician's decision (6 participants [28.6%] in the SoC arm), and parent/subject's decision (4 participants [13.3%] in the macitentan arm and 6 participants
28.6%] in the SoC arm).

Children <2 years

At EOCP total of 9 participants <2 y.o. were enrolled and treated with macitentan. One participant <2 y.o. (11.1%) prematurely discontinued macitentan during the Core Period due to parent/subject's decision.

This study was conducted at 51 centers that enrolled participants ≥2 y.o. in 18countries: Australia (2), Brazil (1), China (1), Colombia (2), Spain (2), France (3), Hungary (1), Israel (2), Republic of Korea (2), Mexico (4), Philippines (1), Poland (3), Portugal (3), Russian Federation (5), Thailand (1), Ukraine (3), United States of America (8), and Viet Nam (4).

Participants <2 y.o. were enrolled in 7 sites across 6 countries: Hungary, Mexico, Malaysia, Philippines, Portugal, and United States of America.

Conduct of the study

Since the original protocol (issued on 2016), there have been 8 global amendments and 27 country-specific amendments (17 of which were implemented). The most important was Amendment 8: Global Version 9 (23 Nov 2021). The following changes were implemented: the study was originally designed to enrol a sufficient number of children to observe at least 187 primary disease progression events. Given recruitment challenges and number of events observed by 2021, the study design was changed from an event-driven study to a PK, safety, and efficacy study with a fixed study duration (calendar-driven analysis timepoints).

The primary objective of the TOMORROW study is to describe PK of macitentan in pediatric patients with PAH. The secondary objectives of the TOMORROW study are the evaluation of safety and efficacy of macitentan in pediatric pulmonary arterial hypertension (PAH) patients. Consequently, previous primary endpoint has been changed to a secondary endpoint.

The study population was extended to children less than 2 years of age since sufficient PK data had been collected in the pediatric population to determine the daily macitentan dose for the youngest cohort.

The FMI was introduced to gradually replace the Clinical Formulation. The FMI introduced new dose strengths (1 mg and 2.5 mg macitentan dispersible tablets) which as opposed to the Clinical Formulation were distinguishable through form and debossing and therefore appropriate for future commercial use.

An open-label SAEP, which was planned as a separate study protocol, was integrated into the present study protocol to allow seamless transition of all participants to macitentan treatment if this was considered in their best interest after the last efficacy analysis (in 2024).

Baseline data

Children ≥ 2 years

The 148 randomized participants ⩾2 y.o. comprised 88 (59.5%) females and 60 (40.5%) males. The mean±SD age of participants was 9.75 years±4.429, with 35 (23.6%) aged ⩾2 to <6 years, 61 (41.2%) aged ⩾6 to <12 years, and 52 (35.1%) aged ⩾12 to <18 years. Fewer Asian (15 [20.5%] versus 22 [29.3%]) and more white (44 [60.3%] versus 32 [42.7%]) participants were randomized to macitentan than to SoC, respectively. The macitentan arm included more participants aged ⩾12 to <18years (31 [42.5%] versus 21 [28.0%]) and more female participants (50 [68.5%] versus 38[50.7%]) than the SoC arm (Table E-07).

Table E-07. Summary of Demographics Characteristics for Participants ⩾2 Years Old; FAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Age, years			
N	73	75	148
Mean (SD)	10.54 (4.430)	8.99 (4.320)	9.75 (4.429)
Median	10.30	8.00	9.60
Range	(2.1; 17.9)	(2.1; 17.8)	(2.1; 17.9)
IQ range	(7.50; 14.40)	(5.40; 12.90)	(6.20; 13.60)
≥ 2 - < 6 years	13 (17.8%)	22 (29.3%)	35 (23.6%)
≥ 6 - < 12 years	29 (39.7%)	32 (42.7%)	61 (41.2%)
≥ 12 - < 18 years	31 (42.5%)	21 (28.0%)	52 (35.1%)
Sex			
N	73	75	148
Female	50 (68.5%)	38 (50.7%)	88 (59.5%)
Male	23 (31.5%)	37 (49.3%)	60 (40.5%)
Race			
N	73	75	148
Asian	15 (20.5%)	22 (29.3%)	37 (25.0%)
Black or African American	1 (1.4%)	1 (1.3%)	2 (1.4%)
White	44 (60.3%)	32 (42.7%)	76 (51.4%)
Other	12 (16.4%)	18 (24.0%)	30 (20.3%)
Not Applicable	1 (1.4%)	2 (2.7%)	3 (2.0%)
Ethnicity			
N	73	75	148
Hispanic or Latino	24 (32.9%)	22 (29.3%)	46 (31.1%)
Not Hispanic or Latino	47 (64.4%)	51 (68.0%)	98 (66.2%)
Unknown	2 (2.7%)	2 (2.7%)	4 (2.7%)
Region			
N	73	75	148
North America	6 (8.2%)	6 (8.0%)	12 (8.1%)
Europe/Israel	28 (38.4%)	23 (30.7%)	51 (34.5%)
Asia/Australia	16 (21.9%)	24 (32.0%)	40 (27.0%)
Other	23 (31.5%)	22 (29.3%)	45 (30.4%)
Weight, kg			
N	73	75	148
Mean (SD)	36.36 (18.295)	30.58 (16.520)	33.43 (17.599)
Median	34.50	24.00	28.15
Range	(10.0; 75.5)	(10.0; 73.3)	(10.0; 75.5)

IQ range	(21.20; 51.00)	(17.00; 40.30)	(18.75; 47.30)
Height, cm			
N	73	75	148
Mean (SD)	134.96 (24.776)	128.75 (24.326)	131.81 (24.663)
Median	139.00	126.30	133.00
Range	(80.0; 176.0)	(79.0; 182.2)	(79.0; 182.2)
IQ range	(118.40; 155.20)	(111.00; 145.50)	(112.15; 152.00)
Down Syndrome			
N	73	75	148
Present	5 (6.8%)	5 (6.7%)	10 (6.8%)
Absent	68 (93.2%)	70 (93.3%)	138 (93.2%)

Key: IQ = Interquartile; SD = Standard deviation.
Note: N's for each parameter reflect non-missing values.
Percentage is calculated as the number of subjects in the category divided by N * 100.

The majority of participants had iPAH (71 participants [48.0%]) at baseline. Fifty-seven participants (out of 73) in the macitentan arm and 62 (out of 75) in the SoC arm declared at least 1 sign and symptom of PAH at Baseline, and in those participants, the mean±SD of signs and symptoms per participant was comparable between arms. Number of participants with WHO FC III was comparable between arms (13 [17.8%]) in the macitentan arm versus 15 [20.0%] the SoC arm). Baseline mean±SD NT-proBNP (pmol/L) was higher in the macitentan arm compared with the SoC arm but the associated median value was lower in the macitentan arm.

The majority of participants ≥2 y.o. had PAH-specific therapies ongoing/planned at randomization, with the exception of 6 participants (4.1%) who had non-PAH-specific therapies ongoing/planned at randomization [Table E-08]. Ongoing /planned SoC at randomization (as per IRT) was captured in IRT prior to randomization for stratification (ERA/non-ERA) and study governing purposes.

Table E-08. Summary of baseline disease characteristics for participants ⩾2 years old

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Pulmonary arterial hypertension etiology			
N	73	75	148
Idiopathic PAH	35 (47.9%)	36 (48.0%)	71 (48.0%)
Heritable PAH	1 (1.4%)	5 (6.7%)	6 (4.1%)
PAH with co-incidental CHD	14 (19.2%)	12 (16.0%)	26 (17.6%)
PAH associated with CHD: post-operative	22 (30.1%)	20 (26.7%)	42 (28.4%)
PAH associated with connective tissue disease	1 (1.4%)	2 (2.7%)	3 (2.0%)
Time from PAH diagnosis to randomization, days			
N	73	75	148
Mean (SD)	698.4 (667.21)	667.2 (791.43)	682.6 (730.48)
Median	491.0	345.0	466.5
Range	(27; 3576)	(29; 4668)	(27; 4668)
IQ range	(131.0; 1157.0)	(100.0; 1031.0)	(105.5; 1076.0)
Right heart catheterization performed to diagnose PAH			
N	73	75	148
Yes	73 (100%)	75 (100%)	148 (100%)
Total number of Signs and symptoms of PAH at baseline reported per subject[1]			
N	57	62	119
Mean (SD)	2.4 (1.68)	2.4 (1.40)	2.4 (1.53)
Median	2.0	2.0	2.0
Range	(1; 9)	(1; 7)	(1; 9)
IQ range	(1.0; 3.0)	(1.0; 3.0)	(1.0; 3.0)
Specification of signs and symptoms of PAH at baseline[1]			
N	57	62	119
Dyspnea with exertion	51 (89.5%)	58 (93.5%)	109 (91.6%)
Dyspnea at rest	4 (7.0%)	3 (4.8%)	7 (5.9%)
Cyanosis with exertion	13 (22.8%)	11 (17.7%)	24 (20.2%)
Cyanosis at rest	5 (8.8%)	8 (12.9%)	13 (10.9%)
Hemoptysis	1 (1.8%)	0	1 (0.8%)
Chest pain/discomfort	7 (12.3%)	12 (19.4%)	19 (16.0%)
Near-syncope/dizziness	8 (14.0%)	2 (3.2%)	10 (8.4%)
Syncope	4 (7.0%)	3 (4.8%)	7 (5.9%)
Fatigue	38 (66.7%)	44 (71.0%)	82 (68.9%)
Hepato-jugular reflux	1 (1.8%)	3 (4.8%)	4 (3.4%)
Hepatomegaly	4 (7.0%)	4 (6.5%)	8 (6.7%)
Peripheral edema	1 (1.8%)	0	1 (0.8%)

	Randomized Macitentan	Randomized Standard of Care	Total
S3 gallop	1 (1.8%)	1 (1.6%)	2 (1.7%)
WHO functional class[2]			
N	73	75	148
I	19 (26.0%)	18 (24.0%)	37 (25.0%)
II	41 (56.2%)	42 (56.0%)	83 (56.1%)
III	13 (17.8%)	15 (20.0%)	28 (18.9%)
Panama functional class			
N	68	72	140
I	16 (23.5%)	19 (26.4%)	35 (25.0%)
II	42 (61.8%)	37 (51.4%)	79 (56.4%)
IIIa	10 (14.7%)	13 (18.1%)	23 (16.4%)
IIIb	0	3 (4.2%)	3 (2.1%)
Ongoing/planned ERA treatment at randomization as per IRT			
N	73	75	148
Yes	33 (45.2%)	34 (45.3%)	67 (45.3%)
No	40 (54.8%)	41 (54.7%)	81 (54.7%)
NT-pro BNP, pmol/L			
N	66	70	136
Mean (SD)	145.33 (414.72)	77.12 (141.14)	110.22 (306.86)
Median	18.23	21.18	20.59
Range	(2.36; 3052.90)	(1.06; 642.04)	(1.06; 3052.90)
IQ range	(7.55; 52.51)	(7.91; 41.42)	(7.85; 51.51)
Baseline BSA-normalized TAPSE[3], mm/m^2			
N	67	69	136
Mean (SD)	14.819 (5.2773)	17.525 (6.8239)	16.192 (6.2382)
Median	13.360	17.610	16.090
Range	(6.44; 29.37)	(5.11; 34.43)	(5.11; 34.43)
IQ range	(10.950; 18.700)	(11.780; 22.570)	(11.220; 20.645)
Baseline left ventricular eccentricity index (diastole)[3]			
N	66	64	130
Mean (SD)	1.462 (0.5036)	1.505 (0.5273)	1.483 (0.5139)
Median	1.380	1.365	1.370
Range	(0.90; 4.20)	(0.90; 4.40)	(0.90; 4.40)
IQ range	(1.100; 1.580)	(1.200; 1.670)	(1.200; 1.600)
Baseline left ventricular eccentricity index (systole)[3]			
N	66	64	130
Mean (SD)	1.815 (0.7144)	1.820 (0.8972)	1.817 (0.8064)
Median	1.535	1.550	1.535
Range	(0.90; 4.30)	(0.80; 5.45)	(0.80; 5.45)
IQ range	(1.300; 2.100)	(1.250; 2.065)	(1.300; 2.100)
Ongoing / Planned SoC at randomization (as per IRT)			
N	73	75	148
Non-PAH-specific therapies	3 (4.1%)	3 (4.0%)	6 (4.1%)

	Randomized Macitentan	Randomized Standard of Care	Total
PDE-5 inhibitor (PDE-5i) monotherapy	39 (53.4%)	36 (48.0%)	75 (50.7%)
ERA monotherapy	7 (9.6%)	5 (6.7%)	12 (8.1%)
PDE-5i + ERA	23 (31.5%)	29 (38.7%)	52 (35.1%)
PDE-5i + inhaled/oral prostanoids	1 (1.4%)	1 (1.3%)	2 (1.4%)
PDE-5i + sGC stimulator	0	1 (1.3%)	1 (0.7%)

Key: BSA = Body surface area; CHD = Congenital heart disease; ERA = Endothelin receptor antagonist; HIV = Human immunodeficiency virus; IQ = Interquartile; IRT = Interactive response technology; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PDE-5i = Phosphodiesterase type 5 inhibitor; SD = Standard deviation; sGC = Soluble guanylate cyclase stimulator; SoC = Standard of care; TAPSE = Tricuspid annular plane systolic excursion; WHO = World Health Organization.

[1] A subject may have more than one sign or symptom denoting PAH reported as present.

[2] Subjects with WHO functional class IV at baseline are not eligible as per inclusion criteria.

[3] As per central review of echocardiogram.

Medical history for participants ≥2 y.o. was comparable between the macitentan and SoC arms.

The more frequent PTs in medical history (>10% of participants in either treatment arm) were atrial septal defect (19 participants [26.0%] in the macitentan arm and 11 participants [14.7%] in the SoC arm), ventricular septal defect (11 participants [15.1%] in the macitentan arm and 11 participants [14.7%] in the SoC arm), and patent ductus arteriosus (8participants [11.0%] in the macitentan arm and 5 participants [6.7%] in the SoC arm) (Attachment TSIMH01).

The most frequent PT in medical history of participants <2 y.o. (reported in more than 1 participant) were atrioventricular septal defect (2 participants [22.2%]) and ventricular septal defect (2 participants [22.2%]).

PAH-specific concomitant therapies in participants ⩾2 y.o. were similar in the Main treatment period and the Overall core period (Table E-09). In the Main treatment period, 60 participants (82.2%) in the macitentan arm and 75 participants (100%) in the SoC arm had at least 1 PAH-specific concomitant therapy. The more frequent PAH-specific concomitant therapies (>10% of participants in either treatment arm) were sildenafil (53 participants [72.6%] in the macitentan arm and 69 participants [92.0%] in the SoC arm), tadalafil (8 participants [11.0%] in the macitentan arm and 4 participants [5.3%] in the SoC arm), and bosentan (3 participants [4.1%] in the macitentan arm and 36 participants [48.0%] in the SoC arm). All 3 participants in the macitentan arm who received bosentan did so either before receiving first dose of randomized macitentan, after a disease progression event, or after discontinuing macitentan.

Table E-09. PAH-specific concomitant therapies - by period for subjects ⩾ 2 years old; FAS1 Analysis Set (Study AC-055-312)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75	73	75
Subjects with at least one therapy	60 (82.2%)	75 (100.0%)	62 (84.9%)	75 (100.0%)
Preferred term				
SILDENAFIL	53 (72.6%)	69 (92.0%)	55 (75.3%)	69 (92.0%)
TADALAFIL	8 (11.0%)	4 (5.3%)	9 (12.3%)	6 (8.0%)
TREPROSTINIL	4 (5.5%)	2 (2.7%)	4 (5.5%)	6 (8.0%)
BOSENTAN	3 (4.1%)	36 (48.0%)	5 (6.8%)	37 (49.3%)
RIOCIGUAT	2 (2.7%)	0	2 (2.7%)	0
SELEXIPAG	2 (2.7%)	0	2 (2.7%)	1 (1.3%)
ILOPROST	1 (1.4%)	0	1 (1.4%)	1 (1.3%)
MACITENTAN	1 (1.4%)	3 (4.0%)	2 (2.7%)	3 (4.0%)
AMBRISENTAN	0	3 (4.0%)	0	4 (5.3%)
EPOPROSTENOL	0	0	0	1 (1.3%)

Key: EOCP = End of core period; PAH = Pulmonary arterial hypertension; SoC = Standard of care.
1 Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
2 Overall core period: from randomization up to EOCP. Note: Preferred Terms are based on WHO-DRUG dictionary version Global-B3-2022-09.
Only PAH specific concomitant therapies with start date or ongoing during the period under consideration are included.

PAH-specific concomitant therapies reported for participants after crossover to macitentan (8 participants) were sildenafil (7 participants [87.5%]), treprostinil (2 participants [25.0%]), and tadalafil (1 participant [12.5%]).

Children <2 years

Of the 9 participants <2 y.o., the majority were male (8 participants [88.9%]). Three participants were Asian, 2 were white, 2 were Black or African American, and 2 were classified as 'Other' for race. Two out of 9 participants were of ethnicity Hispanic or Latino. Age at Baseline was in the range 1.2 to 1.9 years.

PAH etiology for the 9 participants was PAH associated with CHD (post-operative PAH [persisting/recurring/developing ⩾6 months after repair of CHD]) (4 participants), iPAH (4 participants) and PAH with co-incidental CHD (1 participant). Time from PAH diagnosis to enrollment was in the range 20 to 422 days. Four participants had WHO FC II and 5 participants had WHO FC I at Baseline. Baseline NT-proBNP (pmol/L) values were in the range 10.15 to 1496.71 pmol/L. RHC had been performed at Baseline for all 9 participants.

The most frequent PT in medical history of participants <2 y.o. (reported in more than 1 participant) were atrioventricular septal defect (2 participants [22.2%]) and ventricular septal defect (2 participants [22.2%]).

Three participants <2 y.o. (33.3%) had at least 1 prior medication (non-PAH specific). The most frequent prior non-PAH specific therapy (more than 1 participant) was digoxin (2 participants [22.2%]). At Baseline, 6 participants <2 y.o. (66.7%) were on PDE-5i monotherapy (sildenafil, 5 participants [55.6%], and tadalafil, 1 participant [11.1%]). No participant received ERA concomitant to macitentan.

Treatment duration for the 9 participants <2 y.o. ranged from 7.0 to 72.9 weeks. Median duration of treatment of 37.14 weeks.

For participants <2 y.o., dose increases were permitted for changes in age category. Dose changed from 2.5 to 3.5 mg due to change in age category in 4 out of 9 participants (age change from <2 y.o. to ≥2 y.o.). Treatment was temporarily interrupted (not due to an AE) in 2 participants (interrupted for 48 days and 4 days, respectively).

Numbers analysed

Children ≥ 2 years

A total of 148 participants ≥2 y.o. were randomized to receive either macitentan or SoC. In total, 48 participants ≥2 y.o., 17 (23.3%) in the macitentan arm and 31 (41.3%) in the SoC arm, had discontinued treatment.

Major protocol deviations (FAS3 Analysis Set, 157 participants) were reported for 24 participants (32.9%) in the macitentan arm and 17 participants (22.7%) in the SoC arm. Eight participants (5.1%) had at least 1 major protocol deviation related to natural disaster, major disruption, or pandemic.

Children <2 y.o

Nine participants <2 y.o. were enrolled and treated with macitentan. One participant <2 y.o. (11.1%) prematurely discontinued macitentan during the Core Period due to parent/subject's decision. Major protocol deviations were reported for 3 participants (33.3%) and included 'trough PK sample (primary endpoint) is missing' (2 participants [22.2%]) and 'incorrect macitentan dose before PK trough sample'. No protocol deviations related to natural disaster, major disruption, or pandemic were reported for any of the 7 participants <2 y.o.

Exposure

Children ≥ 2 years

There was a difference in exposure between arms (253.0 subject-year in macitentan versus 187.7 subject-year in SoC). Treatment duration for participants ≥2 y.o. ranged from 12.9 to 312.4 weeks in the macitentan arm, and from 0.1 to 316.4 weeks in the SoC arm. Mean±SD duration was 183.36±87.121 weeks in the macitentan arm (72 participants treated) and 130.59±93.102 weeks in the SoC arm (75 participants treated). Fifty-eight percent of participants randomized to macitentan were under treatment for at least 36 months, compared with 32% in the SoC arm (Table E-10).

The overall longer treatment duration in the macitentan arm compared to the SoC arm was driven by participants ≥12 y.o., with a mean treatment duration in the SoC arm reduced by about half as compared to macitentan. Treatment duration for the 8 participants ⩾2 y.o. who had a crossover to

macitentan varied from 26.1 to 107.0 weeks; mean±SD treatment duration was 65.75±27.138 weeks.

Table E-10. Duration of randomized treatment for participants ⩾2 years old; SAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Duration of study treatment (Weeks)		
N	72	75
Mean (SD)	183.36 (87.121)	130.59 (93.102)
Median	168.43	115.00
Range	(12.9; 312.4)	(0.1; 316.4)
Cumulative duration of study treatment		
N	72	75
At least 3 months	71 (98.6%)	69 (92.0%)
At least 6 months	68 (94.4%)	66 (88.0%)
At least 12 months	66 (91.7%)	58 (77.3%)
At least 18 months	64 (88.9%)	46 (61.3%)
At least 24 months	58 (80.6%)	41 (54.7%)
At least 30 months	49 (68.1%)	36 (48.0%)
At least 36 months	42 (58.3%)	24 (32.0%)
At least 42 months	35 (48.6%)	22 (29.3%)
At least 48 months	31 (43.1%)	18 (24.0%)
At least 54 months	29 (40.3%)	16 (21.3%)
At least 60 months	20 (27.8%)	10 (13.3%)
At least 66 months	10 (13.9%)	4 (5.3%)
At least 72 months	0	1 (1.3%)
Subject year exposure[a]		
N	72	75
Exposure (years)	253.0	187.7

Children <2 y.o

Treatment duration for the 9 participants <2 y.o. ranged from 7.0 to 72.9 weeks. Median duration of treatment of 37.14 weeks. Six patients were treated at least for 6 months.

Outcomes and estimation

- Key efficacy endpoint:

  - *Time to First Confirmed Disease Progression Event*

As of EOCP, fewer events of CEC-confirmed disease progression were observed in participants ⩾2 y.o. in the macitentan arm (21 events/73 participants) versus the SoC arm (24 events/75 participants), with a stratified HR of 0.828 (95% CI= [0.46; 1.49]; 2-sided stratified p-value=0.567)]). No statistically significant reduction of risk in disease progression was noted (Tables E-11, E-12).

Table E-11. Time to First CEC-confirmed disease progression event for participants ⩾2 years Old; FAS1 Analysis Set (Study AC-055-312).

Endpoint	Statistic	Macitentan (n=73)	Standard of Care (n=75)
Time to first CEC-confirmed disease progression[a]	Number censored	52 (71.2%)	51 (68.0%)
	Participants with event	21 (28.8%)	24 (32.0%)
	Analysis	*Stratified*[b]	
	Hazard Ratio	0.828	
	95% CI	(0.460, 1.492)	
	2-sided p-value	0.567	
		Unstratified[c]	
	Hazard Ratio	0.800	
	95% CI	(0.445, 1.438)	
	2-sided p-value	0.455	

[a] Includes all participants ongoing in the study at the time of cutoff.
[b] p-value from a log-rank test stratified by the 2 stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard Ratio is from Cox proportional hazards model adjusted for the 2 stratification factors.
[c] p-value is from a log-rank test (unstratified). Hazard ratio is from Cox proportional hazards model (unadjusted).

Table E-12. Time to First CEC-Confirmed Disease Progression Event for Subjects ≥ 2 Years Old; FAS1 Analysis Set (Study AC-055-312) [Attachment TEFCEC01].

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Subjects with event	21 (28.8%)	24 (32.0%)	45 (30.4%)
Death (all causes)	4 (5.5%)	3 (4.0%)	7 (4.7%)
Atrial septostomy or Potts' anastomosis, or registration on lung transplant list	0	0	0
Hospitalization due to worsening PAH	2 (2.7%)	0	2 (1.4%)
Clinical worsening of PAH	15 (20.5%)	21 (28.0%)	36 (24.3%)
Subjects censored	52 (71.2%)	51 (68.0%)	103 (69.6%)
Core period completed*	48 (65.8%)	44 (58.7%)	92 (62.2%)
Study withdrawal: Parent/subject decision	3 (4.1%)	4 (5.3%)	7 (4.7%)
Lost to follow-up	1 (1.4%)	2 (2.7%)	3 (2.0%)
Study withdrawal: Physician decision	0	1 (1.3%)	1 (0.7%)
Time to event (months)			
25th percentile (95% CI)	41.5 (17.7, 61.0)	31.1 (14.3, 41.5)	32.4 (20.5, 42.3)
Median (95% CI)	NE (61.0, NE)	NE (41.5, NE)	NE (61.0, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.3, 61.0)	(1.9, 44.6)	(0.3, 61.0)
Time to censoring (months)+			
25th percentile (95% CI)	27.2 (21.7, 32.0)	22.5 (13.3, 30.2)	24.6 (20.2, 30.2)
Median (95% CI)	43.6 (32.0, 58.1)	35.9 (28.6, 50.4)	38.5 (33.1, 51.6)
75th percentile (95% CI)	61.2 (58.1, 66.2)	59.5 (47.6, 63.5)	60.5 (58.0, 63.7)
Range	(0.0, 71.9)	(3.5, 72.8)	(0.0, 72.8)
Time to premature censoring (months)+[a]			
25th percentile (95% CI)	0.0 (0.0, 33.8)	6.2 (6.0, 11.4)	6.0 (0.0, 11.4)
Median (95% CI)	16.9 (0.0, NE)	11.4 (6.0, 19.3)	11.4 (0.0, 33.8)
75th percentile (95% CI)	47.4 (0.0, NE)	19.3 (8.3, NE)	33.8 (8.3, NE)
Range	(0.0, 60.9)	(6.0, 50.4)	(0.0, 60.9)
6-month event-free rate (95% CI)	95.8 (87.5, 98.6)	91.9 (82.9, 96.3)	93.8 (88.4, 96.7)
Subjects at Risk	68 (93.2%)	67 (89.3%)	135 (91.2%)
Subjects Censored (cum)	2 (2.7%)	2 (2.7%)	4 (2.7%)
Subjects with Event (cum)	3 (4.1%)	6 (8.0%)	9 (6.1%)
12-month event-free rate (95% CI)	90.0 (80.2, 95.1)	87.7 (77.6, 93.4)	88.8 (82.4, 93.0)
Subjects at Risk	62 (84.9%)	60 (80.0%)	122 (82.4%)
Subjects Censored (cum)	4 (5.5%)	6 (8.0%)	10 (6.8%)
Subjects with Event (cum)	7 (9.6%)	9 (12.0%)	16 (10.8%)
18-month event-free rate (95% CI)	85.6 (74.9, 92.0)	81.7 (70.5, 88.9)	83.6 (76.4, 88.8)
Subjects at Risk	58 (79.5%)	54 (72.0%)	112 (75.7%)
Subjects Censored (cum)	5 (6.8%)	8 (10.7%)	13 (8.8%)
Subjects with Event (cum)	10 (13.7%)	13 (17.3%)	23 (15.5%)
24-month event-free rate (95% CI)	81.1 (69.7, 88.6)	80.1 (68.6, 87.7)	80.5 (72.9, 86.2)
Subjects at Risk	51 (69.9%)	48 (64.0%)	99 (66.9%)
Subjects Censored (cum)	9 (12.3%)	13 (17.3%)	22 (14.9%)
Subjects with Event (cum)	13 (17.8%)	14 (18.7%)	27 (18.2%)
30-month event-free rate (95% CI)	79.4 (67.7, 87.3)	76.6 (64.5, 85.0)	78.0 (70.0, 84.1)
Subjects at Risk	43 (58.9%)	41 (54.7%)	84 (56.8%)

	Randomized Macitentan	Randomized Standard of Care	Total
Subjects Censored (cum)	16 (21.9%)	18 (24.0%)	34 (23.0%)
Subjects with Event (cum)	14 (19.2%)	16 (21.3%)	30 (20.3%)
36-month event-free rate (95% CI)	75.5 (62.9, 84.3)	66.0 (52.2, 76.7)	70.8 (61.8, 78.1)
Subjects at Risk	35 (47.9%)	28 (37.3%)	63 (42.6%)
Subjects Censored (cum)	22 (30.1%)	26 (34.7%)	48 (32.4%)
Subjects with Event (cum)	16 (21.9%)	21 (28.0%)	37 (25.0%)
42-month event-free rate (95% CI)	73.0 (59.8, 82.5)	63.5 (49.3, 74.7)	68.3 (58.9, 76.0)
Subjects at Risk	30 (41.1%)	25 (33.3%)	55 (37.2%)
Subjects Censored (cum)	26 (35.6%)	28 (37.3%)	54 (36.5%)
Subjects with Event (cum)	17 (23.3%)	22 (29.3%)	39 (26.4%)
48-month event-free rate (95% CI)	65.7 (51.3, 76.8)	58.4 (43.7, 70.5)	61.9 (51.8, 70.5)
Subjects at Risk	25 (34.2%)	19 (25.3%)	44 (29.7%)
Subjects Censored (cum)	28 (38.4%)	32 (42.7%)	60 (40.5%)
Subjects with Event (cum)	20 (27.4%)	24 (32.0%)	44 (29.7%)
54-month event-free rate (95% CI)	65.7 (51.3, 76.8)	58.4 (43.7, 70.5)	61.9 (51.8, 70.5)
Subjects at Risk	24 (32.9%)	17 (22.7%)	41 (27.7%)
Subjects Censored (cum)	29 (39.7%)	34 (45.3%)	63 (42.6%)
Subjects with Event (cum)	20 (27.4%)	24 (32.0%)	44 (29.7%)
60-month event-free rate (95% CI)	65.7 (51.3, 76.8)	58.4 (43.7, 70.5)	61.9 (51.8, 70.5)
Subjects at Risk	18 (24.7%)	11 (14.7%)	29 (19.6%)
Subjects Censored (cum)	35 (47.9%)	40 (53.3%)	75 (50.7%)
Subjects with Event (cum)	20 (27.4%)	24 (32.0%)	44 (29.7%)
66-month event-free rate (95% CI)	61.0 (44.6, 74.0)	58.4 (43.7, 70.5)	59.2 (48.1, 68.7)
Subjects at Risk	9 (12.3%)	4 (5.3%)	13 (8.8%)
Subjects Censored (cum)	43 (58.9%)	47 (62.7%)	90 (60.8%)
Subjects with Event (cum)	21 (28.8%)	24 (32.0%)	45 (30.4%)
72-month event-free rate (95% CI)	61.0 (44.6, 74.0)	58.4 (43.7, 70.5)	59.2 (48.1, 68.7)
Subjects at Risk	0	1 (1.3%)	1 (0.7%)
Subjects Censored (cum)	52 (71.2%)	50 (66.7%)	102 (68.9%)
Subjects with Event (cum)	21 (28.8%)	24 (32.0%)	45 (30.4%)
78-month event-free rate (95% CI)	61.0 (44.6, 74.0)	58.4 (43.7, 70.5)	59.2 (48.1, 68.7)
Subjects at Risk	0	0	0
Subjects Censored (cum)	52 (71.2%)	51 (68.0%)	103 (69.6%)
Subjects with Event (cum)	21 (28.8%)	24 (32.0%)	45 (30.4%)
Stratified log-rank test p-value[b]	0.567		
Hazard ratio (adjusted) (95% CI)[b]	0.828 (0.460, 1.492)		
Unstratified log-rank test p-value[c]	0.455		
Hazard ratio (unadjusted) (95% CI)[c]	0.800 (0.445, 1.438)		

Key: CEC = Clinical event committee; CI = Confidence interval; Cum = Cumulative; NE = Not estimable; PAH = Pulmonary arterial hypertension.

[a] Includes only subjects who prematurely discontinued the study.

[b] p-value is from a log-rank test stratified by the two stratification factors: ongoing / planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard ratio is from Cox proportional hazards model adjusted for the two stratification factors.

[c] p-value is from a log-rank test (unstratified). Hazard ratio is from Cox proportional hazards model (unadjusted).

[+] Only censored subjects are included.

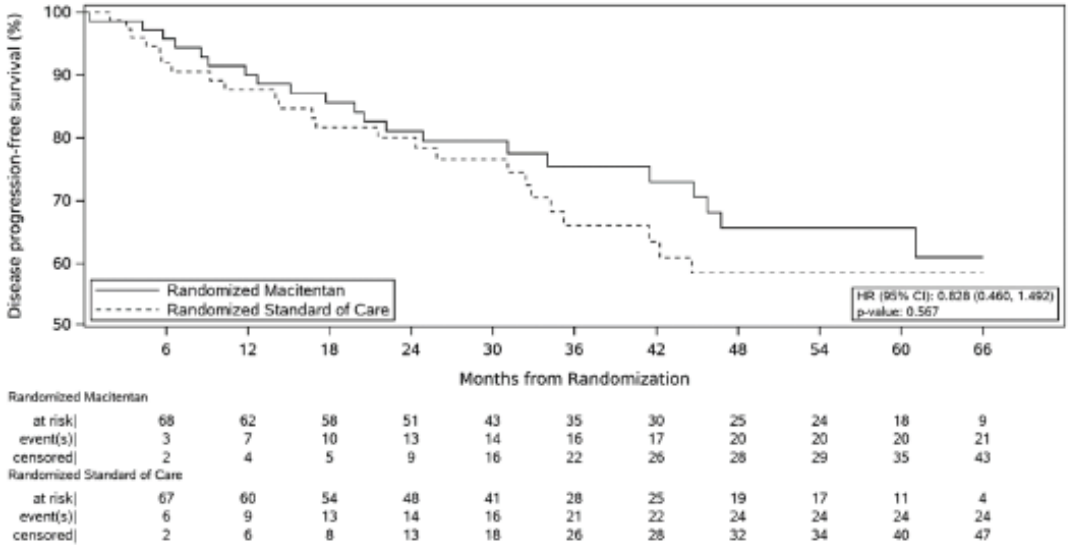
[*] Includes all subjects ongoing in the study at the time of cutoff.

The 12-month event-free rate (95% CI) was 90.0% (80.2, 95.1) in the macitentan arm vs 87.7% (77.6, 93.4) in the SoC arm. The 48-month event-free rate (95% CI) was 65.7% (51.3, 76.8) in the macitentan arm vs 58.4% (43.7, 70.5) in the SoC arm.

Figure E-02: Kaplan-Meier Curves of Time to First CEC-Confirmed Disease Progression Event for Subjects ≥ 2 Years Old; FAS1 Analysis Set (Study AC-055-312).

Figure 4 **Kaplan-Meier Curves of Time to First CEC-Confirmed Disease Progression Event for Participants ≥2 Years Old; FAS1 Analysis Set (Study AC-055-312)**

GEFCEC01: Kaplan-Meier Curves of Time to First CEC-Confirmed Disease Progression Event for Subjects ≥ 2 Years Old; FAS1 Analysis Set (Study AC-055-312)



Randomized Macitentan											
at risk	68	62	58	51	43	35	30	25	24	18	9
event(s)	3	7	10	13	14	16	17	20	20	20	21
censored	2	4	5	9	16	22	26	28	29	35	43
Randomized Standard of Care											
at risk	67	60	54	48	41	28	25	19	17	11	4
event(s)	6	9	13	14	16	21	22	24	24	24	24
censored	2	6	8	13	18	26	28	32	34	40	47

Key: CEC = Clinical event committee; CI = Confidence interval.
Note: p-value is from a log-rank test stratified by the two stratification factors: ongoing / planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard ratio is from Cox proportional hazards model adjusted for the two stratification factors.

[gefcec01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/gefcec01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 13MAR2024, 08:13

The majority of the CEC-confirmed disease progression events had been reported by the investigator and confirmed by CEC (41 out of 45 first CEC-confirmed disease progression events, 91.1%).

- Secondary variables

➢ *Time to First CEC-confirmed Hospitalization for PAH*

The same number of events was observed in the macitentan arm (11 events/73 participants) compared to the SoC arm (11 events/75 participants). The adjusted HR for time to first CEC-confirmed hospitalization for PAH was 0.912 (95% CI: [0.393; 2.118]; 2-sided stratified p-value=0.882) [Table E-13].

Table E-13. Summary of Time to First Confirmed Hospitalization for Pulmonary Arterial Hypertension; FAS1 Analysis Set (Study AC-055-312).

Endpoint	Statistic	Macitentan (n=73)	Standard of Care (n=75)
Time to first CEC-confirmed hospitalization for PAH[a]	Participants censored	62 (84.9%)	64 (85.3%)
	Participants with event	11 (15.1%)	11 (14.7%)
	Analysis	*Stratified*[b]	
	Hazard Ratio	0.912	
	95% CI	(0.393, 2.118)	
	2-sided p-value	0.882	
		Unstratified[c]	
	Hazard Ratio	0.909	
	95% CI	(0.394, 2.100)	
	2-sided p-value	0.824	

[a] Includes all participants ongoing in the study at the time of cutoff.
[b] p-value from a log-rank test stratified by the 2 stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard Ratio is from Cox proportional hazards model adjusted for the 2 stratification factors.
[c] p-value is from a log-rank test (unstratified). Hazard ratio is from Cox proportional hazards model (unadjusted).
Source: Adapted from Attachment TEFCEC02

The 12-month event-free rate (95% CI) was 95.7% (87.3, 98.6) in the macitentan arm vs 94.4% (85.9, 97.9) in the SoC arm. The 48-month event-free rate (95% CI) was 82.7% (69.6, 90.5) in the macitentan arm vs 79.7% (65.3, 88.6) in the SoC arm.

- *Time to CEC-confirmed Death Due to Pulmonary Arterial Hypertension*

More events of CEC-confirmed death due to PAH in participants ≥2 y.o. were observed in participants randomized to the macitentan arm compared with the SoC arm. No statistically significant increase of risk in deaths due to PAH was noted. The stratified HR for time to first CEC-confirmed death due to PAH was 1.530 (95% CI [0.429; 5.457], 2-sided p-value=0.529) [Table E-14].

Table E-14. Summary of Time to Confirmed Death Due to Pulmonary Arterial Hypertension; FAS1 Analysis Set (Study AC-055-312).

Endpoint	Statistic	Macitentan (n=73)	Standard of Care (n=75)
Time to CEC-confirmed death due to PAH[a]	Participants censored	67 (91.8%)	71 (94.7%)
	Participants with event	6 (8.2%)	4 (5.3%)
	Analysis	*Stratified*[b]	
	Hazard ratio	1.530	
	95% CI	(0.429, 5.457)	
	2-sided p-value	0.529	
		Unstratified[c]	
	Hazard ratio	1.440	
	95% CI	(0.406, 5.111)	
	2-sided p-value	0.570	

[a] Includes all participants ongoing in the study at the time of cutoff
[b] p-value from a log-rank test stratified by the 2 stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard Ratio is from Cox proportional hazards model adjusted for the 2 stratification factors.
[c] p-value is from a log-rank test (unstratified). Hazard ratio is from Cox proportional hazards model (unadjusted).

- *Time to Death From all Causes*

The stratified HR for time to first CEC-confirmed death (all causes) was 1.171 (95% CI [0.392; 3.500], 2-sided p-value=0.799) [Table E-15].

Table E-15. Summary of Time to Death from All Causes; FAS1 Analysis Set (Study AC-055-312)

Table 25 Summary of Time to Death From All Causes; FAS1 Analysis Set (Study AC-055-312)

Endpoints	Statistic	Macitentan (n=73)	Standard of Care (n=75)
Time to Death (all Causes)[a]	Participants censored	66 (90.4%)	69 (92.0%)
	Participants with events	7 (9.6%)	6 (8.0%)
	Analysis	*Stratified*[b]	
	Hazard Ratio	1.171	
	95% CI	(0.392, 3.500)	
	2-sided p-value	0.799	
		Unstratified[c]	
	Hazard ratio	1.130	
	95% CI	(0.380, 3.366)	
	2-sided p-value	0.825	

[a] Includes all participants ongoing in the study at the time of cutoff.
[b] p-value from a log-rank test stratified by the 2 stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (I/II vs III) at randomization. Hazard ratio is from Cox proportional hazards model adjusted for the 2 stratification factors.
[c] p-value is from a log-rank test (unstratified). Hazard ratio is from Cox proportional hazards model (unadjusted).

- Other secondary variables

- *WHO Functional Class*

The proportion of participants ≥2 y.o. with WHO FC I or II was higher at Week 12 and at Week 24 in the macitentan arm than in the SoC arm [Table RSI E-16]..

No shifts in WHO FC from I/II to III were observed in participants in the macitentan arm at Week

12 or Week 24, while shifts in WHO FC from I/II to III were observed in 2 participants in the SoC arm both at Week 12 (2.8%) and at Week 24 (3.2%).

All shifts in WHO FC from I/II to III in the macitentan arm occurred in no more than 1 participant (percentage range 1.5% to 9.1% at later timepoints.

Table E-16. WHO Functional Class I or II (Yes vs No) Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Participants for Participants ⩾2 Years Old –Logistic Regression Models; FAS1 Analysis Set (Study AC-055-312).

TEFWHO01: WHO Functional Class I or II (Yes vs No) Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Subjects for Subjects ≥ 2 Years Old - Logistic Regression Models; FAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
Week 12		
N*	63 / 71 (88.7)	58 / 71 (81.7)
Stratified logistic regression		
Odds ratio	4.635	
95% CI for odds ratio	(0.829; 25.910)	
Unstratified logistic regression		
Odds ratio	1.765	
95% CI for odds ratio	(0.682; 4.565)	
Week 24		
N*	63 / 70 (90.0)	52 / 63 (82.5)
Stratified logistic regression		
Odds ratio	6.415	
95% CI for odds ratio	(1.107; 37.164)	
Unstratified logistic regression		
Odds ratio	1.904	
95% CI for odds ratio	(0.689; 5.260)	

Key: ERA = Endothelin receptor antagonist; CI = Confidence interval; FC = Functional class; SoC = Standard of care; WHO = World Health Organization.
* Number of subjects with WHO FC I or II / Total number of subjects with a WHO FC value.
Note: Odds ratio and confidence limit calculated using logistic regression.
Strata are ongoing / planned ERA treatment (yes vs no), WHO FC (I/II vs III).
In case of missing Week 12 values, subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 12, the value of WHO FC will be imputed as the worst case (e.g., IV) at Week 12. The same imputation rule is applied for subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 24, but imputing the worst case at Week 24.

[tefwho01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tefwho01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ;

- *NT-proBNP*

Reductions in NT-proBNP plasma concentration were observed compared to Baseline in both the macitentan and the SoC arms at the majority of visits. Macitentan led to a faster reduction in NT-proBNP plasma concentration as shown by the GLSM ratio between arms equal to 0.72 at Week 12. Afterwards, comparable reductions in NT-proBNP were observed within each treatment group.

Table RSI E-17. Percent of Baseline NT-proBNP (pmol/L) Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Participants for Participants ≥ 2 Years Old - Mixed Model Repeated Measures; FAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
Percent of Baseline NT-proBNP		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	64	65
Week 12		
Geometric LS Mean	0.72	1.01
95% CI of geometric LS Mean	(0.54; 0.98)	(0.75; 1.36)
Geometric LS Means ratio	0.72	
95% CI for geometric LS Means ratio	(0.49; 1.05)	
2-sided p-value	0.086	
Week 24		
Geometric LS Mean	0.76	0.78
95% CI of geometric LS Mean	(0.56; 1.03)	(0.57; 1.07)
Geometric LS Means ratio	0.97	
95% CI for geometric LS Means ratio	(0.66; 1.43)	
2-sided p-value	0.884	
Overall treatment effect[c]		
Geometric LS Mean	0.75	0.86
95% CI of geometric LS Mean	(0.58; 0.96)	(0.66; 1.12)
Geometric LS Means ratio	0.86	
95% CI for geometric LS Means ratio	(0.64; 1.16)	
2-sided p-value	0.333	
Treatment-by-visit interaction p-value	0.258	

[a] Repeated measures mixed model on log-transformed NT-proBNP values.
[b] The subjects included in the analysis are those with baseline and at least one post-baseline value.
The model includes randomized treatment, visit, treatment by visit interaction, the 2 stratification factors and baseline value as fixed effects, and subject as random effect.
[c] The overall treatment effect is estimated using the same model excluding the treatment by visit interaction factor.
Note: After Week 48 only timepoints with a corresponding value in at least 10% of the subjects in the Macitentan arm are displayed.
The treatment effect expressed as geometric means ratio and its associated 95% CI is estimated by inversely transforming the difference in change from baseline between treatment groups and the associated 95% CI, both estimated from the repeated measures mixed model on the log-transformed NT-proBNP values.
Covariance matrix TOEP is used.

Based on the observed data, the mean±SD change from Baseline in NT-proBNP (pmol/L) was greater in the macitentan arm compared with the SoC arm at Week 12 (-49.7965 versus +20.4795 pmol/L) and Week 24 (-55.3517 versus -1.2057 pmol/L).

An analysis to evaluate time to first NT-proBNP value <35.4 pmol/L for participants with a Baseline NT-proBNP value of ≥35.4 pmol/L or a Baseline NT-proBNP value ≤35.4 pmol/L did not show statistical difference between arms .

- *Moderate to Vigorous Physical Activity*

LS mean ±SE change from Baseline in mean daily time spent in MVPA (minutes) for participants ≥2 y.o. are shown in Table RSI E-18. Change from Baseline was greater in the macitentan arm than in the SoC arm at Weeks 12, 24, and 48, however, the difference of LS means between arms was not statistically significant.

Table RSI E-18. Mean Daily Time Spent in Moderate to Vigorous Physical Activity: Change From Baseline Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Subjects for Subjects ≥ 2 Years Old - Mixed Model Repeated Measures; FAS1 Analysis Set (Study AC-055-312).

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
Mean daily time spent in moderate to vigorous physical activity (minutes)		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	64 (87.7%)	65 (86.7%)
Change from baseline to Week 12		
LS Mean (SE)	2.34 (2.995)	1.03 (3.045)
95% CI	(-3.58;8.26)	(-4.99;7.05)
Difference of LS Means (SE) (macitentan minus SoC)	1.31 (3.897)	
95% CI	(-6.40;9.02)	
2-sided p-value	0.737	
Change from baseline to Week 24		
LS Mean (SE)	2.48 (4.039)	1.65 (4.065)
95% CI	(-5.53;10.48)	(-6.41;9.70)
Difference of LS Means (SE) (macitentan minus SoC)	0.83 (5.479)	
95% CI	(-10.05;11.71)	
2-sided p-value	0.880	

	Randomized Macitentan	Randomized Standard of Care
Change from baseline to Week 48		
LS Mean (SE)	2.60 (3.231)	0.24 (3.287)
95% CI	(-3.81;9.01)	(-6.28;6.75)
Difference of LS Means (SE) (macitentan minus SoC)	2.36 (4.280)	
95% CI	(-6.15;10.87)	
2-sided p-value	0.583	
Overall treatment effect[c]		
LS Mean (SE)	3.31 (2.877)	0.19 (2.947)
95% CI	(-2.37;8.99)	(-5.63;6.01)
Difference of LS Means (SE) (macitentan minus SoC)	3.12 (2.876)	
95% CI	(-2.62;8.87)	
2-sided p-value	0.282	
Treatment-by-visit interaction p-value	0.605	

Key: CI = Confidence interval; LS = Least square; SE = Standard error; SoC=Standard of care.
[a] Repeated measures mixed model with randomized treatment, visit, treatment - by - visit interaction, the 2 stratification factors and baseline value as fixed effects, and subject as random effect.
[b] The subjects included in the analysis are those with baseline and at least one post-baseline value.
[c] The overall treatment effect is estimated using the same model excluding the treatment-by-visit interaction factor. Covariance matrix UN is used.
Note: Threshold for moderate to vigorous physical activity is 3200 activity counts per minute.
[tefpa01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tefpa01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-

- *Echocardiography*

No statistically significant differences are observed for echocardiography analyses (TAPSE or LVEI).

BSA-normalized TAPSE: difference between treatment arms in change from Baseline LS means±SE at Week 24 was -0.03±0.580 (95% CI= [-1.18; 1.12], 2-sided p=0.957).

Diastolic LVEI: difference between treatment arms in change from Baseline LS means at Week 24 was 0.03±0.064 (95% CI= [-0.09; 0.16], 2-sided p=0.585).

Systolic LVEI: difference between treatment arms in change from Baseline LS means at Week 24 was -0.06±0.076 (95% CI= [-0.21; 0.09], 2-sided p=0.458).

- *Quality of Life*

The PedsQLTM Pediatric QoL Inventory version 4.0 short form (SF15) was used in this study.

The difference between the treatment arms in the parent report at Week 24 was statistically significant:
6.27±2.666 (95% CI: [0.99; 11.55], 2-sided p=0.020) (Table RSI M-17).

The difference of LS Means (SE) between the treatment arms in the child report at Week 24 was statistically significant: 5.28±2.570 (95% CI=[0.18; 10.37], 2-sided p=0.043) (Table RSI M-17).

Table RSI M-17. Quality of Life Short Form (SF15) Generic Core Scales Total Scores: Change From Baseline Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Subjects -for Participants ⩾2 Years Old -Mixed Model Repeated Measures; FAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
All Ages Total Score - Parent report		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	67 (91.8%)	68 (90.7%)
Change from baseline to Week 12		
LS Mean (SE)	4.24 (1.671)	-0.35 (1.712)
95% CI	(0.94;7.55)	(-3.73;3.04)
Difference of LS Means (SE) (macitentan minus SoC)	4.59 (2.112)	
95% CI	(0.41;8.77)	
2-sided p-value	0.032	
Change from baseline to Week 24		
LS Mean (SE)	4.38 (2.017)	-1.89 (2.065)
95% CI	(0.39;8.37)	(-5.97;2.19)
Difference of LS Means (SE) (macitentan minus SoC)	6.27 (2.666)	
95% CI	(0.99;11.55)	
2-sided p-value	0.020	
Overall treatment effect[c]		
LS Mean (SE)	2.28 (1.581)	0.55 (1.670)
95% CI	(-0.85;5.41)	(-2.75;3.85)
Difference of LS Means (SE) (macitentan minus SoC)	1.73 (1.854)	
95% CI	(-1.94;5.40)	
2-sided p-value	0.353	
Treatment-by-visit interaction p-value	0.049	
Analysis set: FAS1	73	75
All Ages Total Score - Child report		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	55 (75.3%)	55 (73.3%)
Change from baseline to Week 12		
LS Mean (SE)	4.73 (1.786)	0.31 (1.906)
95% CI	(1.19;8.27)	(-3.46;4.09)
Difference of LS Means (SE) (macitentan minus SoC)	4.42 (2.340)	
95% CI	(-0.22;9.06)	
2-sided p-value	0.062	
Change from baseline to Week 24		
LS Mean (SE)	6.10 (1.941)	0.82 (2.040)
95% CI	(2.26;9.94)	(-3.22;4.86)
Difference of LS Means (SE) (macitentan minus SoC)	5.28 (2.570)	
95% CI	(0.18;10.37)	
2-sided p-value	0.043	
	Randomized Macitentan	Randomized Standard of Care
Overall treatment effect[c]		
LS Mean (SE)	4.35 (1.598)	2.12 (1.781)
95% CI	(1.18;7.53)	(-1.40;5.65)
Difference of LS Means (SE) (macitentan minus SoC)	2.23 (1.969)	
95% CI	(-1.68;6.14)	
2-sided p-value	0.260	
Treatment-by-visit interaction p-value	0.086	

[a] Repeated measures mixed model with randomized treatment, visit, treatment - by - visit interaction, the 2 stratification factors and baseline value as fixed effects, and subject as random effect.
[b] The subjects included in the analysis are those with baseline and at least one post-baseline value.
[c] The overall treatment effect is estimated using the same model excluding the treatment-by-visit interaction factor.
Note: A Positive change indicates improved quality of life.
After Week 48 only timepoints with a corresponding value in at least 10% of the subjects in the Macitentan arm are displayed.
For All Ages Total Score - Parent report covariance matrix UN is used.
For All Ages Total Score - Child report covariance matrix UN is used.

- Exploratory Efficacy Analyses

- *Six-Minute Walk*

Change from Baseline in 6MWD in participants ≥2 y.o., is shown in Table RSI E-19. Results must be interpreted with caution due to small sample size, in particular in the SoC arm.

Table RSI E-19. Six-Minute Walk Distance: Change From Baseline Up to End of Randomized Macitentan or SoC + 7 Days, or Up to Start of Macitentan for Crossover Subjects for Subjects ≥ 2 Years Old -Mixed Model Repeated Measures; FAS1 Analysis Set (Study AC-055-312).

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
Six-Minute Walk Distance (m)		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	8 (11.0%)	3 (4.0%)
Change from baseline to Week 12		
LS Mean (SE)	19.64 (39.364)	29.22 (64.281)
95% CI	(-69.41;108.69)	(-116.19;174.64)
Difference of LS Means (SE) (macitentan minus SoC)	-9.58 (75.383)	
95% CI	(-180.11;160.94)	
2-sided p-value	0.902	
Change from baseline to Week 24		
LS Mean (SE)	8.55 (3.330)	94.54 (5.455)
95% CI	(1.02;16.09)	(82.20;106.87)
Difference of LS Means (SE) (macitentan minus SoC)	-85.98 (6.390)	
95% CI	(-100.44;-71.53)	
2-sided p-value	<.001	
Change from baseline to Week 48		
LS Mean (SE)	47.47 (15.746)	71.89 (22.397)
95% CI	(10.73;84.21)	(18.95;124.83)
Difference of LS Means (SE) (macitentan minus SoC)	-24.42 (27.325)	
95% CI	(-88.73;39.90)	
2-sided p-value	0.401	
Overall treatment effect[c]		
LS Mean (SE)	14.40 (12.191)	92.99 (12.231)
95% CI	(-12.87;41.66)	(65.66;120.33)
Difference of LS Means (SE) (macitentan minus SoC)	-78.59 (0.985)	
95% CI	(-81.71;-75.48)	
2-sided p-value	<.001	

- *Panama Functional Class*

The proportion of participants ≥2 y.o. with Panama FC I or II was comparable between the macitentan arm and the SoC arm at all timepoints (stratified and unstratified OR not statistically significant).

No shifts in Panama FC from I/II to III were observed in participants in the macitentan arm at Week 12 or Week 24.

- *Generalized Pairwise comparisons*

Generalized pairwise comparisons supported beneficial trends with macitentan. From 10% (HCE3: 95% CI=[-6%; 26%]) more wins down to 1% (HCE4: 95% CI=[-14%; 16%]) more wins with macitentan were observed across the 4 different HCE endpoints (Table RSI E-20).

Table E-20. Summary of Hierarchical Composite Endpoint (HCE) Results

Endpoint	Statistic	Macitentan (n=62)	Standard of Care (n=64)
HCE1	Proportion of Macitentan Winners		30%
	Proportion of SoC Winners		23%

Time to death or registration for lung transplantation > Time to first CEC-confirmed hospitalization for PAH > Time to first CEC-confirmed clinical worsening > Change in WHO FC from baseline to Week 24	Proportion of Ties	48%
	Difference in proportions of Winners 95% CI	7% [-7% ; 23%]
	Win Ratio 95% CI	1.33 [0.75 ; 2.53]
	Win odds 95% CI	1.16 [0.86 ; 1.59]
	Finkelstein and Schoenfeld one-sided p-value	0.1618
HCE2 *Time to death or registration for lung transplantation > Number of CEC-confirmed hospitalization for PAH > Number of CEC-confirmed clinical worsening > Change in WHO FC from baseline to Week 24*	Proportion of Macitentan Winners	30%
	Proportion of SoC Winners	23%
	Proportion of Ties	48%
	Difference in proportions of Winners 95% CI	7% [-7% ; 23%]
	Win Ratio 95% CI	1.33 [0.75 ; 2.55]
	Win odds 95% CI	1.16 [0.86 ; 1.59]
	Finkelstein and Schoenfeld one-sided p-value	0.1648
HCE3 *Time to death or registration for lung transplantation > Time to first CEC-confirmed hospitalization for PAH > Time to first CEC-confirmed clinical worsening > Change in WHO FC from baseline to Week 24 > Change in PedsQL™ 4.0 SF15 Short Form generic core physical functioning score from baseline to Week 24*	Proportion of Macitentan Winners	48%
	Proportion of SoC Winners	38%
	Proportion of Ties	14%
	Difference in proportions of Winners 95% CI	10% [-7% ; 28%]
	Win Ratio 95% CI	1.27 [0.84 ; 2.00]
	Win odds 95% CI	1.23 [0.87 ; 1.79]
	Finkelstein and Schoenfeld one-sided p-value	0.1230
HCE4 *Time to death or registration for lung transplantation > Time to first CEC-confirmed hospitalization for PAH > Time to first CEC-confirmed clinical worsening > Change in WHO FC from baseline to Week 24 > Percent change in NT-proBNP from baseline to Week 24*	Proportion of Macitentan Winners	38%
	Proportion of SoC Winners	35%
	Proportion of Ties	27%
	Difference in proportions of Winners 95% CI	4% [-14% ; 22%]
	Win Ratio 95% CI	1.11 [0.68 ; 1.86]
	Win odds 95% CI	1.08 [0.76 ; 1.56]
	Finkelstein and Schoenfeld one-sided p-value	0.3273

The main contributing components were:

- Time to first CEC-confirmed clinical worsening with intrinsic effect of +7% (95% CI=[-4%; 18%], WR=1.55, WO=1.15),
- Number of CEC-confirmed clinical worsening with intrinsic effect of +7% (95% CI=[-3%; 18%], WR=1.57, WO=1.15), and
- Change in PedsQLTM 4.0 SF15 generic core physical functioning score from Baseline to Week 24 with intrinsic effect of +13% (95% CI=[-4%; 28%], WR=1.44, WO=1.30).

A non-significant increase in clinical responders is observed with macitentan compared to SoC ((12%, 2-sided p-value=0.1316).

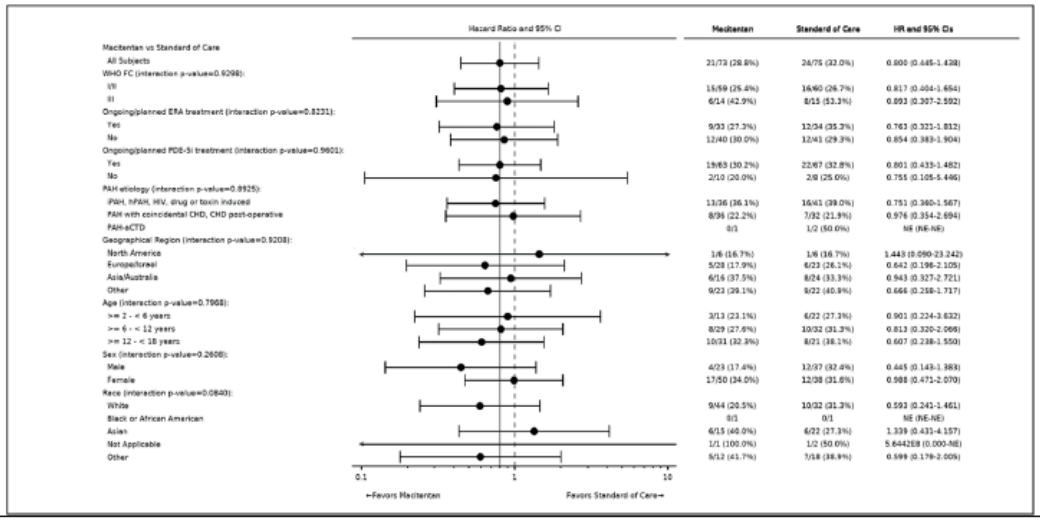
Ancillary analyses

Subgroups Analysis of Time to First CEC-Confirmed Disease Progression Event.

No statistically significant differences in treatment effect with macitentan versus SoC were observed for any of the subgroups. A positive trend favouring macitentan (HR <1) was observed for all subgroups, except for Asia (HR >1), and for subgroups with lower number of participants/events (geographical region 'North America', PAH aetiology subgroup 'PAH-aCTD', and race subgroups 'Black or African American' and 'not applicable'). No multiplicity adjustment was introduced; the subgroup analysis was descriptive in nature.

No multiplicity adjustment was introduced; the subgroup analysis was descriptive in nature.

Figure E-05: Forest Plot of Treatment Effect for Time to First CEC-Confirmed Disease Progression Event for Subjects ⩾ 2 Years Old by Subgroups; FAS1 Analysis Set (Study AC 055 312).



Key: CEC = Clinical event committee; CHD = Congenital heart disease; CI = Confidence interval; ERA = Endothelin receptor antagonist; HIV = Human immunodeficiency virus; hPAH = Heritable pulmonary arterial hypertension; HR = Hazard ratio; iPAH = Idiopathic pulmonary arterial hypertension; PAH = Pulmonary arterial hypertension; PAH-aCTD = PAH associated with connective tissue disease; PDE-5i = Phosphodiesterase type 5 inhibitor; WHO = World Health Organization.

Note: Hazard ratios presented are from unadjusted Cox proportional hazards models.

Children < 2 years:

- *Time to First Confirmed Disease Progression Event*

After a median follow-up of 37.29 weeks, no participants <2 y.o. had experienced a CEC-confirmed disease progression event or an Investigator-reported disease progression event.

- *Time to First Confirmed Hospitalization for Pulmonary Arterial Hypertension*

No participants <2 y.o. had experienced a CEC-confirmed hospitalization for PAH at EOCP.

- *Time to Confirmed Death Due to Pulmonary Arterial Hypertension*

No participants <2 y.o. had experienced a CEC-confirmed death due to PAH at EOCP.

- *Time to Death From all Causes*

No participants <2 y.o. had experienced an event of death (all causes).

- *WHO Functional Class*

No participants <2 y.o. were classified as WHO FC III or IV.

Shifts from Baseline in participants <2 y.o. were observed for 1 participant (20.0%) at Week 24 (from WHO FC II at Baseline to WHO FC I), and 1 participant (16.7%) at Week 36 (from WHO FC II at Baseline to WHO FC I).

- *NT-proBNP*

The mean±SD decrease from Baseline in NT-proBNP (pmol/L) was higher at Weeks 12 and 24 compared to later timepoints. NT-proBNP was reduced by 42.9% (n=6) at Week 12, 53.2% (n=5) at Week 24 and 26.1% (n=6) at Week 36.

- *Moderate to Vigorous Physical Activity and Quality of life*

Per protocol, physical activity and QoL analyses were not performed in the <2 y.o. cohort.

- *Echocardiography*

Mean (SD) change from Baseline in BSA-normalized TAPSE in participants <2 y.o. was -3.74 (12.750) mm/m2 at Week 24. Mean (SD) change from Baseline in diastolic LVEI in participants <2 y.o. was -0.033 (0.0416) at Week 24 (Mean (SD) change from Baseline in systolic LVEI in participants <2 y.o. was 0.020 (0.4232) at Week 24.

2.6.5.3. Supportive study(ies)

2.6.5.3.1. Comparison of Pharmacodynamic Parameters Between Adults, Adolescents, and Children ≥2 to <18 Years of Age [Part 1]

The observed treatment effects of macitentan in the adult, adolescent and paediatric populations were compared in a pharmacodynamic similarity assessment (PIP Study 10) using data from the adult SERAPHIN study and the paediatric TOMORROW study (only children ≥ 2 to <18 years of age).

Table E-21. Similarities Between TOMORROW and SERAPHIN Populations

TOMORROW	SERAPHIN

Included in Study 10:
• Idiopathic PAH
• Hereditary PAH
• PAH associated with HIV
• Drug or toxin induced PAH
• PAH associated with CHD:
  ○ PAH with co-incidental CHD
  ○ Post-operative PAH (persisting/recurring/developing ≥6 months after repair of CHD)
Allowed per the TOMORROW protocol but excluded from Study 10:
• PAH aCTD
• Participants with planned/ongoing ERA
	Included in Study 10
	• Idiopathic PAH
	• Hereditary PAH
	• PAH associated with HIV
	• Drug or toxin induced PAH
	• Participants with simple congenital systemic-to-pulmonary shunts at least 1 year post-surgical repair (atrial septal defect, ventricular septal defect, patent ductus arteriosus)
	Allowed per the SERAPHIN protocol but excluded from Study 10:
	• PAH aCTD
	• Participants randomized to macitentan 3 mg

Participants with PAH aCTD were excluded from the comparison analysis because there was an imbalance in the proportion of these participants in the two studies and the disease course is anticipated to be more severe in PAH aCTD as compared to other PAH aetiologies. Participants randomized in the macitentan 3 mg group in SERAPHIN were excluded since the paediatric macitentan doses given in the TOMORROW study were selected to achieve systemic exposure observed in adults with PAH treated with macitentan 10 mg. To minimize characteristic imbalance between the 2 populations, participants with planned/ongoing ERA in TOMORROW were excluded from the comparison analysis since, in SERAPHIN, treatment with an ERA (other than the macitentan randomized treatment) was prohibited.

Objectives and Endpoints

The following clinical and PD endpoints, common to both the SERAPHIN and TOMORROW studies, were used as outcome variables: Time to first CEC-confirmed disease progression/Time to first hospitalization for PAH/Time to CEC-confirmed death due to PAH/Time to all-cause death/WHO-FC/NT-proBNP concentrations.

Analysis Conventions

Treatment effect was determined using the following 2 analyses:

- A main analysis (SERAPHIN-like) following the analysis conventions for the SERAPHIN study.
- A supportive analysis (TOMORROW-like) following the analysis conventions of the TOMORROW study

Analysis Sets

- *SER-set*: The all-randomized set in SERAPHIN but restricted to participants randomized to either macitentan 10 mg or placebo arms and excluding CTD aetiology.
- *TOM-set:* The Full Analysis Set in TOMORROW but restricted to participants randomized before the first cut-off for analysis (COFA1) in the randomization strata of "not on planned or ongoing ERA" and excluding CTD aetiology. Participants were evaluated according to the intention-to-treat principle.

Comparison of Outcomes Variables

The treatment effect in adults was computed on the SER-set and estimated as macitentan 10 mg compared with placebo. The treatment effect in the paediatric population was computed on the TOM-set and estimated as macitentan compared with SoC. For each outcome variables, the treatment effect and corresponding 2-sided 95% CIs were estimated separately in the adult and paediatric populations for both a SERAPHIN-like analysis following the statistical methodology

outlined in the SERAPHIN study and a TOMORROW-like analysis following the statistical methodology outlined in the TOMORROW study.

[Hospitalizations for PAH were only CEC-confirmed in the TOMORROW study. For this endpoint, participants who died without hospitalization for PAH were included and were considered as having the event at the time of death. In the SERAPHIN study, the date of hospitalization for PAH was taken from the admission date of a hospitalization or from the admission date of hospitalization required for adverse events].

For time-to-event outcomes (time to disease progression/PAH hospitalization/PAH death/all cause deaths), both SERAPHIN-like and TOMORROW-like analyses were performed for the adult and pediatric populations. For NT proBNP and WHO FC, only the TOMORROW like analyses were performed for the adult and pediatric populations.

In addition, adolescents (12 to <18 years of age in TOMORROW) and young adults (12 to ⩽25 years of age in SERAPHIN), considered the most comparable age groups across the studies, were analysed separately. For time to event endpoints, WHO FC, and NT-proBNP the same SERAPHIN-like and TOMORROW-like analyses were performed.

Table E-22: Number of Subjects in Each Analysis Set; All Randomized / Full Analysis Set 1 (Study AC-055-302/AC-055-312)

	SERAPHIN			TOMORROW		
	Placebo	Macitentan 10 mg	Total	Standard of Care	Macitentan	Total
Analysis set: All Randomized / Full Analysis Set 1	250	242	492	75	73	148
SER-set/TOM-set	169 (67.6%)	169 (69.8%)	338 (68.7%)	40 (53.3%)	39 (53.4%)	79 (53.4%)

Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients.

Demographics and Baseline Characteristics

Overall, the TOM-set had a younger population, a higher proportion of male participants, a lower proportion of White/Hispanic participants, and a lower body mass index than participants in the SER-set.

In the SER-set, participants had a median age of 43.0 years (range: 13 to 85 years), with 75.7% of participants ⩾26 and ⩽64 years of age. Most participants were female (70.6%) and White/Hispanic (71.8%). At baseline, participants had a median BMI of 24.8 kg/m2 (range: 15 to 52 kg/m2). The demographic characteristics were comparable between the placebo and macitentan treatment arms. In the TOM-set, participants had a median age of 9.0 years (range: 2 to 17 years), with 24.1% of participants ⩾2 and <6 years of age, 43.0% of participants ⩾6 and ⩽ 12 years of age and 32.9% of participants ⩾12 and <18 years of age. Most participants were female (58.2%), and 50.6% were White/Hispanic. At baseline, participants had a median BMI of 17.0 kg/m2 (range: 12 to 30 kg/m2). The demographic characteristics were comparable between the SoC and macitentan treatment arms.

Compared with the SER-set, participants in the TOM-set had an overall shorter median time from PAH diagnosis to randomization, a greater proportion of participants with CHD-associated PAH, a greater proportion of participants with WHO FC I, and a substantially smaller proportion of participants who were treatment naïve to PAH therapy.

Table E-23. Summary of Baseline Characteristics; SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)

	SERAPHIN			TOMORROW		
	Placebo	Macitentan 10 mg	Total	Standard of Care	Macitentan	Total
Analysis set: SER-set/TOM-set	169	169	338	40	39	79
Time from initial diagnosis of PAH[a], days						
N	166	168	334	40	39	79
Mean (SD)	1057.5 (1553.63)	1002.7 (1408.40)	1029.9 (1480.39)	659.7 (894.95)	553.2 (560.38)	607.1 (745.88)
Median	498.5	511.5	498.5	187.5	377.0	316.0
Range	(6; 13267)	(2; 10199)	(2; 13267)	(29; 4668)	(27; 1839)	(27; 4668)
IQ range	(196.0; 1409.0)	(160.5; 1187.5)	(176.0; 1359.0)	(61.5; 1037.0)	(90.0; 923.0)	(86.0; 927.0)
Down Syndrome[c]						
N	-	-	-	40	39	79
Yes	-	-	-	3 (7.5%)	1 (2.6%)	4 (5.1%)
No	-	-	-	37 (92.5%)	38 (97.4%)	75 (94.9%)
Pulmonary arterial hypertension etiology						
N	166	168	334	40	39	79
Idiopathic PAH	126 (75.9%)	134 (79.8%)	260 (77.8%)	17 (42.5%)	21 (53.8%)	38 (48.1%)
Heritable PAH	3 (1.8%)	2 (1.2%)	5 (1.5%)	2 (5.0%)	0	2 (2.5%)
PAH associated with HIV infection	3 (1.8%)	6 (3.6%)	9 (2.7%)	0	0	0
Drug- or toxin-induced PAH	8 (4.8%)	5 (3.0%)	13 (3.9%)	0	0	0
PAH associated with CHD[b]	26 (15.7%)	21 (12.5%)	47 (14.1%)	21 (52.5%)	18 (46.2%)	39 (49.4%)
WHO functional class						
N	168	169	337	40	39	79
I	0	1 (0.6%)	1 (0.3%)	13 (32.5%)	10 (25.6%)	23 (29.1%)
II	84 (50.0%)	78 (46.2%)	162 (48.1%)	19 (47.5%)	23 (59.0%)	42 (53.2%)
III	81 (48.2%)	88 (52.1%)	169 (50.1%)	8 (20.0%)	6 (15.4%)	14 (17.7%)
IV	3 (1.8%)	2 (1.2%)	5 (1.5%)	0	0	0
PAH-specific therapy at randomization						
N	168	169	337	40	39	79
Non-PAH-specific therapies	63 (37.5%)	58 (34.3%)	121 (35.9%)	3 (7.5%)	2 (5.1%)	5 (6.3%)
PDE-5i monotherapy	101 (60.1%)	98 (58.0%)	199 (59.1%)	32 (80.0%)	35 (89.7%)	67 (84.8%)
PDE-5i + ERA	0	0	0	3 (7.5%)	1 (2.6%)	4 (5.1%)
PDE-5i + sGC stimulator	0	0	0	1 (2.5%)	0	1 (1.3%)
PDE-5i+prostanoids	2 (1.2%)	11 (6.5%)	13 (3.9%)	1 (2.5%)	1 (2.6%)	2 (2.5%)
Prostanoids monotherapy	2 (1.2%)	2 (1.2%)	4 (1.2%)	0	0	0

Key: CHD = Congenital heart disease; HIV = Human immunodeficiency virus; IQ = Interquartile; PAH = Pulmonary arterial hypertension; PDE-5i = Phosphodiesterase type
5 inhibitor; SD = Standard deviation; sGC = Soluble guanylate cyclase; WHO = World Health Organization.
a Time from PAH diagnosis to randomization.
b Includes PAH associated with repaired shunts and PAH with co-incidental CHD.
c Only collected in TOMORROW aCRF.
Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients.

Comparison of Efficacy results

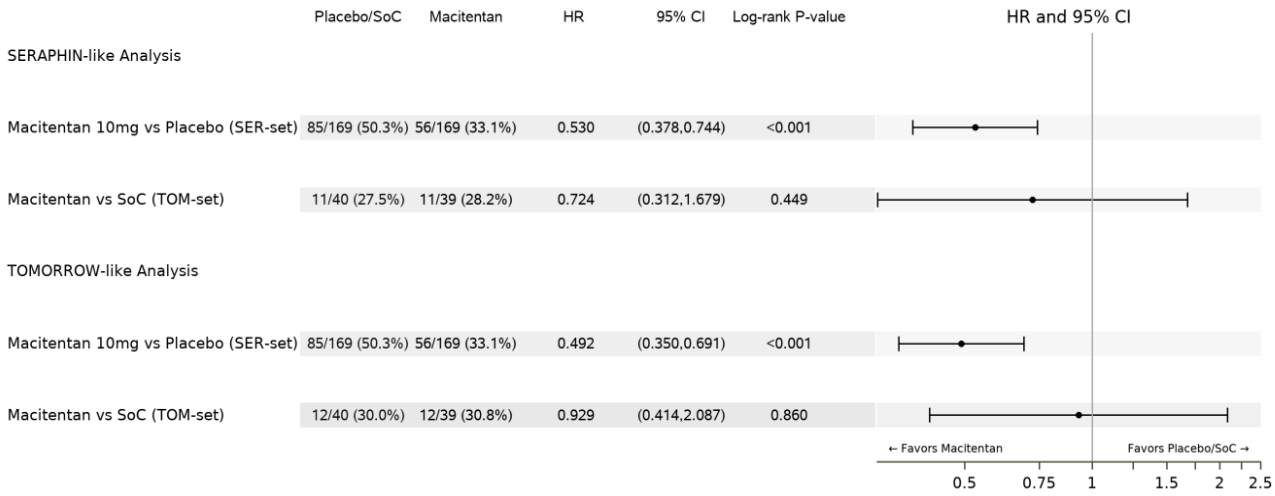
- *Time to First CEC-confirmed Disease Progression*

Overall population

The SERAPHIN-like analysis shows that the treatment response is similar between the adult (SER-set) and paediatric populations (TOM-set), with point estimates favouring macitentan, CIs that overlap, and the point estimate for the TOM-set contained within the CI of the SER-set.

The TOMORROW-like (supportive) analysis shows a similar trend; although the TOM-set point estimate does not fall within the SER-set CI, the point estimates favour macitentan and the CIs overlap.

Figure E-06. Forest Plot of Time to First CEC-Confirmed Disease Progression Event; SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)

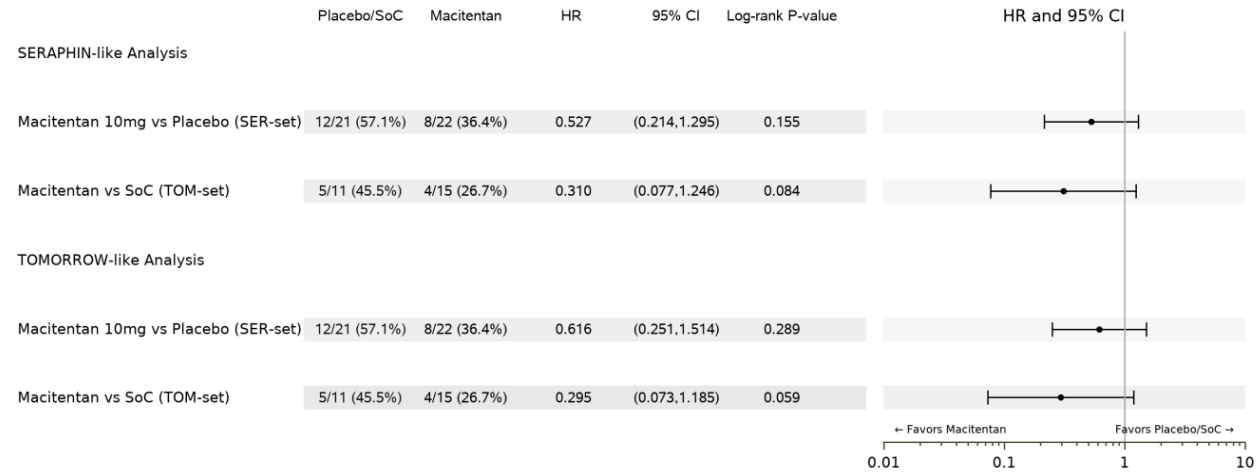


Key: CEC = Clinical Event Committee; CI = Confidence interval; HR = Hazard ratio; WHO FC = World Health Organization Functional class; SoC = Standard of Care. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. In SERAPHIN-like analysis, all CEC-confirmed events up to end of randomized treatment + 7 days (or up to individual End of Core Period date for subjects in TOMORROW) are included and hazard ratio is from unadjusted Cox proportional hazards model. In TOMORROW-like analysis, all CEC-confirmed events up to end of study (or up to individual End of Core Period date for subjects in TOMORROW) are included and hazard ratio is from Cox proportional hazards model adjusted for WHO FC (FC I/II vs FC III/IV) at randomization. A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

Adolescents and Young Adults

For both the SERAPHIN-like analysis and the TOMORROW-like analysis, though not statistically significant, trends favouring the macitentan arm are observed for adolescents and young adults. The small adolescents (n=26) and young adults' (n=43) subgroup sizes in the SER- and TOM sets, hence results should be interpreted with caution.

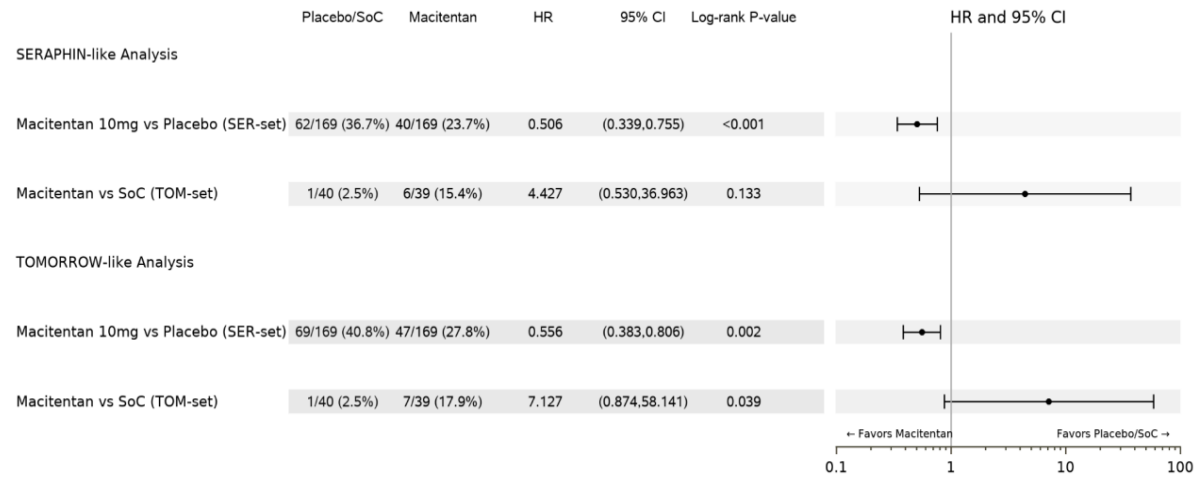
Figure E-07. Forest Plot of Time to First CEC-Confirmed Disease Progression Event for Adolescents-Young Adults; SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)



Key: CEC = Clinical Event Committee; CI = Confidence interval; HR = Hazard ratio; WHO FC = World Health Organization Functional class; SoC = Standard of Care. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. For SERAPHIN young adults include subjects 12 to ≤25 years old at randomization, for TOMORROW adolescents include subjects 12 to <18 years old at randomization. In SERAPHIN like analysis, all CEC-confirmed events up to end of randomized treatment + 7 days (or up to individual End of Core Period date for subjects in TOMORROW) are included and hazard ratio is from unadjusted Cox proportional hazards model. In TOMORROW-like analysis, all CEC-confirmed events up to end of study (or up to individual End of Core Period date for subjects in TOMORROW)are included and hazard ratio is from Cox proportional hazards model adjusted for WHO FC (FC I/II vs FC III/IV) at randomization. A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

- *Time to First Hospitalization due to PAH*

Figure E-08. Forest Plot of Time to First Hospitalization for PAH; SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)



Key: CEC = Clinical Event Committee; CI = Confidence interval; HR = Hazard ratio; WHO FC= World Health Organization Functional class. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. In SERAPHIN-like analysis, all CEC-confirmed events up to end of randomized treatment + 7 days (or up to individual End of Core Period date for subjects in TOMORROW) are included and hazard ratio is from unadjusted Cox proportional hazards model. In TOMORROW-like analysis, all CEC-confirmed events up to end of study (or up to individual End of Core Period date for subjects in TOMORROW)are included and hazard ratio is from Cox proportional hazards model adjusted for WHO FC (FC I/II vs FC III/IV) at randomization. A vertical reference line is displayed at the level of no treatment effect (exploratory analysis). In TOMORROW, hospitalization for PAH was CEC-confirmed. Subjects who died without any hospitalization for PAH are considered as having an event at the time of death.

Adolescents and Young Adults
Too few events (n=2) occurred in the TOM-set for meaningful comparison.

- *Time to CEC-confirmed Death due to PAH*

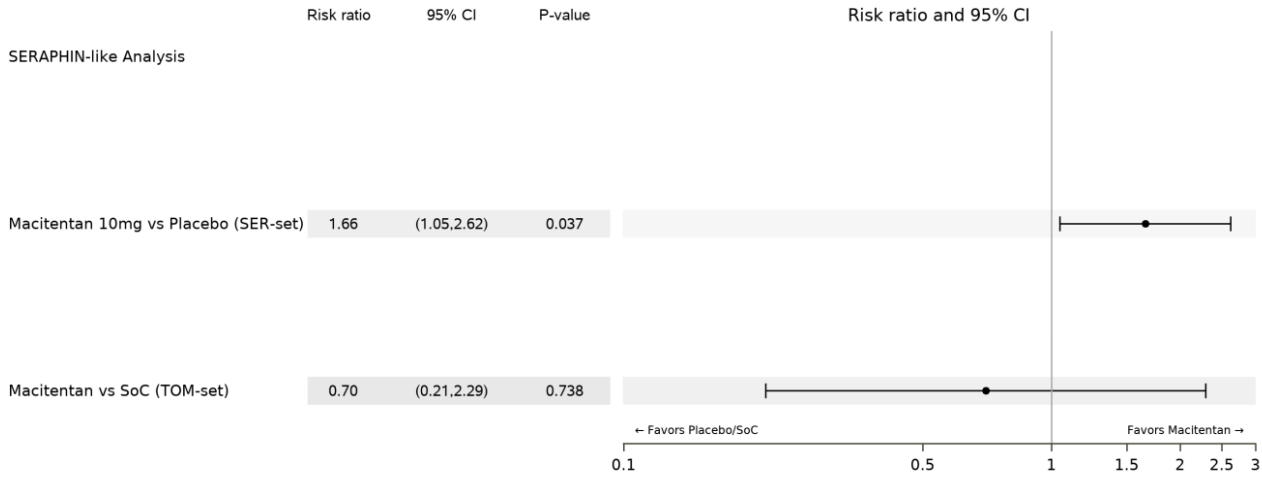
For the SER-set, macitentan 10 mg was favoured over placebo for a longer time to CEC-confirmed death due to PAH, though not statistically significant. For the TOM-set, because no event occurred in the SoC arm, HRs could not be estimated.

- *Time to All-cause Death*

For the SER-set, macitentan 10 mg was favoured over placebo for a longer time to all-cause death, though not statistically significant. For the TOM-set, because no event occurred in the SoC arm, HRs could not be estimated.

- *World Health Organization Functional Class*

Figure E-09. Forest Plot of Improvement from Baseline to Month 6 / Week 24 in WHO FC (SERAPHIN-like Analysis); SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)

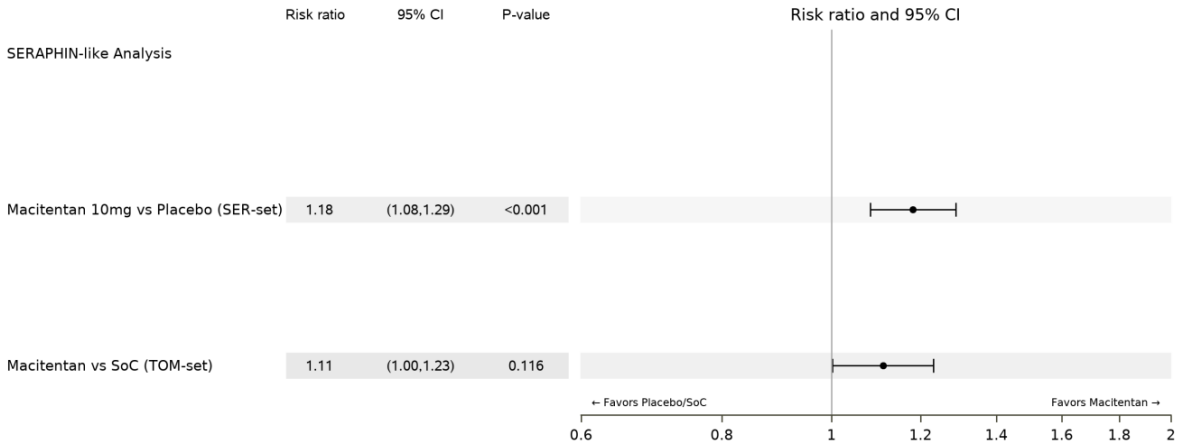


Key: CI = Confidence interval; WHO FC = World Health Organization Functional class; SoC = Standard of Care. P-value is from the Fisher exact test. Risk ratio is not model-based. For subjects with a disease progression or who died prior to Month 6/Week 24, the Month 6/Week 24 value is imputed by WHO FC IV (worst case). Otherwise the last observation is carried forward. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. Only values obtained up to end of randomized treatment + 7 days (or up to start of macitentan for crossover subjects in TOMORROW) are considered for the derivation of Month 6/ Week 24 value (including imputed data). A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

The TOMORROW-like (supportive) analysis favours macitentan treatment over placebo (SER-set) or SoC (TOM-set).

Sensitivity analyses for no worsening of WHO FC from baseline to Month 6/Week 24 showed a similar treatment response between the adult and paediatric populations, with point estimates favouring macitentan.

Figure E-10. Forest Plot of No Worsening from Baseline to Month 6/ Week 24 in WHO FC (SERAPHIN-like Analysis); SER-set/TOM-set Analysis Set (Study AC-055-302/AC-055-312)



Key: CI = Confidence interval; WHO FC = World Health Organization Functional class; SoC = Standard of Care. P-value is from the Fisher exact test. Risk ratio is not model-based. For subjects with a disease progression or who died prior to Month 6/Week 24, the Month 6/Week 24 value is imputed by WHO FC IV (worst case). Otherwise the last observation is carried forward. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. Only values obtained up to end of randomized treatment + 7 days (or up to start of macitentan for crossover subjects in TOMORROW) are considered for the derivation of Month 6/ Week 24 value (including imputed data). A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

Adolescents and Young Adults

Too few events occurred in the small adolescent subgroup of the TOM-set for meaningful comparisons.

- *N-Terminal ProBNP Concentrations*

In the SERAPHIN study, NT-proBNP was determined using the BNP Fragment Enzyme Immunoassay BI-20852 from Biomedica Medizinprodukte Gmbh (Biomedica), and in the TOMORROW study, NT-proBNP was determined using electrochemiluminescence technology for immunoassay analysis run on the Cobas® instrument from Roche (Roche). The mechanistic differences in how each assay detects NT-proBNP, makes it difficult to directly compare NT-proBNP values between the 2 studies.

SERAPHIN-like Analysis

For the SERAPHIN-like analysis, the absolute change in NT-proBNP values from baseline to Month 6/Week 24 were analyzed.

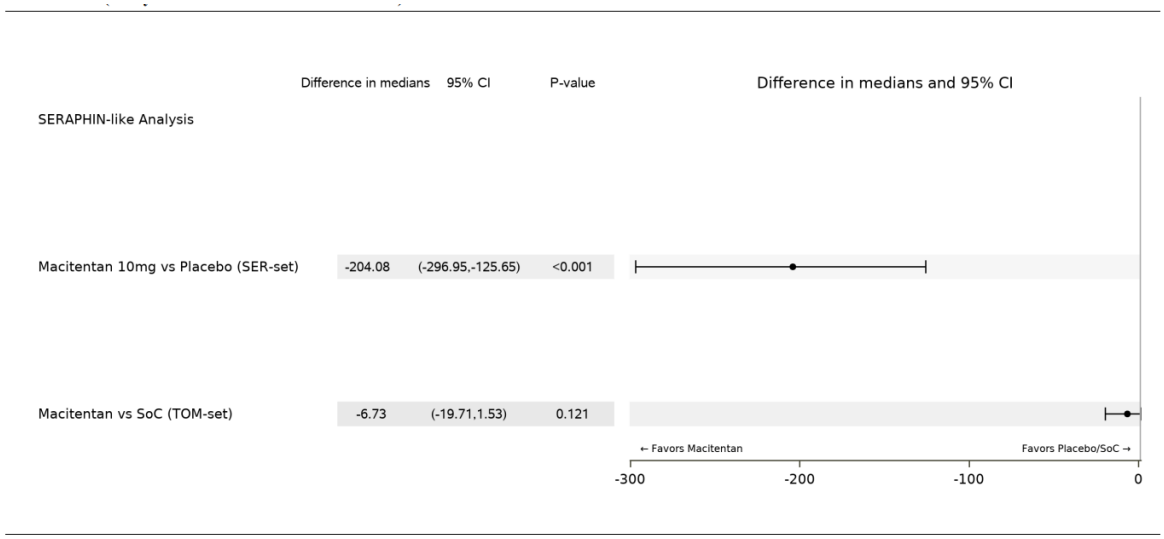
In the SER-set, median NT-proBNP values at baseline were 793 pmol/L (range: 302, 4532) and 844 pmol/L (range: 216, 4729) in the placebo and macitentan 10 mg arms, respectively. Median changes from baseline at Month 6/Week 24 were 54 pmol/L (range: −1027, 2507) and −82 pmol/L (range: −1624, 2326), respectively. The treatment effect (difference in medians) was −204 pmol/L (95% CI: −297, −126).

In the TOM-set, median NT-proBNP values at baseline were 21.0 pmol/L (range: 1.5, 595) and 25.0 pmol/L (range: 4.4, 3053) in the SoC and macitentan arms, respectively. Median changes from baseline at Month 6/Week 24 were −1.5 pmol/L (range: −231, 459) and −7.4 pmol/L (range: −1458, 47.7), respectively. The treatment effect (difference in medians) was −6.7 pmol/L (95% CI: −19.7, 1.53).

For both the SER-set and the TOM-set, changes in NT-proBNP at Month 6/Week 24 favoured macitentan treatment. For this analysis, point estimates and CIs do not overlap, however, the difference in assays used between the 2 studies (showing an approximate 50-fold difference in

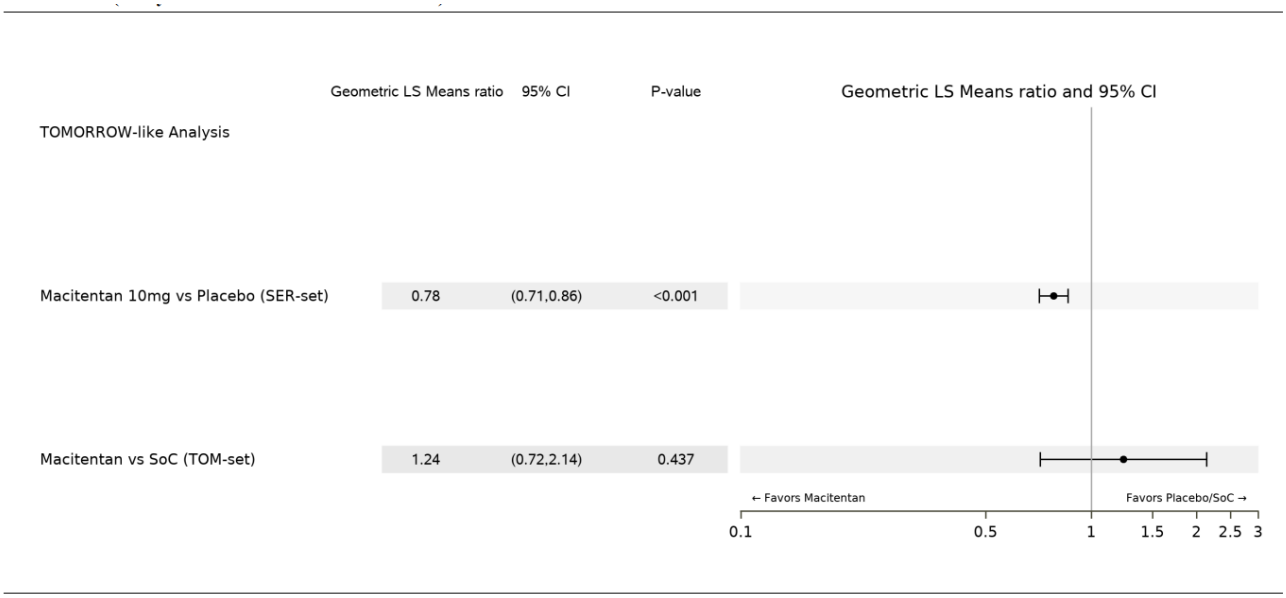
baseline median NT-proBNP values), confound direct comparison of the data and impact the ability for meaningful interpretation of response between the SER-set and the TOM-set.

Figure E-11. Forest Plot of Change from Baseline to Month 6 / Week 24 in NT-pro-BNP (pmol/L) (SERAPHIN-like Analysis); SER-set/TOM-set Analysis Set (Study AC 055 302/AC 055 312)



Key: CI = Confidence interval; SoC = Standard of Care. In order to assess NT-pro-BNP levels, SERAPHIN study used the Biomedica Assay whereas TOMORROW used the Roche Assay. P-value is based on the Wilcoxon rank sum test (normal approximation) - exploratory analysis. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. Only values obtained up to end of randomized treatment + 7 days (or up to start of macitentan for crossover subjects in TOMORROW) are considered for the derivation of Month 6/ Week 24 value. Difference is medians is estimated using the Hodges-Lehmann method. A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

Figure E-12. Forest Plot of Percent of Baseline at Month 6 / Week 24 in NT-pro-BNP (pmol/L) (TOMORROW-like Analysis); SER-set/TOM-set Analysis Set (Study AC 055 302/AC 055 312)



Key: CI = Confidence interval; WHO FC = World Health Organization Functional class; SoC = Standard of Care. In order to assess NT-pro-BNP levels, SERAPHIN study used the Biomedica Assay whereas TOMORROW used the Roche Assay. Note: in TOMORROW daily dose of Macitentan was based on weight categories targeting similar exposure as observed with 10 mg in adult patients. Only values obtained up to end of randomized treatment + 7 days (or up to start of macitentan for crossover subjects in TOMORROW) are considered for the derivation of Month 6/ Week 24 value. Geometric LS Means Ratio is obtained by inversely transforming the difference in change from baseline between treatment groups estimated from ANCOVA model on the logtransformed NT-proBNP values with factors for treatment group and WHO FC at randomization and continuous covariate for baseline log NT-proBNP. A vertical reference line is displayed at the level of no treatment effect (exploratory analysis).

Adolescents and Young Adults (NT-proBNP)

For the SERAPHIN-like analysis, though not statistically significant, the point estimate for the difference in medians for NT-pro-BNP change from baseline to Month 6/Week 24 is in favour of the macitentan arm for adolescents and young adults in the SER-set and for adolescents in the TOM set. Note the small adolescent (n=26) and young adults' (n=43) subgroup sizes in the SER- and TOM sets, hence results should be interpreted with caution.

Comparison of Results in Subpopulations

The first CEC-confirmed disease progression event across subgroups of ongoing PDE-5i treatment, PAH aetiology, WHO FC at baseline, race, and region showed consistent effect, with HRs generally in favour of macitentan treatment, though not statistically significant. The HRs for time to first hospitalization for PAH across subgroups of ongoing PDE-5i treatment, PAH aetiology, WHO FC at baseline, race, and region are generally in favour of macitentan 10 mg in the SER-set. For the TOM-set, HRs were either NE or there were too few events for meaningful interpretation.

2.6.5.3.2. PAH3001 Study (Japanese participants ≥3 Months to <15 Years of Age)

This is an ongoing multicenter, open-label, single-arm, Phase 3 study in Japanese pediatric participants (age between ⩾3 months and <15 years) with PAH, which evaluates the efficacy, safety, and PK of macitentan. A total of 6 Japanese participants (aged ⩾3 months and <15 years) are planned to be enrolled in this study.

Interim analysis: the results up to Week 24 visit are presented for the first 2 enrolled participants who were below 2 years of age.

The study consists of a screening period of 30 days, a treatment period until Week 52 (from Day 1), and a post-treatment follow-up period (end-of-study [EOS]) of 30 days after end-of-treatment (EOT). The EOS is considered as the last visit/assessment for the last participant in the study.

Formal statistical hypotheses testing is not planned for this study. Primary endpoint is the fold change in PVRI at Week 24. The geometric mean of PVRI fold change at Week 24 will be estimated with observed.

Two Japanese participants <2 years of age were treated with macitentan and the study duration time for each participant was 24.7 and 25.3 weeks, respectively. Of the 2 participants <2 y.o. in PAH3001, both were male. Age at Baseline was 21 and 22 months, respectively. The leading etiology was postoperative PAH (persisting/recurring/developing ⩾ 6 months after repair of CHD).

Both participants received macitentan dispersible tablets of 2.5 mg and 3.5 mg (due to increase in age) up to 24 weeks. In both participants, the dose of study intervention was increased due to increase in age.

At time of clinical cutoff, no participants had experienced a CEC-confirmed disease progression event, a CEC-confirmed hospitalization for PAH, a CEC-confirmed death due to PAH event or an event of death from all causes.

WHO FC data were not collected for participants <2 y.o. in PAH3001.

Regarding NT-proBNP, a decrease from Baseline to Week 12 of -8.732 pmol/L and -13.924 pmol/L was reported for each participant, respectively. The corresponding percent of Baseline NT-proBNP were 77.1% and 76.6%, respectively. A decrease from Baseline to Week 24 of -3.894 pmol/L and -16.402 pmol/L was reported for each participant, respectively. The corresponding percent of Baseline NT-proBNP were 89.8% and 72.4%, respectively.

2.6.6. Discussion on clinical efficacy

Opsumit (macitentan) approved in the EU in 2013, as monotherapy or in combination, for the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. This application for macitentan is a Type II variation for adding an indication in paediatric patients aged 2 years to less than 18 years.

To support this application, the Applicant has conducted a multicenter, open-label, randomized phase 3 study, with a single-arm extension period to assess the PK, safety, and efficacy of macitentan versus SoC in children with PAH between 1 month and <18 years of age (Study TOMORROW) [PIP Study 8], which is considered the main trial. Additionally, a PK and safety study in Japanese children with PAH from ≥3 months to <15 years of age (Study PAH3001) [PIP Study 13] and a PK and safety study in children from ≥1 month to <2 years of age (Study PAH1013)[PIP Study 11] have been conducted. TOMORROW and PAH3001 are currently ongoing. Study PAH1013 has been terminated and no participants have been enrolled. Further, to allow clinical comparisons, paediatric data are displayed side-by side with adult data from the phase 3 study SERAPHIN [PIP Study 10)]

For the presentation of paediatric data, the Applicant followed a 2-step approach. In the initial application, the Applicant provided interim efficacy data in children ≥ 2 years (N= 126) and preliminary available data in children < 2 years (N=9; 7 from TOMORROW study and 2 from Study PAH3001).

Thereafter, the Applicant provided all PK, safety, and efficacy data collected during the completed Core Period of the TOMORROW study for participants ⩾2 years of age and older (N=148) and for participants ⩾1 month to <2 years of age (n=9), as well as data from the 2 subjects < 2 years from Study PAH3001.

Design and conduct of clinical studies

Dose response studies

No specific dose finding studies has been conducted. The daily dose of macitentan was targeting similar exposure as the one observed with 10 mg in adult patients. [Refer to the PK section for detailed information].

Study TOMORROW (AC-055-312)

TOMORROW study is an ongoing prospective, multicentre, open label, randomized, controlled, parallel group, Phase 3 study with an open-label, single-arm extension period to assess pharmacokinetics, safety, and efficacy of macitentan versus SoC in paediatric participants with PAH ⩾1 month to <18 years of age.

The primary objective of the TOMORROW study was to gather PK data to stablish therapeutic dose in paediatrics that resemble similar concentrations to those where a benefit has been observed in adults and efficacy was assessed in a secondary way. In this regard, according to Paediatric Addendum to CHMP Guideline on clinical investigation in the treatment of PAH [EMA/CHMP/213972/2010], for medicinal products where the benefit-risk profile is known in adults and extensive paediatric development is not foreseen. The cornerstone is defining the therapeutic dose, short and long safety.

The secondary key objective of the TOMORROW study was to assess the time to first CEC-confirmed disease progression for macitentan compared to SoC. Additional efficacy measurements included changes on WHO functional classification, echocardiography parameters, NT-Pro-BNP

concentrations, mean daily time spent in moderate to vigorous physical [measured by accelerometery] and quality of Life (measured by the PedsQLTM 4.0 Generic Core Scales Short Form [SF15]). Exploratory efficacy measurements in the study included Panama FC, physical activity as measured by accelerometery and 6MWD.

Eligible patients were from 1 months to less than 18 years of age with PAH evidenced by a mPAP ≥ 25 mmHg, PAWP ≤15 mm Hg, and pulmonary vascular resistance index (PVRi) >3 Wood Units x m2) via RHC, weighting ≥3.5 kg and classified as WHO functional Class I, II or III. In this regard, it should be remarked that, contrary to SERAPHIN study in adults, where only patients with WHO FC II-IV were included, patients with WHO FC I were included in TOMORROW study, suggesting that the paediatric population was less severe than the adult population included in SERAPHIN. Patients with WHO FC I are normally asymptomatic. None of current authorized PAH-specific therapy is indicated for FC I patients. In this regard, the Applicant justified that the included population in TOMORROW study mimicked the one included in the real-world TOPP registry [Ploegstra 2024] and that the determination of patient individual risk relies, not only on WHO FC class, but in other clinical parameters.

Eligible PAH aetiologies encompassed idiopathic, heritable, connective tissue, congenital heart disease (both co-incidental CHD and post-operative PAH persisting/recurring/developing ≥ 6 months after repair), drug or toxin-induced and associated with HIV. Patients with PAH with co-incidental CHD (confirmed by BCAC), were not studied in SERAPHIN study, where only patients with simple (atrial septal defect, ventricular septal defect, patent ductus arteriosus) congenital systemic to pulmonary shunts at least 1-year postsurgical repair were included. The Applicant was requested to define in greater detail what means by co-incidental CHD, since there were exclusion criteria, such as open shunts and other cardiac abnormalities that can also be considered CHD. The MAH clarified that co-incidental CHD in these patients only included typically small coincidental defects such as pre-tricuspid, post-tricuspid shunts, atrial septal defect, ventricular septal defect, patent ductus arteriosus. These defects were judged coincidental, and none considered causative of the degree of PAH.

PAH-specific treatment-naïve participants, or participants who are already treated with PAH specific monotherapy or double combination therapy excluding macitentan and IV/SC prostanoids were included in the study, which concurs with the approved indication in adults.

The study consisted of two parts, the core period and the single-arm extension period. In the core period, subjects ≥ 2 years who were confirmed eligible at Visit 2 were randomized in a 1:1 ratio to either receive macitentan or initiate/continue standard of care (SoC), which include PAH non-specific treatment and/or up to 2 PAH-specific medications as per local practice. Participants treated with a PDE-5i and/or other PAH-specific therapy (such as an ERA or inhaled/oral prostanoids) at randomization could continue these medications if randomized to SoC treatment. However, participants taking these medications who were randomized to macitentan could only continue taking PDE-5i (i.e. participants with no PAH-specific therapy at randomization received macitentan monotherapy, participants on a PDE-5i monotherapy at randomization received macitentan as add-on therapy, participants on an ERA or oral/inhaled prostanoids monotherapy at randomization received macitentan monotherapy instead and participants a PDE-5i in combination with another PAH-specific therapy at randomization received the combination of macitentan and the PDE-5i). For participants randomized to SoC, additional PAH-specific therapy (excluding macitentan and intravenous/subcutaneous prostanoids) could be prescribed and initiated during the screening period. No placebo arm was included. In subjects < 2 years old, oral/ inhaled prostanoid treatment were also allowed PAH-specific background therapy in all study periods.

Randomization was stratified by ongoing/planned ERA (yes/no) treatment and by WHO FC (FC I/II vs FC III). The proportion of participants with ERA treatment, as a component of the planned SoC, was limited to a maximum of 40% of the overall number of participants randomized. Subjects < 2 years of age were assigned as a cohort to the macitentan group without randomization (and without ERA cap in this cohort). Enrolment of children <2 years of age was only initiated once sufficient PK data for macitentan were obtained in older children.

The single-arm extension period (SAEP) started when the end of the core period has been announced. The core period ended at analysis 2, a cut-off date to be chosen in the first quarter 2024. Therefore, individual duration depends on time of enrolment. Site visits occur every 12 weeks and the overall study duration is minimum 7 years.

The open-label study design is acceptable for naïve patients. However, it makes the interpretation of results only descriptive/exploratory in the add-on setting. The no inclusion of a placebo in the SoC arm and allowing ERA treatment in the SoC group arm makes impossible to discern the effect of macitentan as combination therapy. As advised in previous scientific advice [EMA/CHMP/SAWP/92854/2015], in the add-on setting a blinded comparison macitentan vs. placebo on top of the specific PAH agents (excluding ERA users), could have been done, which would have been more clinically relevant and it would have allowed a better comparison with adult data, as in the SERAPHIN study in adults, a doubled blind design was performed. Importantly, using *ongoing/planned* ERA treatment (yes/no) as stratification factor no distinction is made between ERA treatment naïve patients planning to receive ERA treatment and patients already receiving ERA treatment at randomization, which may have a large impact on the efficacy results and makes interpretation of the results within a treatment arm and between both treatment arms even more difficult. Moreover, contrary to what is stated in EMA Guideline on Clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension [EMEA/CHMP/EWP/356954/2008], patients were not sufficiently stable on their background medications, as switching at time of randomization was allowed.

Therefore, the used study design, although in line with the PIP, is not considered appropriate and could only be considered supportive in terms of efficacy. As results of the pivotal study efficacy results will be only exploratory and demonstration of efficacy will rely mainly on extrapolation exercise from adults.

The efficacy assessment was not the primary goal of this clinical study, but PK and safety. The efficacy variables were evaluated as secondary endpoints. Key efficacy endpoint (time to first CEC-confirmed disease progression) deviates from the one proposed in the relevant CHMP guideline [EMA/CHMP/213972/2010] and the one that was investigated in SERAPHIN study, making it more difficult to bridge results from adults and children. The composite primary efficacy endpoint of the TOMORROW study includes a "soft" component of "Clinical worsening of PAH" based on a subjective assessment of "*Need for, or initiation of new PAH-specific therapy, or IV diuretics or continuous oxygen use*" that is not in line with the definition used in the SERAPHIN study. Although the MAH was advised to include exercise testing as a secondary investigation, the composite endpoint lacks a measure of exercise capacity.

Six minutes walking distance test (in children ≥ 6 years developmentally able) was only included as an exploratory endpoint in TOMORROW study. However, 6MWT criteria was only implemented with the approval of TOMORROW study protocol version 8.0, at which point, the majority of patients had been already recruited. As a result, change from baseline in 6MWD were only available for assessment at EOCP for a reduced number of participants. Although it is accepted that the utility of the measurement of 6MWD is more limited in children, as it is only reliable in developmentally able children >6 years of age, it is considered that measuring this endpoint, at

least as secondary (as previously advised) in a larger number of patients, would have allowed to have a clearer insight into effect of macitentan in the improvement of symptoms and would have facilitated a comparison with the observed effect in adults and with other PAH specific therapies.

Selected dose for each paediatric weight cohort reflected expected exposures comparable to the approved 10 mg dose of macitentan in adults. Patients ≥ 2 years were treated in an age (children < 2 years) and body weight (for children ≥ 2 years) dependent way, with a dose range from 1 to 10 mg [1mg for ≥1 and <6 months; 2.5 mg for ≥6 and <24 months; 3.5 mg for ≥10 kg and <15 kg; 5.0 mg ≥15 kg and <25 kg; 7.5 mg for ≥25 kg and <50 kg and 10.0 mg for ≥50 kg]. At each 12-weekly study visit, the participant's age body weight was verified for potential dose adjustment. The PK model failed to match the exposure in adults, with a clear underexposure in children < 2 years old at the doses tested [refer to Section: Discussion on Clinical Pharmacology].

Due to feasibility and recruitment challenges, the primary objective of the study drastically shifted from studying efficacy based on the evaluation of disease progression to a PK endpoint. Consequently, the decision to stop the study changed from the initial 187 DP events to an arbitrary date to meet regulatory commitments. Although this can be understood from a practical point of view, the consequence of this decision undermines the reliability of obtaining trustworthy efficacy results in the main comparisons. Time points of analysis where not prespecified and only depend on dates to meet regulatory commitment. Therefore, study duration for each participant depended on time form enrolment.

PAH3001 (Japanese) Study

PAH3001 study is an ongoing multicentre, open-label, single-arm, Phase 3 study in Japanese paediatric participants with PAH, which evaluates the efficacy, safety, and PK of macitentan. An interim analysis of preliminary Week 24 data from 2 subjects < 2 years were provided.

Eligible patients were Japanese PAH patients (aged ≥3 months and <15 years) in WHO FC I-IV. Aetiologies encompassed idiopathic, heritable, connective tissue, congenital heart disease (both co-incidental CHD and post-operative PAH persisting/recurring/developing ≥ 6 months after repair), drug or toxin-induced, and associated with HIV. PAH-specific treatment-naïve patients and patients already treated with PAH-specific treatment were included, being PDE-5 inhibitors the only allowed PAH-specific background medication.

Selected doses were the same as in TOMORROW Study: patients ≥ 2 years were treated in an age (children < 2 years) and body weight (for children ≥ 2 years) dependent way, with a dose range from 1 to 10 mg [1mg for ≥3 and <6 months; 2.5 mg for ≥6 and <24 months; 3.5 mg for <15 kg; 5 mg ≥15 kg and <25 kg; 7.5 mg for ≥25 kg and <50 kg and 10 mg for ≥50 kg].

Primary endpoint is the fold change in PVRI at Week 24. Other secondary efficacy endpoint encompassed effect of macitentan on other hemodynamic parameters (mRAP, mPAP, TPR, CO), improvement in Panama Functional Class; echocardiography parameters and NT-proBNP levels. Exploratory endpoints included time to disease progression.

Efficacy data and additional analyses

Children ≥ 2 years

As of TOMORROW Study EOCP a total of 148 patients, 88 (59.5%)) females and 60 (40.5%%) males were randomly (1:1) assigned to macitentan (n=72) or SoC (n=75) treatment and received at least 1 dose of study medication.

More participants in SoC arm discontinued treatment at EOCP: in total 48 participants ≥2 y.o. (23.3% macitentan arm vs. 41.3% SoC) discontinued treatment, which is reassuring and correlates with the shorter treatment exposure observed for SoC arm (130.59 weeks) vs macitentan arm (183.36weeks). The main reason for study treatment discontinuation was lack of efficacy/ treatment failure (1 in the macitentan arm and 14 in the SoC arm). The difference in the percentage of discontinuations between the SoC arm and the macitentan arm was mainly driven by participants ≥12 years, where the mean treatment duration in the SoC arm was reduced by about half as compared to macitentan. Nonetheless, it is acknowledged that large treatment exposures were achieved, as more than 50% of participants randomized to macitentan were under treatment for at least 36 months compared with 32% in the SoC arm. Major protocol deviations (MPD) were reported for 24 participants (32.9%) in the macitentan arm and 17 participants (22.7%) in the SoC arm. The Applicant discussed the impact that this may have in the interpretation of results. Since efficacy determination in paediatrics is based mainly in the extrapolation concept (based on PK data and similarity of the disease in adults and children), and since none of the MDP reported were considered to have an impact in PK measurement, the overall impact of MDP seems not relevant for the currently assessment.

Regarding baseline data, mean±SD age of participants was 9.75 years±4.429, with 35 (23.6%) aged ⩾2 to <6 years, 61 (41.2%) aged ⩾6 to <12 years, and 52 (35.1%) aged ⩾12 to <18 years, indicating that there is a proper representation of all age categories. Fewer Asian (15 [20.5%] versus 22 [29.3%]) and more white (44 [60.3%] versus 32 [42.7%]) participants were randomized to macitentan than to SoC, respectively. The macitentan arm included more participants aged ⩾12 to <18years (31 [42.5%] versus 21 [28.0%]) and more female participants (50 [68.5%] versus 38[50.7%]) than the SoC arm. The mean time from PAH diagnosis to randomization was comparable between both treatment arms (698.4 vs. 667.2 days for the macitentan and SoC arm, respectively).

The majority of participants had iPAH (71 participants [48.0%]) at baseline, followed by PAH associated with post-operative heart congenital disease (28.4%), PAH with co-incidental CHD (17.6%) heritable PAH (4.1%) and PAH associated with connective tissue disease (2.0%).

The majority of participants ⩾2 y.o. had PAH-specific therapies ongoing/planned at randomization, with the exception of 6 participants (4.1%) who had non-PAH-specific therapies ongoing/planned at randomization. The percentage of subjects with ongoing/planned ERA treatment at randomization is comparable between both treatment groups (45.2 % vs. 45.3% in the macitentan and SoC arm, respectively). The ongoing/planned SoC at randomization was mainly PDE-5i as monotherapy (53.4% macitentan arm vs 48.0% SoC arm), followed by the combination of a PDE-5i and an ERA (31.5% macitentan arm vs 38.7% SoC arm), and ERA as monotherapy (9.6% macitentan vs 6.7% SoC). One participant (1.3%) in the macitentan arm and one participant (1.4%) in SoC arm received PDE-5i in combination with a soluble guanylate cyclase stimulator, which is remarkable considering that co-administration with PDE5i is contraindicated for sGC stimulator therapy.

As already indicated above, the concern with presenting the PAH therapy at randomization by using the definition "ongoing/planned" is that no distinction is made between treatment naïve patients planning to receive a specific PAH treatment and patients already receiving a PAH

treatment at randomization, which may have an large impact on the efficacy results and makes interpretation of the results within a treatment arm and between both arms difficult. The Applicant clarified that although allowed, no subjects in the SoC arm received an oral/inhaled prostanoid at randomization.

Thirty-seven [25%] patients had WHO FC I at baseline (19 [26%] in macitentan arm vs 18 [24.0%] in SoC arm) and 83 patients [56.0%] had WHO FC II (42 [56.2%] macitentan vs 41 [56.0%] in SoC arm. The number of participants with WHO FC III at baseline was also comparable between arms (13 [17.8%] in the macitentan arm versus 15 [20.0%] in the SoC arm).

The Applicant was requested to justify the rationale and appropriateness of the treatment of WHO FC Class I patients as they are usually asymptomatic, which seems to concur to the fact that only 57 participants (out of 73) in the macitentan arm and 62 (out of 75) in the SoC arm declared at least 1 sign and symptom of PAH at Baseline. The argument given by the MAH about the similarity of the included population in TOMORROW study and the one included in the real-world TOPP registry [Ploegstra 2024] and about the fact that the determination of patient individual risk relies, not only on WHO FC class, but in other clinical parameters, is acknowledged. However, although the rationale of intervening early rather that awaiting progression events could be followed and it cannot be ruled out that certain PAH patients with WHO FC I could benefit from an early treatment with PAH specific therapies, TOMORROW study does not provide the adequate evidence to clearly discern the benefit of macitentan in this subpopulation (WHO FC I patients), due to the limitations already highlighted. Since the extension of indication to the paediatric population largely relies on extrapolation from the established efficacy results in adult patients, the inclusion of WHO FC I patients in the wording of the indication was not considered acceptable. Therefore, the indication of the paediatric population was reworded in line with the currently approved indication for adult patients i.e. change "with WHO FC I to III" into "with WHO FC II to III.

There were some disbalances in baseline characteristics between arms related to baseline severity of patients, which could influence the interpretation of results. Baseline mean NT-proBNP was higher in the macitentan arm (145.33 pmol/L) versus SoC (77.12 pmol/L); however, the median NT-proBNP levels at baseline are lower in the macitentan arm compared with the SoC arm (18.23 vs. 21.18 pmol/L, respectively). NT-proBNP levels are in general low for this specific PAH population. The Applicant justified that for the paediatric population in the TOMORROW study and for the adult population in the SERAPHIN study different assays were used resulting in an approximately 50-fold difference in baseline median NT-proBNP values.

Due to the fact that 6MWT criteria was only implemented with the approval of TOMORROW study protocol version 8.0 (25 January 2021), at which point, the majority of patients had been already recruited, only 11 participants (8 in macitentan arm and 3 in SoC arm) had provided 6MWD baseline data. The small sample size (specially for the SoC arm) of the data provided preclude to reach any conclusion about the comparison of the baseline severity of patients between arm in this regard.

Regarding efficacy results, macitentan therapy showed a non-statistically significant numerical trend for time to first CEC-confirmed disease progression compared to SOC (28.8% (n=21 events) vs 32.0% (n=24 events); adjusted HR of 0.828, 95% CI] = [0.460; 1.492], 2-sided stratified p=0.567). Nonetheless, comparative analysis is only exploratory, as a statistical significance cannot be inferred. Moreover, it is difficult to make firm conclusions on this endpoint due to the limited number of events and due to the fact that no distinction has been made between treatment naïve patients planning to receive a specific PAH treatment and patients already receiving a PAH treatment at randomization.

In addition, it should be taken into account that the benefit observed was mainly due to the component of clinical worsening (15 events macitentan vs. 21 events SoC), which is the most subjective component of the endpoint. Subgroup analyses showed a positive trend favouring macitentan (HR <1) for the majority of subgroups.

Clinical worsening of PAH was defined as: need for, or initiation of new PAH-specific therapy or IV diuretics or continuous oxygen use AND at least 1 of the following: worsening in WHO FC, or new occurrence or worsening of syncope, or new occurrence or worsening of at least 2 PAH symptoms or new occurrence or worsening of signs of right heart failure not responding to oral diuretics. In this regard, the MAH was requested to provide the results of the clinical worsening component, broken down into each of its components. Results showed that the main criteria reported for confirming clinical worsening were deterioration in functional class (10 in macitentan vs 16 in SOC) and occurrence or worsening of at least 2 PAH symptoms (11 in macitentan vs 17 in SOC). Both subcomponents were reported to a lesser frequency in the macitentan arm. New occurrence/worsening of syncope and signs of right heart failure were reported to a lesser extent and in similar rate between the two treatments.

At interim analysis, differences were reported between disease progression events adjudicated by the investigator and events CEC-confirmed. At EOCP, a statistical analysis of the concordance rate between disease progression events adjudicated by the investigator and events CEC-confirmed have been provided, as requested. Concordance rates between both assessments were high.

In the macitentan arm, most of the patients (82.2%) received a concomitant PAH specific agent during the treatment period, being sildenafil the most common administered. In the SOC arm around 50% of the patients were treated with another ERA and 92.0% with sildenafil. This data further complicates the comparison with the SOC, since in the control group subjects only with a PDE5 are mixed with 50% who are with ERA+PDE5. This hinders to know the contribution of added macitentan to PDE5 in the experimental group vs. PDE5 without ERA in the control group.

Generally, the subgroup analysis provided (WHO FC (I/II vs III), ongoing/planned ERA at randomization (Yes vs No), ongoing/planned PDE-5i treatment at randomization (Yes vs No), PAH aetiology ([iPAH, hPAH, HIV, drug or toxin induced,] vs. [PAH with coincidental CHD, CHD post-operative] vs [PAH-aCTD]), geographical region, age for participants (≥2 to <6 / ≥6 to <12/ ≥12 to <18), sex and race, did not yield discordant results. Nonetheless, due to the limited number of events and the study design no firm conclusions can be made.

As requested, an exploratory subgroup analysis of macitentan vs. SOC was also provided by regimen of PAH-specific therapy at baseline [naïve vs. monotherapy vs. combination]. The small sample size of the subgroups and the unplanned character of the subgroups analysis, preclude to reach any clinical conclusion. As stated before, study design makes impossible to discern the effect of macitentan as combination therapy and efficacy results will be only exploratory and evidence will rely mainly in extrapolation exercise.

Participants in the macitentan arm continued receiving macitentan after a CEC-confirmed disease progression event. A detailed analysis, not only of time to first event, but also of total number of events (first and subsequent events of disease progression) was provided. Rates of participants having subsequent events of disease progression were low, which is somewhat reassuring.

Four participants in the SoC arm cross over to macitentan. Separated results from these patients were provided. Due to the small sample size, no conclusion can be reached.

In the macitentan arm, the same number of events for first-confirmed hospitalization for PAH were observed (macitentan 11 vs. SoC 11; adjusted HR=0.912, 95% CI= [0.393; 2.118].

In terms of the time to CEC-confirmed death due to PAH and death from all causes, a total of 7 deaths (6 of which were due to PAH as per CEC) were observed in the macitentan arm compared to 6 deaths (4 of which were due to PAH as per CEC) in the SoC arm. Anyway, the low number of events hinders the interpretation of mortality results.

Macitentan treatment tended to reduce the percent of baseline NT-proBNP (pmol/L) at Week 12 compared with the SoC arm, with a GLSM ratio equal to 0.72 (95%CI [0.49; 1.05]) but the results were not statistically significant (2 sided p-value of 0.0862). The non-significant trend was less pronounced at Week 24 (geometric mean ratio: 0.97;95% CI: 0.66 to 1.43;2-sided p-value of 0.884).

However, results regarding decreasing NT-proBNP are difficult to interpret since baseline data between treatment were disbalanced (macitentan arm 145.33 pmol/L vs. SoC arm 77.12 pmol/L). The positive trend observed for macitentan arm in decreasing NT-proBNP levels could be attributed, at least in part, to a higher NT-proBNP level at baseline. The post- hoc analysis performed to evaluate time to first NT-proBNP value <35.4 pmol/L for participants with a baseline NT-proBNP value of ≥35.4 pmol/L, did not show statistical difference between arms.

No shifts in WHO FC from I/II to III were observed in participants in the macitentan arm at Week 12 or Week 24. There was a numerically higher proportion of patients at WHO FC I or II reported at Week 12 in the macitentan arm compared with the SOC arm (88.7% in macitentan arm versus 81.7% in SoC arm) and at week 24 (90.0% in macitentan arm versus 82.5% in SoC arm); stratified odds ratio=6.415; 95%CI [1.107, 37.164]).

No significant differences were seen in echocardiographic parameters between macitentan, and SOC and no effects were observed regarding daily moderate to vigorous physical activity at Week 48. An improvement from baseline both in parent report [treatment difference 6.27±2.666, 95% CI: [0.99; 11.55, 2-sided p=0.020)] and child report [treatment difference: 5.28±2.570 (95% CI: [0.18; 10.37], 2-sided p=0.043] was observed regarding QoL assessed through PedsQLTM version 4.0 short form (SF15). Higher scores indicate better HRQOL (Health-Related Quality of Life). Although a minimal clinical clinically important difference [MCDI] is not clearly stablished for the shorter version of the instrument PedsQL 4.0TM, the observed difference between macitentan and SoC could be regarded as clinically meaningful, taking into account that the comparator arm includes PAH-specific therapies, such as other ERAs.

The change from baseline 6MWD was lower in the macitentan arm (n=8) compared with the SoC arm (n=3) at Week 12 (19.64 vs 29.22 m), Week 24 (8.55 vs. 94.54 m), and Week 48 (47.47 vs. 71.89 m). Results must be interpreted with caution due to the small sample size.

Four hierarchical composite endpoints (HCE) were conducted as exploratory efficacy analyses, which help to contextualize the efficacy results due to the very limited maturity of the efficacy data from TOMORROW study. However, neither of them yielded significant results. Anyway, exploratory results suggest positive trends of macitentan compared with SOC in these composite endpoints, mainly driven by results on CEC-confirmed clinical worsening and in the SF25 questionnaire, which are the most subjective.

In summary, results observed at EOCP for TOMORROW study in children ⩾ 2 years were similar to the ones previously observed for the interim analysis at CCO1. Overall, HRs for most of the time-to-event efficacy endpoints were favouring macitentan (HR <1), with the exception of the HR for time to CEC-confirmed death due to PAH findings (HR>1). Beneficial numerical trends were also observed in WHO FC, NT-proBNP, and QoL. The change from baseline 6MWD was lower in the macitentan arm compared with the SoC arm at Week 12, Week 24, and Week 48. Nonetheless, the

small sample size (macitentan n=8; SoC=3) of the data provided preclude to reach any conclusion regarding exercise capacity.

However, although beneficial trends upon treatment with macitentan in paediatric population ≥2 to <18 years of age are suggested, the results are difficult to interpret due to the study design and therefore firm conclusion cannot be made. By presenting the PAH therapy at randomization using the definition "ongoing/planned" in both treatment arms, no distinction is made between treatment naïve patients planning to receive a specific PAH treatment and patients already receiving a PAH treatment at randomization, which may have an large impact on the efficacy results and makes interpretation of the results within a treatment arm and between both arms difficult. For example, patients already receiving ERA therapy (and/or other PAH specific therapy) at randomization and continuing this therapy during will not show an additional improvement in NT-proBNP, 6MWD, QoL or WHO FC, whereas an improvement will be expected in patients who are ERA (or other PAH specific) treatment naïve at randomization. Therefore, the results of the TOMORROW study can only be considered supportive.

It is widely accepted that it is often not feasible to perform statistically powered clinical studies for efficacy in children, as is done for adults; this is particularly valid for PAH, which is considered to be a rare disease in adults and has an even lower incidence in children (Barst et al. 2011). The *EMA guideline regarding clinical investigations for medicinal products targeting pediatric PAH* allows for extrapolation when the benefit-risk has been characterized in adults. In these cases, the development program focuses on defining the therapeutic dose and collecting data on short- and long-term safety (EMA 2012). Therefore, the totality of evidence included in this submission supporting the efficacy of macitentan for paediatric patients should be based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will results in similar efficacy in children (see extrapolation concept below).

Pharmacodynamic Similarity Assessment between adults, adolescents, and children [Study 10]

As supportive, the observed treatment effects of macitentan in the adult, adolescent and pediatric populations were compared in a pharmacodynamic and clinical similarity assessment using data from the adult SERAPHIN study and the paediatric TOMORROW study.

The study-analysis sets included 338 participants (169 in both the placebo and macitentan 10 mg arms) in the SER-set versus 79 participants in the TOM-set (40 in the SoC arm and 39 in the macitentan arm). Two analyses were performed for both set populations, a SERAPHIN like-analysis (following the statistical methodology outlined in the SERAPHIN Study) and a TOMORROW-like analysis (following the statistical methodology outlined in the TOMORROW study, being SERAPHIN-like analysis, considered the main one.

Despite the Company's attempts to include in the analysis comparable populations (by excluding patients with aCTD, those receiving the 3 mg dose in SERAPHIN and by excluding participants with planned/ongoing ERA in TOMORROW) there are other relevant differences in baseline characteristics in SERAPHIN vs. TOMORROW , apart from the obvious difference in age and aCTD aetiology, that makes between-study comparison challenging.

As stated before, patients in WHO Class I (29.1%) were only included in TOMORROW study. Differences were also observed in FC II and FC III class between both populations [SER–Set: FC Class II (48.1%) and FC Class III (50.1%); TOM-Set: Class II (53.2%) and Class III (17.7%)]. Therefore, more severe patients seem to be included in SERAPHIN study. No baseline data regarding 6MWD were provided for population sets, therefore, there is uncertainty about comparability between populations regarding this aspect. Regarding aetiology, patients with coincidental-CHD PAH were only included in TOMORROROW study. Relevant differences in baseline

NT-pro BNP values were also present between populations, which the Applicant attributes to the difference of assays used between the 2 studies. In the SER-set, NT-proBNP values at baseline were 793 pmol/L for placebo and 844 pmol/L for macitentan, while in the TOM-set, median NT-proBNP values at baseline were 21.0.5 pmol/L for SoC and 25.0 pmol/L for macitentan arms, respectively. Regarding therapy regimen: 35.9% of participants were treatment naïve to PAH therapies in SERAPHIN study while only 6.3% of participants were treatment-naïve in TOMORROW study.

For the endpoints evaluated, the MAH argued that although point estimates differ, most of CIs overlap, which suggests a similar effect between the two populations. However, it should be taken into account that the low number of events on the TOM- set results in very wide CIs, which hinders the accuracy of such affirmation.

Results from time to First CEC-Confirmed Disease Progression Event were similar in both analyses (SERAPHIN analysis and TOMORROW analysis), favoring macitentan. Results seem to reflect what was observed in individual studies: statistical significance over placebo but not over SOC (SERAPHIN like-Analysis: SER-set (over placebo) HR=0.530 (95% CI: 0.378, 0.744); TOM-Set (over SoC): 0.724 (95% CI: 0.312, 1.679). TOMORROW like-Analysis: SER-Set (over placebo) HR=0.492 (95% CI: 0.350, 0.691); TOM-Set (over SoC) HR= 0.929 (95% CI: 0.414, 2.087).

Nonetheless, it should be taken into account the different endpoint definition between the two studies (a more objective definition for SERAPHIN Study was studied, as 15% reduction in the 6MWD was include as a component of clinical worsening, while in TOMORROW study, a less objective definition of clinical worsening was assessed, not including the 6MWD component), This fact may have an impact in the comparison results, specially, taking into account that the effect observed in TOMORROW study was mainly due to the clinical worsening component.

For the endpoint of time to first hospitalization due to PAH, the analyses showed dissimilar results for the SER-set (which favoured macitentan) and TOM-set (which favoured SoC). For the endpoints of time to CEC-confirmed death due to PAH and time to all-cause death), HRs in the TOM-set could not be estimated because no events occurred in the SoC arm, thus precluding comparison between the SER-set and TOM-set.

The similar effect observed between children and adults in the improvement in WHO FC is difficult to interpret due to the wide CIs observed in the TOM-SET. Although sensitivity analysis for ‘no worsening of WHO FC from baseline to Month 6/Week 24’ showed similarity between adults and the pediatric population (favouring macitentan), it should be taken into account that there were differences in baseline WHO FC class between the two populations, with the adults recruited into SERAPHIN having a worse FC than the children recruited in the TOMORROW study), as previously mentioned.

Trends favoring macitentan were noted for decreases in NT-proBNP from baseline to Month 6/Week 24. However, comparison between the two population is challenging due to the different assays used and the different baseline levels.

Adolescents (12 to <18 years of age in TOMORROW) and young adults (12 to ≤25 years of age in SERAPHIN), were analyzed separately. In SERAPHIN-like analysis and TOMORROW-like analysis, though not statistically significant, trends favouring the macitentan arm were observed for adolescents (n=26) and young adults (n=43) for key efficacy endpoint. Nonetheless, due to the abovementioned limitations and due to the limited sample size, interpretation of results should be done with caution. Regarding Time to first hospitalization for PAH/Time to CEC-confirmed death due to PAH/Time to all-cause death too few events occurred in the TOM-set for meaningful comparison.

A subgroup analysis of ongoing PDE-5i treatment (yes/no), PAH etiology (idiopathic, hereditable, HIV, and drug induced vs associated with congenital shunts) WHO FC at baseline (I/II vs. III, IV), race, and region showed consistent effect, with HRs generally in favor of macitentan treatment, though not statistically significant. However, limited sample size makes the interpretation of results limited.

In summary, mentioned differences in baseline characteristics and differences in study design, particularly since in the SERAPHIN study the comparator was placebo, while in the TOMORROW study the controlled group was SoC (including any treatment other than macitentan or IV/SC prostanoids), make the comparison challenging.

The comparative PD and clinical analysis performed yielded results subject to high variability and wide confidence interval, providing limited evidence.

Children < 2 years

Enrollment of children < 2 years old could only be initiated after sufficient PK data in older children in the TOMORROW study was obtained in order to determine the daily macitentan doses necessary to reach similar exposure in the youngest age cohort. Consequently, the recruitment period for children <2 years old is marginally shorter as compared to the recruitment period of the older age groups.

At EOCP, provided data in patients <2 years old were very scarce. The main uncertainty was that none of the subjects enrolled was less than 1 year. In fact, almost all subjects were near to 2 years [range:1.2-1.9]. Thus, none of the subjects were treated with the 1 mg dose, since all subjects initiated treatment with the 2.5 mg dose and 4 subjects undergone a dose increase to 3.5 mg (due to a change in age category from<2 years to ≥2 years). Therefore, no sufficient PK data for the entire age subset of 1 months to < 2 years were available and consequently an accurate posology for paediatric patients aged 1 to < 2 year cannot be estimated [*refer to Section: Discussion on Clinical Pharmacology*].

Therefore, the small sample size, the limited duration of exposure and the impossibility of establishing a posology in this subset, do not allow to establish the efficacy/safety in children <2 years. Thus, therapeutic indication was restricted to patients ≥2 years.

Extrapolation concept

The totality of evidence included in this submission supporting the efficacy of macitentan for paediatric patients should be based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will results in similar efficacy in children. There are several considerations that justify the overall approach to extrapolate efficacy from adults, which are expressed in the *EMA Reflection Paper on extrapolation (EMA 2018)* as well as in the current draft *ICH E11A Guideline on paediatric extrapolation (EMA 2022)*. Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

Disease similarity

Regarding disease similarity, it is considered that the pathophysiology of PAH is similar among children enrolled in TOMORROW (⩾2 to <18 years of age) and adults. Historically, the definition of PH in children has been the same as in adults, i.e. mPAP ⩾25 mmHg and PVR ⩾ 240 dyn s cm-5 (3 Wood units). However, the distribution of PAH aetiologies in children is different from that in

adults, with a larger proportion of PAH associated with CHD in children, whereas in both populations, the majority of patients have IPAH.

Similar drug pharmacology

It is expected that the hemodynamic mechanism of action of macitentan is responsible for PAH efficacy which is expected to be similar in adults and children. However, this does not automatically mean that there is similar drug pharmacology, which besides mechanism of action also refers to absorption, distribution, metabolism, and excretion (ADME) properties. Nevertheless, PK modelling showed that the mean exposure obtained in the paediatric population of ⩾2 to <18 years of age in the TOMORROW study was comparable with that observed in the adult PAH patients, as the GMR point estimates were within the 0.8 to 1.25 reference range for this age category.

Similar exposure response

According to the Reflection Paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) the primary focus will usually be to establish a line of reasoning about the relation between dose, exposure, pharmacodynamic (PD) effects and clinical responses. However, in the current application there was no proof that similar exposures result in similar pharmacodynamic effects since no PK/PD analysis for both the paediatric population and the adult population was provided.

The Applicant provided the results of PIP study 10, in which the observed treatment effects of macitentan in the adult, adolescent and pediatric populations were compared in a pharmacodynamic and efficacy similarity assessment using data from the adult SERAPHIN study and the pediatric TOMORROW study (only children ⩾2 to <18 years of age). Since in the SERAPHIN study the comparator was placebo, while in the TOMORROW study the controlled group was SoC (including any treatment other than macitentan or IV/SC prostanoids) and the data is presented in comparison to placebo or SoC in specific forest plots, the comparisons were still difficult to interpret and firm conclusions on a consistent effect size could not be made.

In addition, the below statement from section 4.1 in adults was removed:

Adults

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

~~Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease~~ (see section 5.1).

This was requested by the CHMP as the information regarding etiologies is already included in section 5.1 and the extension of the indication to the paediatric population relies mainly on extrapolation from adult patients with PAH.

2.6.7. Conclusions on clinical efficacy

The main efficacy data of macitentan in children with PAH derived from TOMORROW study (AC-055-312).

In patients aged ≥2 years to <18 years (N=148), macitentan showed a non-statistically significant numerical trend for time to first CEC-confirmed disease progression compared to SOC (28.8%

(n=21 events) vs 32.0% (n=24 events); adjusted HR of 0.828, 95% CI] = [0.460; 1.492], 2-sided stratified p=0.567). Nonetheless, comparative analysis is only exploratory, as a statistical significance cannot be inferred. Positive numerical trends were also observed in other secondary endpoints like NT-proBNP, WHO FC and also in parent report and child report of QoL, measured using the SF15 questionnaire. Four hierarchical composite endpoints (HCE) were conducted as exploratory efficacy analyses, which suggest positive trends of macitentan, mainly driven by results on CEC-confirmed clinical worsening and in the SF25 questionnaire. On the contrary, no significant trends were seen in echocardiographic parameters between macitentan and SOC and no effects were observed regarding daily moderate to vigorous physical activity at Week 48. The change from baseline 6MWD was lower in the macitentan arm compared with the SoC arm at Week 12, Week 24, and Week 48. The small sample size (macitentan n=8; SoC=3) of the data provided preclude to reach any conclusion regarding exercise capacity.

Although the efficacy outcomes of the TOMORROW study suggested favourable trends, the study design is considered inappropriate in order to draw firm conclusions. Therefore, the totality of evidence included in this submission supporting the efficacy of macitentan for paediatric patients should be based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will results in similar efficacy in children as expressed in the EMA reflection paper on extrapolation (EMA 2018) as well as in the current draft ICH E11A guideline on paediatric extrapolation (EMA 2022) [refer to Section: *Clinical Pharmacology*].

In this regard, the comparative PD and clinical analysis performed between adult population (SERAPHIN Study) and paediatric (TOMORROW STUDY) yielded results subject to high variability and wide confidence interval, providing limited evidence. Differences in baseline characteristics and differences in study design, particularly since in the SERAPHIN study the comparator was placebo, while in the TOMORROW study the controlled group was SoC (including any treatment other than macitentan or IV/SC prostanoids), make the comparison challenging. Nonetheless, in children > 2 years, similar effects to adults are suggested. If considered them, in conjunction with the similar mechanism of action of macitentan in both populations, the pharmacological principles and the literature data provided, it is accepted that results can be viewed as supportive for the extrapolation exercise. Nonetheless, such exercise is mainly supported by matching a similar systemic exposure in paediatrics to those observed in adults at the proposed doses.

In patients aged < 2 years, the small sample size, the limited duration of exposure and the impossibility of establishing a posology in this subset, do not allow to establish the efficacy/safety in children <2 years. Thus, therapeutic indication has been restricted to patients ≥2 years.

Since in this application, the extension of indication to the paediatric population largely was relying on extrapolation from the established efficacy results in adult patients, the inclusion of WHO FC I patients in the wording of the indication was not considered acceptable. Consequently, the indication of the paediatric population has been reworded in line with the currently approved indication for adult patients i.e. "*WHO FC I to III*" changed into with "*WHO FC II to III*".

2.6.8. Clinical safety

Patient exposure

Table S-01 presents the cumulative duration of exposure from the Phase 3 TOMORROW study and supportive studies.

Table S-01. Overall Extent of Exposure.

Pediatric Studies	Intervention	N	Median Duration of Exposure: Weeks (Range)	Cumulative Duration of Exposure			
				≥3 months	≥6 months	≥24 months	≥54 months
TOMORROW (≥2 years)	Macitentan 10 mg Dispersible tablets (0.5, 1.0, 2.5, and 5.0 mg; dose based on weight)	72[a]	168.43 (12.9; 312.4)	71 (98.6%)	68 (94.4%)	58 (80.6%)	29 (40.3%)
	SoC	75	115.00 (0.1; 316.4)	69 (92.0%)	66 (88.0%)	41 (54.7%)	16 (21.3%)
			Weeks (Range)	**≥3 months**	**≥6 months**	**≥12 months**	**-**
TOMORROW (<2 years)	Macitentan (based on age)[b]	9[a]	37.14 (7.0; 72.90)	7 (77.8%)	6 (66.7%)	1 (11.1%)	-
67896062PAH3001 (<2 years)	Macitentan 2.5 mg, 3.5 mg (doses were based on age for <2 years and based on weight for >2 years)[c]	2[c]	(24.7; 25.3)	2	2	2	-
Supportive Studies			**Weeks (Range)**	**≥4 weeks**	**≥12 weeks**	**≥24 weeks**	**≥52 weeks**
SERAPHIN (AC-055-302)	Macitentan 10 mg	6	98.71 (3.7; 149.0)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)
MAESTRO (AC-055-305)	Macitentan 10 mg	13	16.14 (16.0; 17.0)	13 (100.0%)	13 (100.0%)	0	0
RUBATO (AC-055H301)	Macitentan 10 mg	8	52.71 (51.6; 63.1)	8 (100.0%)	8 (100.0%)	8 (100.0%)	7 (87.5%)

- [a] Database lock for the EOCP date of 28 February 2024
  - [b] Doses were based on age or weight (<24 months based on age, ≥24 months based on weight).
  - [c] Each participant had an individual cutoff date corresponding to the participant's Week 24 Visit/Collection date.

Demographics and baseline patient characteristics have already been summarised in Efficacy's Section (Tables **E-07 and E-09**).

Regarding prior and concomitant medications, in the TOMORROW study, PAH nonspecific therapies (eg, diuretics, anticoagulants, oxygen, calcium channel blockers) and changes to such medications were allowed during all study periods. PDE-5 inhibitor treatment ongoing at randomization was allowed to continue during the main treatment period. Intravenous prostanoids were allowed only for vasoreactivity testing. Any PAH-specific medication (including IV/SC prostanoids), except ERA, could be administered in addition to macitentan following a disease progression event. Use of

macitentan was forbidden in participants ≥2 years old at any time before study entry. Participants <2 years old were allowed to use macitentan during screening and oral/ inhaled prostanoids concomitantly with macitentan during the main treatment period.

In study AC-055-302 (SERAPHIN), oral or inhaled prostanoids, PDE5 inhibitors, calcium channel blockers, L-arginine and oral diuretics were allowed. Endothelin receptor antagonists, prostanoids, immune suppressants and CYP3A inducers were prohibited. In Study AC-055-305 (MAESTRO) diuretics and PDE5 inhibitors were allowed if present at a stable dose prior to randomization as well as any background medication for ES (antiarrhythmics, oral anticoagulants and digoxin). Endothelin receptor antagonists, prostanoids, CYP3A inducers and iron supplementation were not allowed. In Study AC-055H301 (RUBATO), medication for managing Fontan palliation and all pulmonary hypertension-specific drugs except ERAs were allowed. Endothelin receptor antagonist, CYP3A inducers and iron implementation were forbidden.

Adverse events

For all studies, AEs were coded to the preferred terms (PTs) using the MedDRA (Medical Dictionary for Regulatory Activities) version 25.1.

For TOMORROW, the treatment-emergent period is called "main treatment period" and is defined as:

- For participants ≥2 y.o., from the randomization date up to end of randomized macitentan + 30 days (or end of Core period whichever comes first).
- For participants <2 y.o., from Visit 2 up to end of macitentan + 30 days (or end of Core period whichever comes first).

For Study 67896062PAH3001, the treatment-emergent period was from Visit 2 (Day 1) to 30 days after the EOT visit (Week 52).

For AC-055-302 (SERAPHIN), the treatment-emergent period was from the start of macitentan up to 28 days after macitentan discontinuation.

For AC-055-305 (MAESTRO), the treatment-emergent period was from the start of macitentan up to 30 days after macitentan discontinuation.

For AC-055H301 (RUBATO), the treatment-emergent period was from the start of macitentan up to 30 days after macitentan discontinuation, or until initiation of study drug in the OL extension study, whichever occurred first.

Disease progression events (including associated symptoms) were not documented on the AE page of the eCRF but were reported on a separate specific dedicated eCRF page. Overview of Adverse Events.

TOMORROW Study (≥2 years)

As of EOCP (end of core period) 67/72 (93.1%) participants had at least one TEAE. Of these, 15 (20.8%) were assessed as related to macitentan. A total of 26 (36.1%) participants had an SAE, 2 (2.8%) of which were assessed as related to macitentan. Four AEs (5.6%) related to macitentan led to premature discontinuation of study drug. Finally, 12 AEs (16.7%) were associated to COVID-19 infections.

Table S-02. Overall Summary of Adverse Events - by Period for Participants ≥2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75	72	75
Subjects with 1 or more:				
AEs	67 (93.1%)	51 (68.0%)	67 (93.1%)	57 (76.0%)
Macitentan related AEs [a]	15 (20.8%)	NA	15 (20.8%)	1 (1.3%)
Serious AEs	26 (36.1%)	16 (21.3%)	26 (36.1%)	21 (28.0%)
Macitentan related serious AEs	2 (2.8%)	NA	2 (2.8%)	0
AEs leading to premature discontinuation of randomized macitentan or SoC	4 (5.6%)	2 (2.7%)	4 (5.6%)	2 (2.7%)
Macitentan related AEs leading to premature discontinuation of macitentan [a]	4 (5.6%)	NA	4 (5.6%)	0
AEs leading to death [b]	0	1 (1.3%)	0	2 (2.7%)
Macitentan related AEs leading to death [b]	0	NA	0	0

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
COVID-19 associated AEs [c]	12 (16.7%)	8 (10.7%)	12 (16.7%)	11 (14.7%)

Key: AE = Adverse event; EOCP = End of core period; NA = Not applicable; SoC = Standard of care.
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term.
[1] Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[2] Overall core period: from randomization up to EOCP. It might include crossover data.
Note: Only AEs with onset date occurring during the period under consideration are included.

TOMORROW Study (<2 years)

As of the EOCP, AEs were reported for 7 of the 9 participants <2 y.o. A total of 4 patients (44.4%) had a SAE. No AEs were related to macitentan or led to premature discontinuation or death. No participants had prematurely discontinued study treatment due to an AE. Two patients presented COVID-19 associated AEs.

Table-S03. Overall Summary of Adverse Events - by Period for Participants <2 Years Old; SAS2 Analysis Set (Study AC-055-312)

TSFAE01b: Overall Summary of Adverse Events - by Period for Subjects < 2 Years Old; SAS2 Analysis Set (Study AC-055-312)

	Main treatment period[1]	Overall core period[2]
	Macitentan (< 2 Years Old)	Macitentan (< 2 Years Old)
Analysis set: SAS2	9	9
Subjects with 1 or more:		
AEs	7 (77.8%)	7 (77.8%)
Macitentan related AEs [a]	0	0
Serious AEs	4 (44.4%)	4 (44.4%)
Macitentan related serious AEs	0	0
AEs leading to premature discontinuation of macitentan	0	0
Macitentan related AEs leading to premature discontinuation of macitentan[a]	0	0
AEs leading to death [b]	0	0
Macitentan related AEs leading to death [b]	0	0
COVID-19 associated AEs [c]	2 (22.2%)	2 (22.2%)

Key: AE = Adverse event; EOCP = End of core period; NA = Not applicable.
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term.
[1] Main treatment period: from Visit 2 up to end of macitentan + 30 days (or EOCP, whichever comes first).
[2] Overall core period: from Visit 2 up to EOCP.
Note: Only AEs with onset date occurring during the period under consideration are included.

AEs reported for more than 1 participant were upper respiratory tract infection (4 participants), gastroenteritis (3 participants [1 event of gastroenteritis was an SAE]), COVID-19 (2 participants), and pneumonia (2 participants). No AEs were assessed as related to macitentan or led to premature discontinuation or death. No disease progression events were reported for participants at the EOCP.

Study 67896062PAH3001 (<2 years)

In Study 67896062PAH3001, both participants experienced a total of 12 AEs, and 1 participant experienced an SAE of bronchitis during the study period.

Supportive Studies

In the supportive clinical studies, the majority of participants had at least 1 treatment-emergent AE, with the highest incidence in Study AC-055-302 (SERAPHIN) with 100% of participants having experienced at least 1 treatment-emergent AE. Study AC-055-305 (MAESTRO) had 76.9% of participants and Study AC-055H301 (RUBATO) had 62.5% of participants having experienced at least 1 treatment-emergent AE (Tables S-04, S-05 and S-06).

Table S-04. Overall Summary of Treatment-Emergent Adverse Events; SCS Safety Analysis Set (Study AC-055-302) (SERAPHIN)

	Macitentan 10 mg (age ≥12 to <18 years)
Analysis set: SCS Safety	6

Subjects with 1 or more:	
AEs	6 (100.0%)
Related AEs [a]	0
AE's leading to death [b]	3 (50.0%)
Serious AEs	4 (66.7%)
Related serious AEs [a]	0
AEs leading to study treatment discontinuation	1 (16.7%)

Key: AE = Adverse Event, SCS = Summary of Clinical Safety.
[a] An AE is categorized as related if assessed by the investigator as "Related" and "Not Related" to study treatment.
[b] AEs leading to death are based on AE outcome of fatal.
Note: Treatment-emergent AE's are all AE's with onset date in the period from the start to the end of macitentan 10 mg administration + 30 days (limits included).

Table S-05. Overall Summary of Treatment-Emergent Adverse Events; SCS Safety Analysis Set (Study AC-055-305) (MAESTRO).

	Macitentan 10 mg (age ≥12 to <18 years)
Analysis set: SCS Safety	13
Subjects with 1 or more:	
AEs	10 (76.9%)
Related AE's [a]	5 (38.5%)
AEs leading to death [b]	0
Serious AEs	0
Related serious AEs [a]	0
AE's leading to study treatment discontinuation	0

Key: AE = Adverse Event, SCS = Summary of Clinical Safety.
[a] An AE is categorized as related if assessed by the investigator as related to study treatment.
[b] AEs leading to death are based on AE outcome of fatal.
Note: Treatment-emergent AEs are all AE's with onset date in the period from the start to the end of macitentan 10 mg administration + 30 days (limits included)

Table S-06. Overall Summary of Treatment-Emergent Adverse Events; SCS Safety Analysis Set (Study AC-055H301) (RUBATO).

	Macitentan 10 mg (age ≥12 to <18 years)
Analysis set: SCS Safety	8
Subjects with 1 or more:	
AEs	5 (62.5%)
Related AEs [a]	2 (25.0%)
AEs leading to death [b]	0
Serious AEs	1 (12.5%)
Related serious AEs [a]	0
AEs leading to study treatment discontinuation	0

Key: AE = Adverse Event, SCS = Summary of Clinical Safety.
[a] An AE is categorized as related if assessed by the investigator as "Related" and "Not Related" to study treatment.
[b] AEs leading to death are based on AE outcome of fatal.
Note: Treatment-emergent AEs are all AEs with onset date in the period from the start to the end of macitentan 10 mg administration + 30 days (limits included)

Common Adverse Events

TOMORROW Study (≥2 years)

A higher rate of participants randomized to macitentan reported at least 1 AE; 67 participants (93.1%) as compared with 51 participants (68.0%) randomized to SoC. The difference in the mean duration of exposure in macitentan arm (183.36 weeks) and SoC arm (130.59 weeks) may have contributed to the observed PT imbalance. Imbalances in AE frequency ≥10% between both arms were reported for the following system organ classes:

-Infections and infestations (80.6% in the macitentan arm versus 50.7% in the SoC arm, primarily driven by AEs upper respiratory tract infection [31.9% versus 16.0%], gastroenteritis [11.1% versus 1.3%], and influenza [11.1% versus 4.0%, a listed macitentan ADR]), – The majority of AEs in the Infections and infestations system organ class during the Main treatment period were non-serious. – The only SAEs in the Infections and Infestations system organ class reported in more than 1 participant per arm were pneumonia (5 participants in the macitentan arm and 1 participant in the SoC arm), and respiratory tract infection (1 participant in the macitentan arm and 2 participants in the SoC arm).

- Gastrointestinal disorders (34.7% in the macitentan arm versus 21.3% in the SoC arm, with a difference in frequency for individual AEs < 5%),

- General disorders and administration site conditions (25.0% versus 10.7%, primarily driven by AEs pyrexia [9.7% versus 2.7%] and fatigue [6.9% versus 0%]),

- Injury, poisoning and procedural complications (22.2% in the macitentan arm versus 10.7% in the SoC arm),

- Blood and lymphatic system disorders (18.1% versus 4.0%, primarily driven by AE anaemia [a listed macitentan ADR], 9.7% versus 1.3%), and

- Reproductive system and breast disorders (15.3% in the macitentan arm versus 2.7% in the SoC arm, with a difference in frequency for individual AEs < 5%).

Adverse events by demographic subgroups

No trends in AE PT frequency were observed by sex or race groups for participants ≥2 y.o. in the Main treatment period. AEs of interest of macitentan specific to females (menstrual disorders) or more prevalent in females (AESI of anemia) are discussed below.

The most common AEs reported by age group (>20% of randomized participants in one age group) during the Main treatment period were:

-In the ≥2 - <6 y.o. group: upper respiratory tract infection (5 participants [38.5%] in the

macitentan arm and 4 [18.2%] in the SoC arm) and pneumonia (3 participants [23.1%] in the macitentan arm and 1 [4.5%] in the SoC arm).

-In the ≥6 - <12 y.o. group: upper respiratory tract infection (9 participants [31.0%] in the macitentan arm and 4 [12.5%] in the SoC arm), nasopharyngitis (10 participants [34.5%] in the macitentan arm and 2 [6.3%] in the SoC arm), COVID-19 (6 participants [20.7%] in the macitentan arm and 3 [9.4%] in the SoC arm), pyrexia (7 participants [24.1%] in the macitentan arm and 1 [3.1%] in the SoC arm), and headache (6 participants [20.7%] in the macitentan arm and 4 [12.5%] in the SoC arm).

-In the ≥12 - <18 y.o. group: upper respiratory tract infection (9 participants [30.0%] in the macitentan arm and 4 [19.0%] in the SoC arm), nasopharyngitis (3 participants [10.0%] in the macitentan arm and 5 [23.8%] in the SoC arm), and headache (7 participants [23.3%] in the macitentan arm and 4 [19.0%] in the SoC arm).

The most frequent AE in the 3 age groups of participants ≥2 y.o. was upper respiratory tract infection in both arms, with higher frequency in the younger age group in the macitentan arm (5 participants [38.5%] in the ≥2 - <6 y.o. group, 9 participants [31.0%] in the ≥6 - <12 y.o. group, and 9 participants [30.0%] in the ≥12 - <18 y.o. group) . Interpretation of AE frequency by age group should take into account the small sample size in the age groups.

Exposure-adjusted incidence rate (EAIR)

A post hoc analysis was performed for exposure-adjusted incidence rate (EAIR) during the Main treatment period. EAIR per 100 patient-years was comparable between arms, with 26.48 EAIR per 100 patient-years in the macitentan arm and 27.17 EAIR per 100 patient-years in the SoC arm. A numerical imbalance with higher EAIR in the macitentan arm after adjustment by exposure was reported for the SOCs Blood and lymphatic system disorders (5.14 in the macitentan arm versus 1.60 in the SoC arm), Reproductive system and breast disorders (4.35 in the macitentan arm versus 1.07 in the SoC arm, primarily driven by AE PT heavy menstrual bleeding [1.58 in the macitentan arm versus 0.53 in the SoC arm]), and General disorders and administration site conditions (7.11 in the macitentan arm versus 4.26 in the SoC arm). No imbalance in exposure-adjusted AE incidence was observed between arms in the SOCs which showed an imbalance of non-adjusted AE incidence (summarized in Section 5.3.1.2): Infections and infestations (22.92 in the macitentan arm versus 20.24 in the SoC arm, with the exception of an imbalance in PTs Upper Respiratory Tract Infection, Gastroenteritis, Rhinitis, COVID-19, and Influenza), and Gastrointestinal disorders (9.88 in the macitentan arm versus 8.52 in the SoC arm).

TOMORROW Study (<2 years)

As of the EOCP, in the TOMORROW study, AEs were reported for 7 of the 9 participants < 2 years of age. AEs reported for more than 1 participant were upper respiratory tract infection (4

participants), gastroenteritis (3 participants [1 event of gastroenteritis was an SAE]), COVID-19 (2 participants), and pneumonia (2 participants). A total of 6 SAEs were reported in 4 participants. Most AEs were of mild intensity. One AE of gastroenteritis, 1 AE of pneumonia, 1 AE of conjunctivitis, 1 AE of acute otitis media, 1 AE of influenza like illness, and 1 AE of pyrexia were of moderate intensity, and 1 AE each of constipation, pneumonia, influenza, and salmonella bacteremia were reported as severe (Mod5.3.5.2/AC-055-312EOCP). No AEs were reported as related to macitentan or led to premature discontinuation or death. No participants had prematurely discontinued study treatment due to an AE. No disease progression events were reported for participants at the EOCP.

Study 67896062PAH3001 (<2 years)

In Study PAH3001, both participants experienced a total of 12 AEs with the majority of the AEs mild in intensity. All the AEs were considered as not related to study intervention by the investigator. No action on study intervention was observed due to the AEs and all the AEs were resolved at the time of this report. One participant experienced an SAE of bronchitis during the study period that led to interruption of study intervention for a single day.

Supportive Studies

The observed AEs in the adolescent participants in the supportive studies, Study AC-055-302 (SERAPHIN), Study AC-055-305 (MAESTRO), and AC-055H301 (RUBATO) were consistent with the observed results in the TOMORROW study.

Adverse Drug Reactions

All adverse drug reactions (ADRs) per current SmPC are considered ADRs for the pediatric population.

To assess for potential new ADRs, the data from TOMORROW were reviewed using a structured approach for selection and evaluation.

The AEs that were selected for further examination met 1 or more of the following criteria: they were events reported in ≥5% of participants ≥2 y.o. (at least 4 participants) in the macitentan arm, regardless of any imbalances between the 2 arms; they were categorized as AESIs according to the protocol, or they were identified as an important identified or important potential risks based on the Risk Management Plan (RMP); they were causally linked to the investigational drug as determined by the investigator; or they were considered medically relevant.

The evaluation considered several factors, including the presence of imbalance at the PT level, (of note, no imbalance was defined as any higher percentage in SoC compared with the macitentan arm or the numbers of participants were the same). Other considerations involved seriousness and severity of an event, causal association per investigator, and discontinuation.

Based on the available data, the PTs upper respiratory tract infection, rhinitis, and gastroenteritis are new ADRs considered pediatric-specific. This classification is supported by the reported imbalance between the macitentan and SoC group without evidence of a plausible explanation as shown below. The difference in the mean duration of exposure in macitentan arm (168.43 weeks) and SoC arm (115.0 weeks) may have contributed to the observed PT imbalance.

- Upper respiratory tract infection was reported in 23 of 72 participants [31.9%] in the macitentan arm compared with 12 of 75 participants [16.0%] in the SoC arm). Of note, the incidence of respiratory tract infection is known to be high in children and tends to decrease with age (Chen 2014). In participants < 2 years old URTI was reported in 4 of 9 participants, (44.4%).

- Rhinitis was reported in 6 of 72 participants (8.3%) in the macitentan arm compared with 2 of 75 (2.7%) in the SoC arm. The assessment considered that nasopharyngitis and nasal congestion are listed as ADRs for macitentan. Rhinitis was not reported in any participant <2 years of age.
- Gastroenteritis was reported in 8 of 72 participants (11.1%) in the macitentan arm compared with 1 of 75 participants (1.3%) in the SoC arm. No latency pattern was identified. Gastroenteritis in the macitentan arm occurred between 64 and 1343 days after randomization (mean ± SD: 603±401.8). In participants < 2 years old gastroenteritis was reported in 3 of 9 participants (33.3%).

In summary, all ADRs per the current SmPC Section 4.8, are also considered ADRs for the pediatric population. Based on the above structured approach for selection and evaluation the AE data from the TOMORROW study, AE PTs upper respiratory tract infection, rhinitis and gastroenteritis remain identified as additional macitentan ADRs for pediatric PAH participants.

Based on the analysis of adult and adolescent females treated with macitentan in the SERAPHIN and TOMORROW studies, increased uterine bleeding has been added as a common ADR in the tabulated list of adverse reactions for the overall macitentan-treated population in the EU SmPC. No additional AE PT qualified for inclusion as an ADR in Section 4.8 of the SmPC Serious adverse events, deaths, and other significant events.

Serious Adverse Events

TOMORROW (≥2 years)

SAEs occurring in more than 1 participant were pneumonia (5 participants [6.9%] in the macitentan arm), anaemia, gastritis, and non-cardiac chest pain (2 participants each [2.8%] in the macitentan arm), and respiratory tract infection (2 participants [2.7%] in the SoC arm).

Overall, SAEs were similarly distributed across system organ classes for the 2 treatment arms, with differences in frequency between treatment arms below 5% for all SOCs except Infections and infestations. SAEs considered related to macitentan were anaemia and alanine aminotransferase increased (1 participant each [1.4%]) (table S-07).

Table S-07. Number of participants with serious adverse events by system Organ Class and preferred term-by period for participants ≥2 y.o. SAS1 Analysis set (study AC-055-312)

TSFAE04: Number of Subjects With Serious Adverse Events by System Organ Class and Preferred Term – by Period for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75	72	75
Subjects with 1 or more SAEs	26 (36.1%)	16 (21.3%)	26 (36.1%)	21 (28.0%)
System organ class Preferred term				
Infections and infestations	11 (15.3%)	7 (9.3%)	11 (15.3%)	11 (14.7%)
Pneumonia	5 (6.9%)	1 (1.3%)	5 (6.9%)	1 (1.3%)
Cellulitis	1 (1.4%)	0	1 (1.4%)	0
Dengue fever	1 (1.4%)	0	1 (1.4%)	0
Gastroenteritis	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Lower respiratory tract infection	1 (1.4%)	0	1 (1.4%)	0
Pneumonia mycoplasmal	1 (1.4%)	0	1 (1.4%)	0
Respiratory syncytial virus bronchiolitis	1 (1.4%)	0	1 (1.4%)	0
Respiratory tract infection	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Respiratory tract infection viral	1 (1.4%)	0	1 (1.4%)	0
Salpingo-oophoritis	1 (1.4%)	0	1 (1.4%)	0
Upper respiratory tract infection	1 (1.4%)	0	1 (1.4%)	0
Urinary tract infection	1 (1.4%)	0	1 (1.4%)	0
Viral infection	1 (1.4%)	0	1 (1.4%)	0
Wound infection	1 (1.4%)	0	1 (1.4%)	0
COVID-19	0	0	0	2 (2.7%)
Gastroenteritis viral	0	1 (1.3%)	0	1 (1.3%)
Influenza	0	1 (1.3%)	0	1 (1.3%)
Laryngitis	0	1 (1.3%)	0	2 (2.7%)
Mediastinitis	0	1 (1.3%)	0	1 (1.3%)
Tonsillitis	0	0	0	1 (1.3%)
Cardiac disorders	4 (5.6%)	2 (2.7%)	4 (5.6%)	2 (2.7%)
Cardiac arrest	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Cardiogenic shock	1 (1.4%)	0	1 (1.4%)	0
Right ventricular failure	1 (1.4%)	0	1 (1.4%)	0
Sinus tachycardia	1 (1.4%)	0	1 (1.4%)	0
Supraventricular tachycardia	1 (1.4%)	0	1 (1.4%)	0
Pericarditis	0	1 (1.3%)	0	1 (1.3%)
Respiratory, thoracic and mediastinal disorders	4 (5.6%)	3 (4.0%)	4 (5.6%)	4 (5.3%)
Asthma	1 (1.4%)	0	1 (1.4%)	0
Asthmatic crisis	1 (1.4%)	0	1 (1.4%)	0
Bronchospasm	1 (1.4%)	0	1 (1.4%)	0
Haemoptysis	1 (1.4%)	0	1 (1.4%)	0
Laryngeal stenosis	1 (1.4%)	0	1 (1.4%)	0
Pleural effusion	1 (1.4%)	0	1 (1.4%)	0
Acute respiratory failure	0	1 (1.3%)	0	1 (1.3%)
Pulmonary arterial hypertension	0	0	0	1 (1.3%)
Pulmonary embolism	0	1 (1.3%)	0	1 (1.3%)
Respiratory failure	0	0	1 (1.4%)	0
Systemic sclerosis pulmonary	0	1 (1.3%)	0	1 (1.3%)
Blood and lymphatic system disorders	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Anaemia	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)

TSFAE04: Number of Subjects With Serious Adverse Events by System Organ Class and Preferred Term – by Period for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Antiphospholipid syndrome	1 (1.4%)	0	1 (1.4%)	0
Gastrointestinal disorders	3 (4.2%)	0	3 (4.2%)	0
Gastritis	2 (2.8%)	0	2 (2.8%)	0
Abdominal pain	1 (1.4%)	0	1 (1.4%)	0
General disorders and administration site conditions	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Non-cardiac chest pain	2 (2.8%)	0	2 (2.8%)	0
Asthenia	1 (1.4%)	0	1 (1.4%)	0
Influenza like illness	0	1 (1.3%)	0	1 (1.3%)
Injury, poisoning and procedural complications	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Concussion	1 (1.4%)	0	1 (1.4%)	0
Overdose	1 (1.4%)	0	1 (1.4%)	0
Thermal burn	0	1 (1.3%)	0	1 (1.3%)
Nervous system disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	3 (4.0%)
Headache	1 (1.4%)	0	1 (1.4%)	0
Status epilepticus	1 (1.4%)	0	1 (1.4%)	0
Brain oedema	0	0	0	1 (1.3%)
Dizziness	0	0	0	1 (1.3%)
Hypoxic-ischaemic encephalopathy	0	1 (1.3%)	0	1 (1.3%)
Renal and urinary disorders	2 (2.8%)	0	2 (2.8%)	0
Acute kidney injury	1 (1.4%)	0	1 (1.4%)	0
Urethral stenosis	1 (1.4%)	0	1 (1.4%)	0
Reproductive system and breast disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Heavy menstrual bleeding	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Uterine haemorrhage	1 (1.4%)	0	1 (1.4%)	0

Reproductive system and breast disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Heavy menstrual bleeding	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Uterine haemorrhage	1 (1.4%)	0	1 (1.4%)	0
Investigations	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Alanine aminotransferase increased	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Oxygen saturation decreased	0	1 (1.3%)	0	1 (1.3%)
Musculoskeletal and connective tissue disorders	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Costochondritis	1 (1.4%)	0	1 (1.4%)	0
Camptodactyly acquired	0	1 (1.3%)	0	1 (1.3%)
Systemic scleroderma	0	0	0	1 (1.3%)
Psychiatric disorders	1 (1.4%)	0	1 (1.4%)	0
Depression	1 (1.4%)	0	1 (1.4%)	0
Skin and subcutaneous tissue disorders	1 (1.4%)	0	1 (1.4%)	1 (1.3%)
Dermatomyositis	1 (1.4%)	0	1 (1.4%)	0
Rash	0	0	0	1 (1.3%)
Urticaria	0	0	0	1 (1.3%)
Surgical and medical procedures	1 (1.4%)	0	1 (1.4%)	0
Hospitalisation	1 (1.4%)	0	1 (1.4%)	0
Vascular disorders	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Hypotension	1 (1.4%)	0	1 (1.4%)	0
Extremity necrosis	0	1 (1.3%)	0	1 (1.3%)
Thrombosis	0	1 (1.3%)	0	1 (1.3%)
Congenital, familial and genetic disorders	0	1 (1.3%)	0	1 (1.3%)
Atrial septal defect	0	1 (1.3%)	0	1 (1.3%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care

Key: SAE = Serious adverse event; EOCP = End of core period; SoC = Standard of care.
[1] Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[2] Overall core period: from randomization up to EOCP.
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 26.1.
Only AEs with onset date occurring during the period under consideration are included.

SAEs and/or serious disease progression events occurring in more than 1 participant were pulmonary arterial hypertension (4 participants [5.6%] in the macitentan arm and 6 participants [8.0%] in the SoC arm), pneumonia (5 participants [6.9%] in the macitentan arm and 1 participant [1.3%] in the SoC arm, anaemia (3 participants [4.2%] in the macitentan arm, 1 [1.3%] participant in the SoC arm), right ventricular failure (2 participants [2.8%] in the macitentan arm, 1 [1.3%] participant in the SoC arm), and gastritis, and non-cardiac chest pain (2 participants each [2.8%] in the macitentan arm), and respiratory tract infection (2 participants [2.7%] in the SoC arm, and 1 participant in macitentan arm [1.4%]).

Exposure-adjusted incidence rate showed SAEs and/or serious disease progression events were balanced between arms: 11.86 EAIR per 100 patient-years in the macitentan arm versus 10.66 EAIR per 100 patient-years in the SoC arm.

TOMORROW (<2 years)

SAEs were reported for 4 participants <2 y.o. (44.4%). None of the SAEs in participants <2 y.o. was related to macitentan nor led to dose change. All SAEs recovered/resolved as treatment with macitentan remained ongoing. (table S08).

Table S-08. Number of participants with serious adverse events by system organ class and preferred term and relationship to macitentan for participants< 2 y.o. SAS2 analysis set (study AC-055-312)

TSFAE14b: Number of Subjects With Serious Adverse Events by System Organ Class and Preferred Term and Relationship to Macitentan Occurring During the Main Treatment Period – for Subjects < 2 Years Old; SAS2 Analysis Set (Study AC-055-312)

	Macitentan (< 2 Years Old)		
		Relationship	
	Total	Not Related	Related
Analysis set: SAS2	9		
Subjects with 1 or more SAEs	4 (44.4%)		
System organ class			
Preferred term			
Infections and infestations	4 (44.4%)	4 (44.4%)	0
Pneumonia	2 (22.2%)	2 (22.2%)	0
Gastroenteritis	1 (11.1%)	1 (11.1%)	0
Influenza	1 (11.1%)	1 (11.1%)	0
Gastrointestinal disorders	2 (22.2%)	2 (22.2%)	0
Constipation	1 (11.1%)	1 (11.1%)	0
Haematemesis	1 (11.1%)	1 (11.1%)	0

Study 67896062PAH3001 (<2 years)

One participant experienced a treatment-emergent SAE of bronchitis during the treatment period which led to interruption of study intervention for a single day.

Supportive Studies

In the supportive studies, the rate of SAEs ranged from none (0/13) in Study AC-055-305 (MAESTRO) to 4/6 (66.7%) in Study AC-055-302 (SERAPHIN).

In Study AC-055-302 (SERAPHIN), out of the 6 participants, 4 (66.7%) experienced at least 1 SAE (Table S-09).

In Study AC-055-305 (MAESTRO), none of the 13 participants experienced any SAEs during the study.

In Study AC-055H301 (RUBATO), 1 participant (12.5%) out of 8 experienced an SAE of bronchitis during the treatment period.

Table S-09. Number of Subjects With Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term; SCS Safety Analysis Set (Study AC-055-302) (SERAPHIN).

	Macitentan 10 mg (age ≥12 to <18 years)
Analysis set: SCS Safety	6
Subjects with 1 or more SAEs	4 (66.7%)
System organ class	
Preferred term	
Cardiac disorders	2 (33.3%)
Arrhythmia	1 (16.7%)
Right ventricular failure	1 (16.7%)
Respiratory, thoracic and mediastinal disorders	2 (33.3%)
Pulmonary arterial hypertension	1 (16.7%)
Pulmonary embolism	1 (16.7%)
Infections and infestations	1 (16.7%)
Bronchitis	1 (16.7%)
Pneumonia	1 (16.7%)
Investigations	1 (16.7%)
Hepatic enzyme increased	1 (16.7%)

Nervous system disorders	1 (16.7%)
Syncope	1 (16.7%)

Key: SAE = Serious Adverse Event, SCS = Summary of Clinical Safety.
Note: Subjects are counted only once for any given event, regardless of the number of times they experienced the event.
Note: Adverse events are coded using MedDRA Version 25.1.
Note: Treatment-emergent AEs are all AEs with onset date in the period from the start to the end of macitentan 10 mg administration + 30 days (limits included)

Deaths

TOMORROW Study (≥2 years)

A total of 13 participants ≥2 y.o. died during the study (7 in the macitentan arm and 6 in the SoC arm). Causes of the 13 deaths are presented in Table S-10 (6 in the macitentan arm and 4 in the SoC arm were due to PAH disease progression confirmed by the CEC).

None of the deaths were reported as related to macitentan, and no causality assessment was collected for SoC. Deaths related to disease progression were not to be reported as AEs; these were documented on a separate specific dedicated disease progression eCRF page. All 7 deaths in the macitentan arm occurred during the Main treatment period. Two deaths in the SoC arm occurred during the Main treatment period (sudden death and hypoxic-ischaemic encephalopathy), and 4 occurred after the end of the Main treatment period.

One participant discontinued from the study assessments and went into survival follow-up on Day 29 (due to withdrawal of consent) and died of unknown cause on Day 741 (712 days from the last dose of planned SoC).

Table S-10. Summary of primary cause of death for participants ⩾2 y.o. SAS1 analysis set (study AC-055-312)

TSFDTH01: Summary of Primary Cause of Death for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Primary cause of death	7 (9.7%)	6 (8.0%)
PULMONARY ARTERIAL HYPERTENSION	2 (2.8%)	0
CARDIAC FAILURE ACUTE	1 (1.4%)	0
CARDIAC FAILURE CONGESTIVE	1 (1.4%)	0
HYPERTROPHIC CARDIOMYOPATHY	1 (1.4%)	0
MYOCARDIAL INFARCTION	1 (1.4%)	0
RIGHT VENTRICULAR FAILURE	1 (1.4%)	0
COVID-19 PNEUMONIA	0	1 (1.3%)
DEATH	0	2 (2.7%)
HYPOXIC-ISCHAEMIC ENCEPHALOPATHY	0	1 (1.3%)
PULMONARY HYPERTENSIVE CRISIS	0	1 (1.3%)
SUDDEN DEATH	0	1 (1.3%)

Out of the 13 deaths of participants ≥2 y.o., 2 deaths were also reported as AEs with fatal outcome: COVID-19 and hypoxic-ischaemic encephalopathy, both in the SoC arm.

TOMORROW Study (<2 years)

No participants <2 y.o. had died by EOCP.

No AEs with fatal outcome were reported for participants <2 y.o.

Study 67896062PAH3001 (<2 years)

None of the participants in Study 67896062PAH3001 died.

Supportive Studies

Three adolescent participants aged ≥12 to <18 years in Study AC-055-302 (SERAPHIN) died. The reported causes of death were arrhythmia, disease progression, and right ventricular heart failure, occurring at 0, 66, and 1 day(s), respectively, after the last study treatment. (Table S-1111).

None of the adolescent participants (<18 years) in the other supportive studies died.

Table S-11. Listing of Deaths. SCS Safety Analysis Set (Study AC-055-302) (SERAPHIN).

Treatment Group	Days From Last Study Treatment Administration to Death[a]	Study Day of Death[b]	Treatment-Emergent Death	Cause of Death Preferred Term/Reported Term
Macitentan 10 mg	0	26	Y	Arrhythmia/ARRYTHMIA
	66	640	N	Disease progression/SEVERE CLINICAL WORSENING OF PULMONARY ARTERIAL HYPERTENSION TO FUNCTIONAL CLASS IV Pulmonary arterial hypertension/SEVERE CLINICAL WORSENING

				OF PULMONARY ARTERIAL HYPERTENSION TO FUNCTIONAL CLASS IV
	1	408	Y	Right ventricular failure/RIGHT HEART FAILURE

Adverse Events of Special Interest

Adverse events of special interest for the TOMORROW study, Study 67896062PAH3001, and the supportive studies, which were selected based on the well-characterized safety profile of macitentan, were predefined as anemia, edema/fluid retention, hypotension, symptomatic hypotension, and hepatic disorders and are summarized below.

The majority of AESIs in all studies were related to anemia. The frequency of these occurrences was within the expected rates.

TOMORROW Study (≥2 years)

AESI in participants ≥2 y.o. during the Main treatment period were more frequent in the macitentan arm (18 participants [25.0%]) than in the SoC arm (7 participants [9.3%]). The most often reported AESI was anemia in 11 participants (15.3%) who received macitentan versus 2 participants (2.7%) who received SoC. AESIs of edema/fluid retention were reported in 4 participants (5.6%) who received macitentan versus 1 participant (1.3%) who received SoC. Events denoting hypotension, and hepatic events were each reported in less than 5% of participants.

Interpretation of AESI frequency should take into account the longer treatment exposure in the macitentan arm compared to the SoC arm. In addition, anemia is more prevalent in females of reproductive age, hence the difference in sex and age group composition between arms should be considered (more female participants in the macitentan arm than in the SoC arm, 68.5% versus 50.7%). In total, 35 (71.4%) female participants randomized to macitentan and 15 (39.5%) randomized to SoC were of childbearing potential at study enrolment or became of childbearing potential during the study participation.

Anemia

A total of 11 (15.3%) participants in macitentan arm and 2 (2.7%) in SoC arm had at least 1 event denoting AESI anaemia.

Of the total 8 participants with AESI with PT of anaemia (7 in the macitentan arm and 1 in the SoC arm), SAEs of anaemia were reported in 2 participants in the macitentan arm (2.8% of participants in this arm) (both SAEs were of severe intensity, recovered/resolved [1 with sequelae], and 1 of them leading to drug withdrawal) and in 1 participant in the SoC arm (1.3% of participants in this arm) (SAE of moderate intensity and recovered/resolved). All AESI of anaemia were considered not related to macitentan, except 2 (1 non-serious AE of anaemia which resulted in drug interruption and 1 SAE of anaemia which resulted in drug withdrawal).

Of the 4 participants (5.6%) with haemoglobin decreased (all 4 in the macitentan arm), 1 participant had 5 AEs of haemoglobin decreased, all reported as non-serious, all related to macitentan, and 1 resulting in drug interruption. The last AE of haemoglobin decreased in this participant had an outcome of not recovered/not resolved. The same participant had 1 SAE of anaemia.

Both AEs of iron deficiency anaemia (1 in the macitentan arm and 1 in the SoC arm) were non-serious, not related to macitentan, and had an outcome of recovered/resolved.

Of note, at Baseline, 9 participants (12.3%) in the macitentan arm and 1 (1.3%) in the SoC arm were treated with ferrous sulfate. One participant in the SoC arm and no participants in the macitentan arm received a transfusion after an AESI of anemia.

Edema/fluid retention

Of the 5 AESI of edema/fluid retention (4 in the macitentan arm and 1 in the SoC arm), 1 AE of pleural effusion in the macitentan arm was reported as a SAE.

The 4 AESI of edema/fluid retention in the macitentan arm were reported as not related to macitentan and did not lead to treatment interruption; 3 AESI recovered/resolved.

Hepatic disorders

6 participants had AESI of hepatic disorders (3 in the macitentan arm and 3 in the SoC arm), 1 AESI of alanine aminotransferase increased in the macitentan arm was serious, of severe intensity, considered related to macitentan, resulted in drug withdrawal, and was reported as recovered/resolved. In the SoC arm, 1 AESI of alanine aminotransferase increased was serious, of mild intensity, and was reported as recovered/resolved. The AESI of aspartate aminotransferase increased in the macitentan arm was reported as non-serious, not related to macitentan, and not recovered/not resolved (AST value reported at the EOCP visit). The AESI of transaminases increased in the macitentan arm was reported as non-serious, related to macitentan, led to drug withdrawal, and recovered/resolved.

Hypotension

Four AESI of hypotension were reported (3 in the macitentan arm and 1 in the SoC arm). The 3 AESI of hypotension in the macitentan arm (2 AEs of hypotension [1 serious and 1 non-serious] and 1 AE of orthostatic hypotension [non-serious]) were reported as not related to macitentan and recovered/resolved without treatment interruption.

The AESI of hypotension in the SoC arm was non-serious and recovered/resolved.

TOMORROW Study (<2 years)

No AESI were reported for participants <2 y.o.

Study 67896062PAH3001 (<2 years)

No AESI were reported in the 2 participants up to Week 24.

Supportive Studies

Adverse events of special interest in the supportive studies showed a similar pattern to the TOMORROW study.

The number of participants with at least 1 TEAE in AC-055-302 (SERAPHIN), AC-055-305 (MAESTRO), and AC-055H301 (RUBATO) is presented in table S-12. There was 1 participant with a hepatic disorder in each of these supportive studies.

There was 1 case of anemia in Study AC-055-305 (MAESTRO), and 1 case in Study AC-055H301 (RUBATO). There were no cases of hypotension in any of the participants from the supportive studies. There was 1 case of edema / fluid retention in Study AC-055H301 (RUBATO) (Table S-12).

Table S-12. Number of Subjects with at Least One Treatment-Emergent AESI by Preferred Term; SCS Safety Analysis Set (AC-055-302, AC-055-305, AC-055H301).

	Study AC-055-302 (SERAPHIN) Macitentan 10 mg (age ≥12 to <18 years)	Study AC-055-305 (MAESTRO) Macitentan 10 mg (age ≥12 to <18 years)	Study AC-055H301 (RUBATO) Macitentan 10 mg (age ≥12 to <18 years)
Analysis set: SCS Safety	6	13	8
Subjects with 1 or more AESIs	1 (16.7%)	1 (7.7%)	3 (37.5%)
AESI category			
Preferred term			
Anemia	0	1 (7.7%)	1 (12.5%)
Haemoglobin decreased		1 (7.7%)	
Microcytic anaemia			1 (12.5%)
Edema and fluid retention	0	0	1 (12.5%)
Pleural effusion			1 (12.5%)
Hepatic disorders	1 (16.7%)	1 (7.7%)	1 (12.5%)
Hepatic enzyme increased	1 (16.7%)		
Ischaemic hepatitis	1 (16.7%)		
Alanine aminotransferase increased		1 (7.7%)	1 (12.5%)
Hypotension	0	0	0
Symptomatic hypotension	0	0	0

Key: AESI = Adverse Event of Special Interest, SCS = Summary of Clinical Safety.
Note: Subjects are counted only once for any given event, regardless of the number of times they experienced the event.
Note: Adverse events are coded using MedDRA Version 25.1.
Note: Treatment-emergent AESIs are all AESIs with onset date in the period from the start to the end of macitentan 10 mg administration + 30 days or until initiation of study drug in the AC-055H302 OL extension study, whichever occurs first.

No relevant incidence of AESIS by age or race have been reported.

Other Adverse Events of Interest

TOMORROW Study (≥2 years)

Other AEs of interest for macitentan as reported in the macitentan RMP include menstrual disorders, ovarian cysts, and pulmonary edema associated with veno-occlusive disease (PVOD).

No events of ovarian cyst nor pulmonary edema associated with PVOD were reported. Eleven participants ≥2 y.o. (15.3%) in the macitentan arm (9 females and 2 males) experienced AEs of Reproductive system and breast disorders during the Main treatment period (heavy menstrual

bleeding in 4 participants [5.6%], dysmenorrhea in 3 participants [4.2%], and intermenstrual bleeding, penile swelling, priapism, and uterine haemorrhage in 1 [1.4%] participant each). Two participants (2.7%) in the SoC arm (1 female and 1 male) experienced AEs of Reproductive system and breast disorders during the Main treatment period (heavy menstrual bleeding and gynaecomastia in 1 participant [1.3%] each). The majority of these AEs of interest in the macitentan arm were non-serious, except:

One participant (1.4%) in the macitentan arm had a SAE of heavy menstrual bleeding (reported as SAE of mild severity, with an outcome of recovered/resolved); the participant's prolonged menses was associated with immature hypothalamic pituitary ovarian (HPO) axis.

One participant (1.4%) in the macitentan arm had SAEs of uterine haemorrhage (the SAEs were reported as SAE of moderate severity, with an outcome of recovered/resolved with sequelae). The participant's medical conditions at Baseline included violation of the menstrual cycle.

One participant (1.3%) in the SoC arm had a SAE of heavy menstrual bleeding, concomitant to a SAE of anaemia. The participant's medical conditions at Baseline included heavy menstrual bleeding.

None of the AEs of Reproductive system and breast disorders led to study treatment discontinuation or dose modification. The AEs of intermenstrual bleeding and priapism were considered related to macitentan. The male participant who experienced priapism was receiving a PAH-specific concomitant medication (sildenafil 10 mg TID) at the time of the priapism AE onset and while the AE was ongoing (sildenafil 10 mg TID was replaced by tadalafil 10 mg Q24H). Priapism is an ADR of both PDE-5i, sildenafil and tadalafil. No pregnancies were reported during the Core Period of the study.

Although the incidence of menstrual bleeding was within the expected incidence rates as compared with data reported in the literature for adolescent and adult females, there was an imbalance in these events between macitentan and control arms in adult and adolescent females treated with macitentan in SERAPHIN and TOMORROW studies. The majority of events were nonserious and resolved while macitentan was ongoing. In the SERAPHIN study, the incidence of menstrual bleeding in females aged 18 to 52 years was low and within the expected incidence rate in the general population, however higher in the macitentan 10 mg group as compared with placebo: 7.3% (9/123) and 1.9% (2/104), respectively. The event denoting menstrual bleeding (as "increased uterine bleeding") has been proposed to be added as an ADR within the tabulated list of ADRs in the overall macitentan-treated population in the EU SmPC and is also in the process of being added in the macitentan Company Core Data Sheet with a frequency of common.

Growth Measurements

Change from Baseline in growth variables (body mass index, height/length, and weight) in participants ≥2 y.o. was comparable between the macitentan and SoC arms at the majority of timepoints. Despite a difference between arms was observed for height/length (cm) after Week 192, and for weight (kg) after Week 252 (change from Baseline was smaller in the macitentan arm compared with the SoC arm, with a statistically significant difference of LS means [SE]), an individual assessment of growth over time for each participant showed continuous growth during the study.

Changes from Baseline in body mass index, height/length, and weight in participants <2 y.o. as well as ≥2 y.o. were at the expected range at the participant's ages.

No clinically meaningful trends in growth by age and sex were observed (all participants, SAS3).

Based on the analysis of the evolution of the growth parameters over time and by treatment groups, macitentan or SoC treated patients continued growing throughout their study participation and treatment.

Tanner Stage

Sexual maturation (Tanner stage) was assessed in female participants ≥8 years of age and in male participants ≥9 years of age (i.e., examination started once they were 8 and 9 years old, respectively). Tanner stage assessment was stopped once full sexual maturation was reached.

Assessment of Tanner stage over time for individual participants showed progression of sexual maturation during the study. Of the 49 female participants treated with macitentan, 23 were of childbearing potential (including 2 who were <12 years old) at the time of study enrolment and additional 12 females became of childbearing potential during the study. Of the 38 female participants treated with SoC, 11 were of childbearing potential (including 1 who was <12 years old) at the time of study enrolment and additional 4 females became of childbearing potential during the study. In total, 71.4% (35/49) female participants randomized to macitentan and 39.5% (15/38) randomized to SoC were of childbearing potential at study enrolment or became of childbearing potential during the study participation.

Continued development towards sexual maturation in participants during their puberty was observed during treatment with macitentan. Tanner Stage measurements were not applicable to participants <2 y.o.

TOMORROW Study (<2 years)

No other AESI were reported for participants.

Study 67896062PAH3001 (<2 years)

No AESI were reported in the 2 participants up to Week 24.

Supportive Studies

In the supportive studies, there was 1 adolescent participant with amenorrhea in the SERAPHIN study.

Clinical Chemistry

TOMORROW Study (≥2 years)

Marked clinical chemistry laboratory abnormalities based on central and local laboratory in participants ≥2 y.o. were observed during the Main treatment period for AST (2 participants [2.8%] with >3×ULN and >5×ULN in the macitentan arm and no participants in the SoC arm), ALT (2 participants [2.8%] with >3×ULN and >5×ULN in the macitentan arm and 3 participants [4.2%] with >3×ULN in the SoC arm), alkaline phosphatase (1 participant [1.4%] in each arm

with >2.5×ULN), bilirubin (5 participants [6.9%] in the macitentan arm, of which 1 had a value >5×ULN, and 1 participant [1.4%] with >2×ULN in the SoC arm), direct bilirubin (3 participants [4.2%] with >2×ULN in the macitentan arm, and 1 participant [1.4%] with >5×ULN in the SoC arm).

No clinically meaningful trends over time in serum creatinine values in participants ≥2 y.o. were observed in either treatment arm. High creatinine was observed in 1 participant (1.4%) in the macitentan arm (with >3×ULN or >3× Baseline if Baseline is above ULN; laboratory abnormality value on study Day 931 was assessed as not clinically significant). Low creatinine clearance (<1.0) was observed in 4 participants (7.0%) in the macitentan arm (of which 1 with <0.5) versus no participants in the SoC arm. In these 4 participants, low creatinine clearance values were observed in 4 visits for 1 participant (values in the range 0.4.6676 to 0.60012 mL/s; serum creatinine values for this participant were in the reference range at all visits), in 2 visits for 1 participant (0.60012 and 0.81683 mL/s; with low serum creatinine values [out of reference range] at the majority of visits from screening), and in 1 single visit for 2 participants (0.6728 and 0.88351 mL/s, respectively; both participants had low serum creatinine values at the majority of visits from screening). None were reported as an AE by the investigator.

Other marked abnormalities were sodium (3 participants [4.2%] in the macitentan arm [1 with low values and 2 with high values] versus no participants in the SoC arm), potassium (2 participants [2.8%] with high values in the macitentan arm and 1 participant [1.5%] with high value in the SoC arm), and calcium (1 participant [1.4%] with low value in the macitentan arm and 1 participant [1.5%] with low value in the SoC arm). No participants in the macitentan arm had marked abnormalities for blood urea nitrogen or glucose, 1 participant [1.5%] in the SoC arm had high blood urea nitrogen, and 4 participants (6.0%) in the SoC arm had marked glucose abnormalities (1 low and 3 high).

TOMORROW Study (<2 years)

Marked abnormalities for clinical chemistry values including local laboratories for participants <2 y.o. were reported for 1 participant (33.3%), with creatinine clearance <1.0 (0.7668 mL/s).

Elevated Liver Test

TOMORROW Study (≥2 years)

Elevated ALT and/or AST of >3×ULN and TBIL >2×ULN reported in participants ≥2 y.o. during the Main treatment period based on central and local laboratory data are shown in Table S-13. One participant in the SoC arm met the biochemical criteria for Hy's Law case (ALT and/or AST >3 ULN + TBIL >2 ULN + AP <2 ULN) (Table 60). The 5 participants with elevated ALT or AST of >3×ULN had AEs of alanine aminotransferase increased (4 participants) and transaminases increased (1 participant), reported as hepatic disorders ~~AESI~~.

For the 2 participants in macitentan arm with aminotransferase increases to > 8×ULN, macitentan was discontinued as per protocol. The events occurred in the context of RHF and respiratory tract infection in 1 of the 2 participants, no specific context was reported for the second participant, and the hepatic event resolved in both cases. Of the 3 participants (4.2%) in the SoC arm who experienced elevated ALT and/or AST>3×ULN, 1 event met the biochemical criteria for Hy's Law case (ALT and/or AST > 3 ULN + TBIL > 2 ULN + AP <2 ULN) and occurred in the context of non-alcoholism like disease with increased fatty content in the liver in an overweight participant. The aminotransferase values returned to WNR as SoC treatment continued.

Table S-13. Elevated Liver Tests (Hy's Law) During the Main Treatment Period for Subjects ≥ 2 Years Old; SAS1 Safety Analysis Set (Study AC-055-312).

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
N	72	71
ALT > 3 ULN at any time	2 (2.8%)	3 (4.2%)
ALT and/or AST > 3 ULN at any time	2 (2.8%)	3 (4.2%)
ALT > 5 ULN at any time	2 (2.8%)	0
ALT and/or AST > 5 ULN at any time	2 (2.8%)	0
ALT > 8 ULN at any time	2 (2.8%)	0
ALT and/or AST > 8 ULN at any time	2 (2.8%)	0
ALT and/or AST > 3 ULN + TBIL > 2 ULN at any time	0	1 (1.4%)
ALT and/or AST > 3 ULN + TBIL > 2 ULN at the same time	0	1 (1.4%)
ALT and/or AST > 3 ULN + TBIL > 2 ULN + AP < 2 ULN at the same time	0	1 (1.4%)
TBIL > 2 ULN at any time	5 (6.9%)	1 (1.4%)

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; EOCP = End of core period; SoC = Standard of care; TBIL = total bilirubin; ULN = upper limit of normal.
Note: The number of percent of subjects with the applicable condition for at least one visit post-baseline visit, where the same condition was not met at baseline is displayed.
Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.

TOMORROW Study (<2 years)

No participant <2 y.o. had elevated ALT and/or AST of >3×ULN nor TBIL >2×ULN based on central and local laboratories. No participant <2 y.o. met the biochemical criteria for Hy's Law case (ALT and/or AST >3 ULN + TBIL >2 ULN + AP <2 ULN).

Liver parameters out of the reference range but not reported as marked abnormalities in participants <2 y.o. were: 1 participant had low AP values of 111 U/L at Week 4 and 85 U/L at Week 36, respectively (reference range 125-320 U/L), 1 participant had high AP values at all visits, including Baseline, 1 participant had high AP values at 1 unscheduled visit (186 U/L, reference range 46-116 U/L), 1 participant had a low AP value of 5 U/L at an unscheduled visit (reference range 125-320 U/L), 1 participant had 2 low TBIL values of 5.13 and 3.42 µmol/L at 2 unscheduled visits (reference range 6.84-25.65 µmol/L and 5.13–20.52, respectively), 1 participant had low AST of 51.3 U/L at the EOCP Visit, and 1 participant had high AST of 62 U/L at Week 26.

No cases were reported in the 2 participants up to Week 24 in the Study 67896062PAH3001 and no cases were reported in any of the adolescent participants <18 years of age in the supportive studies.

Haematology

TOMORROW Study (≥2 years)

Based on central laboratory data, marked hematology laboratory abnormalities in participants ≥2 y.o. during the Main treatment period were more frequent in the macitentan arm compared with the SoC arm. The most common marked hematology abnormalities by parameter were hemoglobin decreased (15 participants [20.8%] in the macitentan arm and 9 participants [13.0%] in the SoC arm) and low hematocrit (8 participants [11.1%] in the macitentan arm and 2 participants [2.9%] in the SoC arm). The most common marked laboratory abnormalities during the Main treatment

period (and not present at Baseline) by value (>5% of participants in any treatment arm) were low hemoglobin (<100 g/L, 11 participants [15.3%] in the macitentan arm and 1 participant [1.4%] in the SoC arm) high hemoglobin (increase >20 g/L above ULN or above baseline if baseline is above ULN, 6 participants [8.5%] in the macitentan arm and 8 participants [11.6%] in the SoC arm), high hematocrit (>0.55 F, >0.60 M) (5 participants [6.9%] in the macitentan arm) and low leukocytes (< 3.0 x 10^9 /L, in 7 participants (9.7%) in the macitentan arm and 2 participants [2.9%] in the SoC arm).

Most mean changes from Baseline in hemoglobin and hematocrit values (decreased) were observed in participants ≥2 y.o. in the macitentan arm up to Week 96. Mean change from Baseline in hemoglobin up to Week 96 was in the range -1.9 to -6.6 g/L. Mean change from Baseline in hematocrit up to Week 96 was in the range -0.002 to -0.017. No trends over time in decrease from Baseline in hematology values were observed in the SoC arm.

TOMORROW Study (<2 years)

No trends over time in change from Baseline in hematology values were observed in participants <2 y.o. Marked laboratory abnormalities for hematology parameters were reported for 2 participants <2 y.o. (low hematocrit [<0.28 F, <0.32 M] in 1 participant [11.1%], and low leukocytes [<3.0x10^9/L] in 1 participant [11.1%]).

In Study 67896062PAH3001, 1 haematological laboratory abnormality of neutropenia was observed as TEAE in 1 of the participants. In the supportive studies, no cases were reported in any of the adolescent participants <18 years of age.

Renal Clearance

TOMORROW Study (≥2 years)

Lower creatinine clearance was observed in 4 participants (7.0%) in the macitentan arm (of which 1 with < 0.5 mL/s) versus no participants in the SoC arm. In these 4 participants, low creatinine clearance values were in the range 0.46676 to 0.60012 mL/s. It is to be noted that baseline creatinine clearance was not available for any of these 4 participants. All 4 cases of low creatinine clearance shown serum creatinine values within normal range or below the lower limit of normal. No participants in the macitentan arm had marked abnormalities for blood urea nitrogen or glucose, 1 participant [1.5%] in the SoC arm had high blood urea nitrogen, and 4 participants (6.0%) in the SoC arm had marked glucose abnormalities (1 low and 3 high).

TOMORROW Study (<2 years)

As of the EOCP, no participants had marked abnormalities for creatinine or blood urea nitrogen. One abnormal value for creatinine clearance of LL (< 1.0 mL/s) was reported for 1 participant in the macitentan arm.

No cases were reported in in the 2 participants up to Week 24 in the study 67896062PAH3001 and no cases were reported in any of the adolescent participants <18 years of age in the supportive studies.

High Sodium, High Potassium, or Low Calcium

TOMORROW Study (≥2 years)

Other marked abnormalities were sodium (3 participants [4.2%] in the macitentan arm [1 with low values and 2 with high values] versus no participants in the SoC arm), potassium (2 participants [2.8%] with high values in the macitentan arm and 1 participant [1.5%] with high value in the SoC arm), and calcium (1 participant [1.4%] with low value in the macitentan arm and 1 participant [1.5%] with low value in the SoC arm.

TOMORROW Study (<2 years)

As of EOCP, no marked abnormalities for clinical chemistry values and no marked abnormalities for other laboratory values were reported for participants.

No cases were reported in in the 2 participants up to Week 24 in the study 67896062PAH3001 and no cases were reported in any of the adolescent participants <18 years of age in the supportive studies.

Additionally, no abnormalities in vital signs, physical findings, or other observations related to safety were recorded in any of the studies included.

2.6.8.1. Safety related to drug-drug interactions and other interactions

Safety data related to drug-drug interactions and other interactions have not been submitted and no new interactions are explored within this submission. Known interactions of macitentan are already included in SmPC.

Discontinuation due to adverse events

In the TOMORROW study ≥2 y.o., as of EOCP, AEs leading to premature discontinuation of study treatment were reported during the main treatment period in 4 participants (5.6%) who received macitentan (alanine aminotransferase increased [recovered without sequelae], transaminases increased [recovered without sequelae], headache [recovered without sequelae]), and anemia [event of hemoglobin decreased improved to a mild nonserious AE which was ongoing at the time of discontinuation] (Table S-14).

Table S-14. Number of Subjects ≥2 to <18 Years of Age With Adverse Events Leading to Premature Discontinuation of randomized Macitentan or SoC During the Main Treatment Period by System Organ Class and Preferred Term; SAS1 Analysis Set (Study AC-055-312)

TSFAE06: Number of Subjects With Adverse Events Leading to Premature Discontinuation of Randomized Macitentan or SoC During the Main Treatment Period by System Organ Class and Preferred Term for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Subjects with 1 or more AEs	4 (5.6%)	2 (2.7%)
System organ class Preferred term		
Investigations	2 (2.8%)	0
Alanine aminotransferase increased	1 (1.4%)	0
Transaminases increased	1 (1.4%)	0
Blood and lymphatic system disorders	1 (1.4%)	0
Anaemia	1 (1.4%)	0
Nervous system disorders	1 (1.4%)	0
Headache	1 (1.4%)	0
Cardiac disorders	0	1 (1.3%)
Cardiac arrest	0	1 (1.3%)
Eye disorders	0	1 (1.3%)
Eye swelling	0	1 (1.3%)
Ocular hyperaemia	0	1 (1.3%)
Gastrointestinal disorders	0	1 (1.3%)
Abdominal pain upper	0	1 (1.3%)
Faeces discoloured	0	1 (1.3%)
Vomiting	0	1 (1.3%)

Key: AE = Adverse event; EOCP = End of core period; SoC = Standard of care.
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 26.1.
Only AEs with onset date occurring during the period under consideration are included.
Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.

In the TOMORROW study (< 2 years), no participants had prematurely discontinued study treatment due to an AE.

Additionally, none of the 2 participants in the study 67896062PAH3001 (<2 years) discontinued study treatment.

In the supportive studies, AEs leading to premature discontinuation of study treatment in participants were reported in 1 participant (16.7%) who received macitentan in the SERAPHIN study due to hepatic enzyme increased.

2.6.8.2. Post marketing experience

Cumulatively (from 18 October 2013 [international birth date] to 30 September 2022), an estimated 132,805 patients have been exposed to commercial macitentan worldwide.

Information on the safety of macitentan use in adults in the postmarketing setting is available from 12 Periodic Benefit Risk Evaluation Report (PBRERs)/Periodic safety update reports (PSURs), covering data from 18 October 2013 up to 17 October 2022. The conclusion of the most recent PBRER was that macitentan continues to have a favorable benefit-risk profile for the treatment of patients with the authorized indication.

The MAH also provides a summary of safety information from the GMS global safety database on the off-label use, including doses reported, of macitentan 10 mg tablet in children below 18 years of age. All cases retrieved from the GMS global safety database, through 17 October 2022, which was the data lock date of the most recent PBRER/PSUR, were included in the analysis, including postmarketing, literature and noninterventional clinical study cases. Results have been submitted as aggregate data and also as case review reults. The following important identified risks and potential risks have been described: anaemia/decrease in haemoglobin concentration, hepatotoxicity, teratogenicity, hipotension, menstrual disorders (primary bleeding), ovarian cysts, pulmonary oedema associated with PVOD, and testicular disorders and male infertility. Data have been presented in the following groups: below 2 y.o., from 2 to 12 and from 12 to 18 years of age.

The search retrieved 172 cases reported in participants under 2 years of age, (101 nonserious, 1 serious) reporting a total of 616 events; 417 cases in patients from 2 to below 12 years of age, (277 nonserious, 140 serious) reporting a total of 1384 events and 546 cases in patients from 12 to below 18 years of age, (259 nonserious, 287 serious) reporting a total of 2328 events.

An additional review of the literature revealed 13 citations. Among the 13 articles, 8 were observational studies, 3 were case series studies and 2 were case reports pertaining to the same patient. These studies included a total of 111 children, ranging in age from 0.1 to 18 years, and weighing between 3.1 kg and 106 kg. Out of the 111 children, 32 were females, 39 were males and sex were not reported in the remaining 40 children. The indications for macitentan use varied and included idiopathic/heritable PAH, PAH in relation to congenital heart disease, repaired congenital systemic-to-pulmonary shunts, and portopulmonary hypertension. A total of 79 patients (reported from 8 articles) switched to macitentan from another PAH treatment, primarily bosentan. The starting dose of macitentan ranged from 1 to 10 mg per day and was adjusted based on the patient's weight.

The studies did not reveal any new or significant safety signals. Where reported, AEs such as headache, nasopharyngitis, peripheral edema, and itching were consistent with the safety profile of macitentan. Additionally, 1 retrospective study elucidated a decrease in the anticoagulant index of warfarin by a median of 2.25 units, despite macitentan not being known to activate pregnane X receptor (PXR). However, no other safety concerns were identified.

Furthermore, 11 articles concluded that macitentan effectively improved PAH in children.

Overall, macitentan was well tolerated in the pediatric age group.

The review of data received for pediatric patients from postmarketing sources including the ad hoc reports Description of Cumulative Postmarketing Cases Reporting Off-Label Macitentan Use in Pediatric Patients (up to 17 October 2022) and Description of Post-marketing Cases Reporting Off Label Macitentan Use in Pediatric Patients Covering Interval From 18 October 2022 Through 17 October 2023, showed that the reported AEs were consistent with the well-known safety profile of macitentan as documented in the EU-PI or were in line with the underlying conditions. No new safety signals were identified.

2.6.9. Discussion on clinical safety

Two pivotal dedicated pediatric studies comprise the safety database, but they have different designs, sample sizes, age ranges, macitentan doses and selected control: TOMORROW study (n=72 ≥2 y.o. and n=9 < 2 y.o.) is a phase 3, open-label randomized study that enrolled patients aged ≥1 month to <18 years with PAH. The selected control was SoC except children <2 y.o. who were not randomized and entered directly into the macitentan arm. The macitentan dose was based on body weight in children ≥2 y.o. and based on age in children < 2 y.o. The second pivotal study, the Japanese study 67896062PAH3001 (n=2, both < 2 y.o.) is a phase 3 open-label and single arm study that enrolled Japanese children ≥3 months to <15 years with PAH. Macitentan dose was based on body weight in children ≥2 y.o. and based on age in patients < 2 y.o.

Of note, only data from 11 patients < 2 y.o. have been submitted (9 from the pivotal study, and 2 patients from the 67896062PAH3001 study). In this group (< 2 years old), children were not randomized and were entered directly into the macitentan arm. Regarding study 67896062PAH3001, it was conducted in Japanese pediatric participants, and no data from European patients are going to be available, therefore, only limited safety evidence may be extracted from Study 67896062PAH3001.

The low number of enrolled patients < 2 y.o. in clinical trials, is considered a limitation as very limited clinical safety data are available to establish a robust safety conclusion in this subgroup.

The applicant has also submitted three supportive studies (SERAPHIN, MAESTRO and RUBATO), which were double-blind, randomized, placebo controlled, phase 3 studies, and they included pediatric patients aged ≥12 to <18 years (n=6, 13 and 8 respectively). The selected dose of macitentan in the supportive studies was 10 mg. The SERAPHIN study included patients with symptomatic PAH, and MAESTRO and RUBATO included patients with Eisenmenger syndrome and Fontan-palliated participants respectively. The Applicant has provided safety data (AEs, SAEs, AESIS, deaths, AEs leading to discontinuation and other adverse events of interest) from the double- blind and open label extension studies (SERAPHIN OL, MAESTRO OL, and RUBATO OL). Safety data provided are in line with the known safety profile of macitentan and no new safety signals have been reported.

Due to the significant differences among studies in relation to designs, sample sizes, and age ranges, as well as in macitentan dose and the selected control (SoC, placebo or none), safety data have been presented individually, which is considered acceptable.

In the TOMORROW study, intravenous prostanoids were allowed only for vasoreactivity testing. PDE-5 inhibitor treatment ongoing at randomization was allowed to continue during the main treatment period. Use of macitentan was forbidden in participants ≥2 y.o. at any time before study entry. Participants <2 y.o. were allowed to use macitentan during screening and oral/ inhaled prostanoids concomitantly with macitentan during the main treatment period. In addition, information regarding adverse events by concomitant medications have been provided.

Additionally, supportive safety data from the Global Medical Safety database and literature have been presented.

Safety data in pediatric patients are discussed below, separately for children ≥ 2 years old (y.o.) and children < 2 y.o.

Children ≥ 2 years old (y.o.)

Safety data in children ≥ 2 years old are based on the EOCP analysis results of the pivotal ongoing pediatric study TOMORROW (72 patients receiving macitentan and 75 SoC) and data from the following supportive studies in children between 12 and 18 y.o. (≥12 to <18 years): SERAPHIN (n=6, in symptomatic PAH), MAESTRO (n=13, in Eisenmenger Syndrome) and RUBATO (n=8, in Fontan-palliated participants).

In study TOMORROW ≥2 y.o., 58 patients (80.6%) in the macitentan arm (vs 41 [54.7%] in the SoC arm) completed the 24-month follow up, and data from 29 patients (40.3%) and 16 (21.3%) patients in the macitentan and SoC arms, respectively, are available at month 54. The median duration of exposure in the macitentan arm was 168.43 (12.9;312.4) weeks (115.00 [0.1;316.4] in the SoC group). The macitentan exposure in the adult studies was shorter than in the pediatric studies, with median exposures in the SERAPHIN, MAESTRO, and RUBATO studies of 98.7 (3.7; 149.0), 16.14 (16.0; 17.0), and 52.71 (51.6; 63.1) weeks, respectively. The adults open label studies were previously assessed in their corresponding P46 procedures: EMEA/H/C/002697/P46/008 (MAESTRO OL), EMEA/H/C/002697/P46/009 (SERAPHIN OL) and EMEA/H/C/002697/P46/011 (RUBATO OL). Safety findings were considered in line with the known safety profile of macitentan. Regarding the SERAPHIN OL study, the safety data from the few patients included (n=6) (report EMEA/H/C/002697/P46/009) suggested a bad prognosis of these children in the long-term. The fatal outcome in the 6 children seems to be related to PAH disease progression and underlying congenital cardiac malformations.

In the TOMORROW study (≥ 2 years), higher rates of participants in the macitentan arm versus the SoC arm reported AEs during the main treatment period: AEs were reported in 67 participants (93.1%) randomized to macitentan versus 51 participants (68.0%) randomized to SoC. However, there was a difference in exposure between randomized treatments (253.0 subject-year in macitentan versus 187.7 subject-year in SoC) due to a higher discontinuation rate in the SoC arm (17 participants [23.6%] in the macitentan arm versus 31 participants [41.3%] in the SoC arm).

Fifteen of 72 (20.8%) patients included in the macitentan arm had an adverse event related to macitentan and most of them were mild to moderate in intensity. Adverse events reported as related to macitentan during the main treatment period included: in 1 participant each (1.0%), nasopharyngitis, epistaxis, nasal congestion, wheezing, diarrhea, abdominal pain, paraesthesia, alanine aminotransferase increased, heart rate increased, transaminases increased, intermenstrual bleeding, priapism, palpitations, urticaria, vascular skin disorder, and flushing. Adverse events reported as related to macitentan reported in 2 participants each (2.1%) included: headache, anemia, and insomnia. Hemoglobin decreased was reported in 3 participants (3.1%) and was considered related to macitentan. No patients below 2 years had an AE assessed as related to macitentan.

Reported AEs are in line with the known safety profile of macitentan. Regarding to the new ADRs considered pediatric-specific (upper respiratory tract infection, rhinitis and gastroenteritis) no specific causes or other plausible explanations for any of them were identified and no relationship between the discussed ADRs and the COVID-19 pandemic could be identified.

Palpitations and skin disorders were reported in one participant each. These AEs have been previously described for ambrisentan, however, pooled data from studies with macitentan in adults, adolescents and pediatric patients do not suggest new "palpitations" or "skin disorders" ADRs for macitentan and no additional modifications of the product information are needed.

Despite the reported imbalance between the macitentan and the SoC group, the AEs pyrexia (9.8% vs 4.7% in the macitentan and SoC arm, respectively), fatigue (8.2% vs 0%), and non-cardiac chest pain (8.2% vs 4.7%) have not been identified as ADRs. Of note, the Applicant has comprehensively described the approach for selection and evaluation of potential new ADRs. Final data from the TOMORROW study EOCP were also reviewed using this approach. It is acknowledged that besides upper respiratory tract infection, rhinitis and gastroenteritis no additional ADRs of macitentan has been identified based on the TOMORROW study EOCP.

No clinical differences have been shown regarding SAEs and AESIs related to macitentan between age-subgroups, however a higher proportion of AEs related to macitentan was shown in the subgroup of patients ≥2 - <6 years (46%). Nonetheless, due to the small number of patients included in the mentioned subgroup, no safety conclusions can be drawn, and it is not possible to establish a correlation between age-subgroups and safety profile.

The Applicant has submitted safety data (AEs, SAEs and AESIs) by PAH specific concomitant medications in the macitentan arm and in the SoC arm. In the TOMORROW study ≥ 2 y.o. in the macitentan arm (N= 72), 37 patients received PDE-5i as concomitant medication, 18 received ERA+PDE-5i, 6 received ERA and 11 patients received no PAH specific medication. In the SoC arm (n=75), 41 patients received PDE-5i as concomitant medication, 25 received ERA+PDE-5i, 4 patients received ERA and 5 patients did not receive PAH concomitant medications. Overall, PAH-specific concomitant medications do not appear to present safety concerns in pediatric patients, however, due to the small sample size of the subgroups provided, no conclusions can be drawn from these results and data should be interpreted with caution.

The applicant has discussed the safety profile of macitentan in terms of growth, neurological and sexual maturity in children (≥ 2 years) as it was recommended by the SAWP in a previous advice. Overall, 2 macitentan-treated participants (1 <2 years of age and 1 ≥2 years of age) and 9 participants ≥2 years of age in SoC arm with BMI indicative of normal weight at baseline decreased their BMI category to underweight, however, no specific pattern indicative of clinically meaningful changes could be discerned. Additionally, no AEs related to the childbearing potential status were reported in any treatment arms and there is no pattern of neurocognitive impairment or deterioration of pre-existing neuro-psychiatric condition during macitentan use.

In the TOMORROW study (≥ 2 years), twenty-six participants (36.1%) in the macitentan arm versus 16 participants (21.3%) in the SoC arm experienced at least 1 SAE (11.86 and 10.66 EAIR per 100 patient-years respectively). SAEs occurring more than 1 participant were pneumonia (5 participants [6.9%] in the macitentan arm), anaemia, gastritis, and non-cardiac chest pain (2 participants each [2.8%] in the macitentan arm), and respiratory tract infection (2 participants [2.7%] in the SoC arm). SAEs considered related to macitentan were anaemia and alanine aminotransferase increased (1 participant [1.4%] each) (both listed as macitentan ADRs).

In the supportive studies, the number of subjects with treatment-emergent serious adverse events ranged from none (0/13) in study MAESTRO to 4/6 (66.7%) in study SERAPHIN (arrhythmia, right ventricular failure, PAH, pulmonary embolism, bronchitis, pneumonia, hepatic enzyme increased and syncope). In study RUBATO, 1 participant (12.5%) experienced an SAE of bronchitis during the treatment period.

A total of 13 participants ≥2 y.o. died during the study (7 in the macitentan arm and 6 in the SoC arm). No deaths were related to macitentan, the exposure period to macitentan when deaths occurred ranged from 360 to 1944 days (314-1379 in the SoC arm) and patients had severe pre-existing PAH disease or significant comorbidities. Therefore, reported deaths are consistent with the progressive evolution of the PAH disease or its complications and a relationship between deaths and macitentan has not been detected.

In the supportive studies, three adolescents aged ≥12 to <18 years in study SERAPHIN died. The Applicant has provided individual data from adolescent participants who died during SERAPHIN DB or OL studies. All 9 pediatric participants who died during SERAPHIN DB/OL were WHO FC III (n=6) or II (n=3). Seven patients had iPAH and 2 had PAH associated with congenital heart disease (ventricular septal defect, atrial septal defect). PAH progression was reported as cause of death in 4 participants and arrhythmia, right heart failure, sudden death, pulmonary embolism and ventricular fibrillation were reported each in 1 participant. Time from PAH diagnosis to fatal outcome ranged from 1.6 to 13.5 years and all deaths were assessed as not related to macitentan. In addition, a comparison of pediatric and adult data in the SERAPHIN DB/OL has been submitted. Overall, 9/12 pediatric patients and 192/598 adults treated with macitentan 10 mg died at any time-point during SERAPHIN DB and OL studies and the exposure-adjusted incidence rate of death was 25.42 and 7.69 for pediatrics and adults respectively. However, due to the small number of children included and the difference in exposure between pediatric (35.4 patient-years) and adult populations (2495.7 patient-years), no conclusions can be drawn from this comparison. Regarding the MAESTRO DB/OL and RUBATO DB/OL studies, no pediatric patients died during the study. Overall, based on data from the SERAPHIN DB/OL study and data from the literature, no safety signals have been found regarding a potential increase in mortality in pediatric population compared to adults while treated with macitentan.

The adverse events of special interest selected were anemia, edema/fluid retention, hypotension, symptomatic hypotension, and hepatic disorders. In the TOMORROW study ≥2 y.o. 18 (25.0%) participants had an AESI (vs 7 patients (9.3%) in the SoC arm). The AESI most often reported was

anemia in 11 participants (15.3%) who received macitentan (vs 2 patients (2.7%) in the SoC arm). In the macitentan arm, AESIs of edema/fluid retention were reported in 4/18 (5.5%), hepatic disorders in 3/18 (4.2%), and hypotension in 3/18 (4.2%) participants. AESIs of anaemia were considered not related to macitentan, except 2 (1 non-serious AE of anaemia which resulted in drug interruption and 1 SAE of anaemia which resulted in drug withdrawal). Of the 4 participants (5.6%) with haemoglobin decreased, 1 participant had 5 AEs of haemoglobin decreased, all reported as non-serious, all related to macitentan, and 1 resulting in drug interruption. The 4 AESI of edema/fluid retention were reported as not related to macitentan. Regarding the hepatic disorders, of the 3 participants with an AESI, the AESI of alanine aminotransferase increased was serious, of severe intensity, considered related to macitentan, resulted in drug withdrawal, and was reported as recovered/resolved. The AESI of transaminases increased was reported as nonserious, related to macitentan, led to drug withdrawal, and recovered/resolved. The 3 AESIS of hypotension were reported as not related to macitentan.

Regarding other adverse events of interest, in the TOMORROW study ≥2 y.o, 11 participants (15.3%) in the macitentan arm experienced AEs of reproductive system and breast disorders during the main treatment period: heavy menstrual bleeding in 4 participants (5.6%), dysmenorrhea in 3 participants (4.2%) and intermenstrual bleeding, menstrual disorder, priapism, and uterine hemorrhage in 1 (1.4%) participant each. Of the 11 participants, 2 had SAEs (heavy menstrual bleeding and menstrual disorder/uterine hemorrhage), respectively. Confounding factors were reported for the 2 participants who experienced the above-mentioned SAEs (immature hypothalamic pituitary ovarian (HPO) axis and violation of the menstrual cycle).

No relevant incidence of AESIS by age or race have been reported.

As requested, the Applicant has provided a literature review regarding the anemia (prevalence and pathogenesis) and menstrual bleedings (prevalence, etiologies and menstrual disorders) and has provided the following data from the SERAPHIN DB and TOMORROW studies: adverse events denoting anemia, adverse events denoting menstrual disorders, and adverse events denoting menstrual disorders and anemia. The incidence of anemia in macitentan-treated pediatric females in TOMORROW study (18.4% in overall female population and 20.0% in females of child-bearing potential) was consistent with the incidence observed in SERAPHIN females (18.0% in overall female population and 20.3% in females of child-bearing potential). Regarding the menstrual disorders, in the SERAPHIN study females aged 18-52 the incidence was higher in the macitentan group (8.1% (10/123)) as compared to placebo (2.9% (3/104)). When excluding dysmenorrhea without menstrual bleeding event, the incidence of menstrual bleeding was 7.3% (9/123) and 1.9% (2/104) respectively. None of the events resulted in discontinuation of study treatment and most menstrual bleeding events were reported as resolved while participants continued treatment with macitentan. In the TOMORROW study the incidence of menstrual disorder in females of child-bearing population was 25.7% (9/35) in the macitentan group and 6.7% (1/15) in SoC group; with the exposure adjusted incidence rate of menstrual disorders per 100 participant years for overall females was 5.17 and 1.05, respectively. When excluding events of dysmenorrhea without bleeding events, the incidence of menstrual bleeding event in females was 17.1% (6/35) and 6.7% (1/15) in macitentan and SoC, respectively. None of these events led to macitentan study drug discontinuation and all but one event (non-serious intermenstrual bleeding) resolved while macitentan remained ongoing. In SERAPHIN study, 123 macitentan-treated females were aged 18-52 years and 3 (3/123) out of the 9 participants with menstrual bleeding also had an event of anemia. Of note, none of the events resulted in discontinuation of study treatment. In the TOMORROW study, 38 macitentan treated females were of child-bearing potential at baseline or during the study. Three (3/38) out of the 6 macitentan-treated participants who experienced menstrual bleeding also had an event of anaemia. Limitations as differences in sample size,

treatment period or different designs between the SERAPHIN and the TOMORROW studies have been taken into account, as well as differences between the macitentan and SoC arms in the TOMORROW study. In summary, based on the available data, there is no convincing evidence of a correlation between anemia and menstrual bleeding, and the incidence of anemia is similar in adolescent and adult females. However, there was an imbalance in menstrual bleeding between macitentan and control arms in adult and adolescent females treated with macitentan. Therefore, the Applicant proposed to add the event increased uterine bleeding as a common ADR in the SmPC, which is agreed.

AEs leading to premature discontinuation of study treatment in participants ≥2 y.o. in the TOMORROW study were reported during the main treatment period in 4 participants (5.6%) who received macitentan (alanine aminotransferase increased [recovered without sequelae], transaminases increased [recovered without sequelae], headache [recovered without sequelae]), and anemia [event of hemoglobin decreased improved to a mild nonserious AE which was ongoing at the time of discontinuation] vs 2 patient (2.7%) in the SoC arm due to cardiac arrest. All of these AEs in macitentan arm are included in the current authorized SmPC of Opsumit.

In the supportive studies, AEs leading to premature discontinuation of study treatment in participants were reported in 1 participant (16.7%) who received macitentan in study SERAPHIN due to hepatic enzyme increased. In conclusion, no relevant incidence of discontinuations due to adverse events were reported.

Safety data related to drug-drug interactions and other interactions have not been submitted and no new interactions are explored within this submission. Known interactions of macitentan are already included in SmPC.

In the TOMORROW study ≥2 y.o, elevated ALT and/or AST of >3 X ULN was reported during the main treatment period in 2 participants (2.8%) in the macitentan arm (both participants had elevated ALT and/or AST >8 X ULN) and 3 participants (4.2%) in the SoC arm (the 3 had elevated ALT and/or AST> 3 x ULN). For the 2 participants in the macitentan arm with aminotransferase increases >8 X ULN, macitentan was discontinued per protocol. The events occurred in the context of right heart failure and respiratory tract infection in 1 of the 2 participants, no specific context was reported for the second participant, and the hepatic event resolved in both cases. Of the 3 participants (4.8%) in the SoC arm who experienced elevated ALT and/or AST>3 x ULN, one event met the biochemical criteria for Hy's Law case and occurred in the context of non-alcoholism like disease with increased fatty content in the liver in an overweight participant. Total bilirubin >2 x ULN was reported in 5 participants (6.9%) in the macitentan arm and 1 participant (1.4%) in the SoC arm. Based on data provided by the Applicant, 3/5 patients had increased total bilirubin at baseline and additional confounding factors as underlying disease, venous and hepatic congestion or Gilbert's syndrome were detected in these patients. Therefore, an increase of total bilirubin >2 x ULN with macitentan as main cause of this increase is not expected. No elevated liver tests were reported in any of the adolescent participants <18 years of age in the supportive studies.

Regarding the hematology in the TOMORROW study ≥2 y.o, the most common marked abnormalities by parameter were low hemoglobin (15 participants [20.8%] in the macitentan arm and 9 participants [13.0%] in the SoC arm) and low hematocrit (8 participants [11.1%] in the macitentan arm and 2 participants [2.9%] in the SoC arm). Mean change from baseline in hemoglobin up to Week 96 was in the range -1.9 to -6.6 g/L. Mean change from baseline in hematocrit up to Week 96 was in the range -0.002 to 0.017. Additionally, low leukocytes (< 3.0 x 109 /L, in 7 participants (9.7%) in the macitentan arm and 2 participants (2.9%) in the SoC arm) was shown. In conclusion, hematological abnormalities in the study TOMORROW (≥2 y.o.) were

more frequent in the macitentan arm compared with the SoC arm. No cases were reported in any of the adolescent participants (<18 y.o.) in the supportive studies.

The laboratory abnormalities observed are considered in line with the known safety profile of macitentan and are included in the current SmPC of Opsumit. Regarding the creatinine clearance, in 4/72 participants randomized to macitentan versus none of 75 participants to SoC reported abnormally low creatinine clearance values. Of note, serum creatinine values were within the normal range or below the lower limit. None of them were reported as an AE by the investigator. Additionally, although baseline values were not available, no trends over time in serum creatinine values were observed. Due to the limited data and the presence of factors that can affect the renal function in patients with PAH treated with macitentan (underlying PAH disease, use of diuretics, underweight), no conclusions regarding a relationship between decreased creatinine clearance and macitentan can be made.

The MAH states that the off-label use of macitentan 10 mg tablet in children below 18 years through 17 October 2022, non-interventional clinical study cases, literature and postmarketing data, were included in the most recent PBRER/PSUR.

The number of cases of off-label use reported in children and adolescents from the global medical safety (n=1,135 cases) is much higher than the number of patients included in the TOMORROW study (n=77). The applicant states that the review of the off-label paediatric data in patients aged below 18 y.o. shows a similar safety profile to that of the adult population with the adverse reactions reported being consistent with those seen in adults, with platelet count decreased, blood pressure decreased, aspartate aminotransferase increased, alanine aminotransferase increased, anaemia, and hepatic function abnormal identified as important risks for macitentan. The adverse events reported in off-label use in paediatric subjects are within expected for adults, however, no conclusions can be made with respect to compare incidence rates versus adults.

Additionally, the Applicant has reviewed literature and safety data from the off-label use of macitentan in pediatric patients <2 y.o., patients ≥2 to <12 y.o. and patients ≥12 to <18 y.o. from 18 October 2022 through 17 October 2023 and has provided a summary of safety information from the Global Medical Safety database and published literature. Overall, no new safety signals have been detected and available data are in line with the known safety profile of macitentan.

Children < 2 y.o.

Data from patients < 2 y.o. come from the pivotal study TOMORROW (n=9), and from the 67896062PAH3001 phase 3 study in Japanese children (n=2). Data from 6 patients < 2 y.o. included in the TOMORROW study are available at 6 months with median exposure of 37.14 (7.0; 72.90) weeks. Data from the 2 children < 2 y.o. included in the study 67896062PAH3001 are available at week 24.

No AESIS were reported for children <2 y.o. (TOMORROW and 67896062PAH3001 studies) and in the supportive studies, a similar pattern to the TOMORROW study was shown.

AEs were reported for 7 of the 9 participants < 2 y.o. (TOMORROW study). AEs reported for more than 1 participant were upper respiratory tract infection (4 participants), gastroenteritis (3 participants [1 event of gastroenteritis was an SAE]), COVID-19 (2 participants), and pneumonia (2 participants). No AEs were assessed as related to macitentan or led to premature discontinuation or death. No disease progression events were reported for participants at the EOCP. In Study 67896062PAH3001, both participants experienced a total of 14 AEs (not related to macitentan), and 1 participant experienced an SAE of bronchitis during the study period.

In children < 2 y.o (TOMORROW study), the sample size is smaller than the group of patients ≥ 2 y.o. Of the 9 participants <2 years of age treated with macitentan, 2 had no PAH specific therapies ongoing at baseline, 6 were treated with PDE5i and 1 was receiving ERA and PDE5i at baseline. None of the participants treated with PAH-specific therapy at baseline had any AESI reported during treatment with macitentan. The higher incidence of AEs corresponds to the group of patients with PDE-5i as concomitant medication (100% of them with ≥1 AE) vs no concomitant medications (0 patients with AEs), which is also expected. Additionally, in patients < 2 y.o. there was no SoC arm and therefore, no comparisons can be made.

No participants <2 y.o. from the TOMORROW and 67896062PAH3001 studies died or experienced AEs with a fatal outcome.

In the subgroup < 2 y.o. of the study TOMORROW four SAEs were reported in 2 of the 7 participants. One participant experienced SAEs of gastroenteritis and constipation, and 1 participant experienced SAEs of pneumonia and hematemesis. None of the SAEs were related to macitentan or led to dosage change. In the study 67896062PAH3001 (<2 years), one participant experienced a treatment-emergent SAE of bronchitis during the treatment period which led to interruption of study intervention for one day.

None of the participants < 2 y.o. in the TOMORROW and 67896062PAH3001 studies discontinued study treatment due to an AE.

Marked laboratory abnormalities for hematology parameters were reported for 2 participants <2 y.o. (low hematocrit [<0.28 F, <0.32 M] in 1 participant [11.1%], and low leukocytes [<3.0x109/L] in 1 participant [11.1%]). In study 67896062PAH3001, 1 hematological laboratory abnormality of neutropenia was observed in 1 of the participants. Regarding the renal clearance, and levels of sodium, potassium and calcium, no participants < 2 y.o. had any abnormalities.

2.6.10. Conclusions on clinical safety

The safety database supporting this application in children and adolescents ≥ 2 years old is based on 72 patients included in the pivotal ongoing pediatric study TOMORROW and data from patients between 12 and 18 y.o. included in the supportive studies SERAPHIN (n=6), MAESTRO (n=13) and RUBATO (n=8). In study TOMORROW ≥2 y.o., 58 patients (80.6%) completed the 24-month follow up, and data from 29 patients are available at month 54. Additionally, the applicant has submitted the results of the open label extension of supportive studies SERAPHIN, MAESTRO and RUBATO.

The median duration of exposure in the macitentan arm (TOMORROW study) was 168.43 (12.9;312.4) weeks (115.00 (0.1;316.4) in the SoC group). The macitentan exposure in the adult studies was shorter than in the pediatric studies, with median exposures in the SERAPHIN, MAESTRO, and RUBATO studies of 98.7 (3.7; 149.0), 16.14 (16.0; 17.0), and 52.71 (51.6; 63.1) weeks, respectively.

In patients < 2 y.o., safety data come from patients from the pivotal study TOMORROW (n=9), and from 2 children from the 67896062PAH3001 phase 3 study. The low number of enrolled patients < 2 y.o. in clinical trials is considered an important limitation, as very limited clinical safety data are available to establish a robust safety conclusion in this subgroup.

Adverse events reported as related to macitentan during the TOMORROW study in the ≥2 years subset included, nasopharyngitis, epistaxis, nasal congestion, wheezing, diarrhea, abdominal pain, paraesthesia, alanine aminotransferase increased, heart rate increased, transaminases increased, intermenstrual bleeding, priapism, palpitations, urticaria, vascular skin disorder, flushing,

headache, anemia, insomnia, and hemoglobin decreased. No patients below 2 years had an AE assessed as related to macitentan.

Reported AEs are in line with the known safety profile of macitentan and no new safety signals have been identified. There was an imbalance in menstrual bleeding between macitentan and control arms in adult and adolescent females treated with macitentan. Therefore, the event "increased uterine bleeding" was added as a common ADR in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety Specification

The applicant proposed the following summary of safety concerns in the RMP, including the deletion of "paediatric patients" from the missing information and the deletion of the important potential risk "menstrual disorders (primarily bleeding)".

2.7.1.1. Summary of safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Anemia, decrease in hemoglobin concentration Hepatotoxicity Teratogenicity Symptomatic hypotension
Important potential risks	Ovarian cysts Pulmonary edema associated with PVOD Testicular disorders and male infertility
Missing information	None

2.7.1.2. Discussion on safety specification

No new safety concerns were identified since the last EU RMP (v 13.1). The company has updated the RMP including pediatric data from the TOMORROW, SERAPHIN and MAESTRO studies, to update the information related to important identified risks (anemia, hepatotoxicity, teratogenicity and symptomatic hypotension) and important potential risks (ovarian cysts, pulmonary edema associated with pulmonary veno-occlusive disease, testicular disorders and male fertility).

Safety data in children ⩾ 2 years old are based on the interim analysis results of the pivotal ongoing pediatric study TOMORROW (72 patients receiving macitentan and 75 SoC) and data from the following supportive studies in children between 12 and 18 y.o. (⩾12 to <18 years): SERAPHIN (n=6, in symptomatic PAH), MAESTRO (n=13, in Eisenmenger Syndrome) and RUBATO (n=8, in Fontan- palliated participants). Only data from 11 patients < 2 y.o. have been submitted (9 from the pivotal study TOMORROW, and 2 patients from the 67896062PAH3001 study).

The MAH has removed pediatric patients as missing information in light of the available data on pediatric use of macitentan obtained from the pediatric study (TOMORROW; DLP 21 July 2023) as well as from the SERAPHIN and MAESTRO studies, and postmarketing data. Additionally, an imbalance in menstrual bleeding between macitentan and control arms in adult and adolescent

females treated with macitentan has been shown and the event "increased uterine bleeding" as a common ADR has been added in the SmPC. Therefore, the important potential risk "menstrual disorders (primarily bleeding)" has been deleted as safety concern.

2.7.1.3. Conclusions on the safety specification

The company has updated the RMP including pediatric data from the TOMORROW, SERAPHIN and MAESTRO studies, to update the information related to important identified risks (anemia, hepatotoxicity, teratogenicity and symptomatic hypotension) and important potential risks (ovarian cysts, pulmonary edema associated with pulmonary veno-occlusive disease, testicular disorders and male fertility). "Paediatric patients" and "menstrual disorders (primarily bleeding)" have been deleted as missing information and important potential risk respectively.

2.7.2. Pharmacovigilance plan

No new additional pharmacovigilance activities have been proposed on the basis of the new proposed indication. Only routine pharmacovigilance activities are proposed to address all the safety concerns.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance could be sufficient to identify and characterise the risks of the product. The proposed post-authorisation PhV development plan could be sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Anemia, decrease in hemoglobin concentration	**Routine risk minimization measures:** SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects' Recommendation to not use Opsumit in patients with severe anemia and recommendation for monitoring of hemoglobin	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	concentration are included in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None.	
Hepatotoxicity	**Routine risk minimization measures:** SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects' Instructions for liver function monitoring and actions to be taken in case of elevated hepatic enzymes are provided in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Risk minimization tools (patient card)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Teratogenicity	**Routine risk minimization measures:** SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Macitentan Pregnancy and Outcome Follow-Up Questionnaire (TV-eFRM-11818).

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	section 2 'What you need to know before you take Opsumit' SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit' Instructions for the use of Opsumit in women of childbearing potential and recommendation for monthly pregnancy tests during treatment are provided in SmPC section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Risk minimization tools (patient card)	**Additional pharmacovigilance activities:** None.
Symptomatic hypotension	**Routine risk minimization measures:** SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects' Advice on the use of Opsumit in patients with renal impairment who are at risk of experiencing hypotension and recommendation for monitoring BP are provided in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Ovarian cysts	**Routine risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None.	**reactions reporting and signal detection:** TOIQ. **Additional pharmacovigilance activities:** None.
Pulmonary edema associated with PVOD	**Routine risk minimization measures:** SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Testicular disorders and male infertility	**Routine risk minimization measures:** SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit' Legal status: medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 14.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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

2.9. Product information

2.9.1. User consultation

Conclusion from the checklist for the review of user consultation

The methodology of the user consultation survey is considered satisfactory, and the results 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'. Indeed, the user consultation complies with the requirements and recommendations of articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC. This package leaflet was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Marketing Authorisation Holder (MAH) submitted an application for Opsumit (macitentan) for the extension of indication to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years of age of WHO Functional Class (FC) II to III for OPSUMIT based on from TOMORROW study (AC-055-312).

Pulmonary arterial hypertension (PAH) is a rare, progressive, highly debilitating disease characterised by vascular obstruction and the variable presence of vasoconstriction, leading to increased pulmonary vascular resistance (PVR) and right-sided heart failure [Moledina, 2010; Newman, 2004]. If left untreated, PAH ultimately leads to right ventricular failure and death [Krum, 2000].

Paediatric PAH is a rare and complex condition associated with diverse cardiac, pulmonary, and systemic diseases, with significant morbidity and mortality. It shares some similarities with adult PAH, but there are important known differences in vascular function, foetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right

ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups [Abman et al. Circulation. 2015].

The most common forms of paediatric PAH are idiopathic Pulmonary Arterial Hypertension (IPAH), hereditable (HPAH), and associated Pulmonary Arterial Hypertension (aPAH).

Because of the limitations in conducting paediatric studies, therapeutic strategies used for adult PAH have not been studied sufficiently in children to allow the definition of potential toxicities or optimal dosing. Hence, the lack of randomized clinical trials in paediatrics makes it difficult to deliver strong guidelines [Ollivier et al, 2019, Humbert et al, 2023].

Common hurdles for testing PAH therapies in children include: a) the rarity of the paediatric PAH; b) the many associated conditions that fragment the classification of paediatric PAH (e.g., idiopathic PAH [IPAH], familial PAH, corrected congenital PAH, PAH associated with connective tissue disease, pulmonary hypertension of the newborn [PPHN]) which leaves only a relatively small number of patients with PAH at each center; c) competing number of medicinal products for such a small population; d) The lack of suitable clinical end points in children: the 6-Minute Walking Distance (6MWD) Test cannot be used in all pediatric age subsets (ie.: not reliable in children <7 years), while there is a lack of consensus about the use of right sided heart catheterization to obtain hemodynamic end points in paediatric clinical trials [Ollivier et al, 2019].

This situation has resulted in a lack of equipoise after marketing authorization for new investigational drugs in adults, making it even more difficult to enrol children, and contributes to off-label use, which can increase the risk of inadequate dosing and results in lack of paediatric safety data. The main points of tension are related to finding the adequate balance between early access and sufficient exposure of children during paediatric trials for safety and adequate dosing. Methodological tools, such as extrapolation, could optimize obtaining information about children involved in clinical studies by predicting how a medicine may work in children and adolescents on the basis of studies conducted in adults [Ollivier et al, 2019], but dedicated studies in children are needed [CHMP/EWP/356954/08 guideline on PAH and its paediatric addendum (EMA/CHMP/213972/2010)].

3.1.2. Available therapies and unmet medical need

The ultimate goal of treatment should be to improve survival and facilitate normal childhood activities without limitations (Humbert 2023).

Therapies that are currently approved for the treatment of PAH in adults, in various geographies around the world, include prostacyclin and its analogues (epoprostenol, treprostinil, iloprost and beraprost), endothelin receptor antagonists (ERAs; bosentan, macitentan and ambrisentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat) and selective prostacyclin receptor agonist (selexipag).

To date, only 5 of 10 drugs approved for treatment of PAH in adults have also been approved for pediatric use in the EU (bosentan, ambrisentan, sildenafil, tadalafil and riociguat). Due to limited clinical data in children, significant off label use is observed, and the treatment algorithm is predominantly based on evidence from adult studies and expert opinion, rather than evidence from clinical trials in paediatric patients (Rosenzweig et al, 2019, Humbert 2023). Therefore, there is a need to provide physicians with safety and efficacy results of all treatment options, including macitentan, in the paediatric population.

Bosentan is subject to clinically significant drug-drug interactions with several important concomitant medications and is also associated with potential hepatotoxicity [Hansmann, 2016].

Results of a network meta-analysis [Zhao 2022] suggest that ambrisentan is similar to bosentan in efficacy, while it exhibits better tolerability with respect to abnormal liver function in comparison with bosentan. Sildenafil is associated with a significantly increased risk of mortality at higher doses in children and adolescents [Hansmann, 2016]. Although not approved for use in the paediatric population, there is evidence that prostanoid therapies are effective in children and adolescents [Frank, 2018]. However, in common with their use in adults, the pharmacokinetic (PK) properties of these drugs and routes of administration (e.g., intravenous [IV]), present substantial challenges to their successful use in a paediatric population. There is an unmet need for an approved treatment that provides clear clinical benefit without the complexities associated with managing potential issues.

Despite therapies approved, pediatric PAH is still a complex condition associated with significant morbidity and mortality (Hansmann 2016, Ploegstra 2023) and the unmet medical need in pediatric PAH remains high.

3.1.3. Main clinical studies

To support this application, the Applicant has conducted a multicenter, open-label, randomized phase 3 study, with a single-arm extension period to assess the PK, safety, and efficacy of macitentan versus SoC in children with PAH between 1 month and <18 years of age (Study TOMORROW) which is considered the main trial.

Additionally, a PK and safety study in Japanese children with PAH from ≥3 months to <15 years of age (Study PAH3001) have been conducted. Further, to allow clinical comparisons, paediatric data are displayed side-by side with adults' data from the phase 3 study SERAPHIN [PIP Study 10)].

For the presentation of paediatric data, the Applicant followed a 2-step approach. In the initial application, the Applicant provided interim efficacy data in children ≥ 2 years (N= 126) and preliminary available data in children < 2 years (N=9; 7 from TOMORROW study and 2 from Study PAH3001).

Thereafter, the Applicant provided all PK, safety, and efficacy data collected during the completed Core Period of the TOMORROW study for participants ⩾2 years of age and older (N=148) and for participants ⩾1 month to <2 years of age (n=9), as well as data from the 2 subjects < 2 years from Study PAH3001.

3.1.3.1. TOMORROW study

TOMORROW study is a a multicenter, open-label, randomized phase 3 study, with a single-arm extension period to assess the PK, safety, and efficacy of macitentan versus SoC in children with PAH between 1 month and <18 years of age.

Due to feasibility and recruitment challenges, the primary objective of the study drastically shifted from studying efficacy based on the evaluation of disease progression to a PK endpoint. Consequently, the decision to stop the study changed from the initial 187 DP events to an arbitrary date to meet regulatory commitments. Although this can be understood from a practical point of view, the consequence of this decision undermines the reliability of obtaining trustworthy efficacy results in the main comparisons. Time points of analysis where not pre-specified and only depend on dates to meet regulatory commitment. Therefore, study duration for each participant depended on time form enrolment.

The final primary objective of the TOMORROW study was to gather PK data to stablish therapeutic dose in paediatrics that resemble similar concentrations to those where a benefit has been observed in adults and efficacy, was assessed in a secondary way. In this regard, according to *Paediatric Addendum to CHMP Guideline on clinical investigation in the treatment of PAH [EMA/CHMP/213972/2010]*, for medicinal products where the benefit-risk profile is known in adults and extensive paediatric development is not foreseen. The cornerstone is defining the therapeutic dose, short and long safety.

The secondary key objective of the TOMORROW study (the primary was PK) was to assess the time to first CEC-confirmed disease progression for macitentan compared to SoC. Additional efficacy measurements included changes on WHO functional classification, echocardiography parameters, NT-Pro-BNP concentrations, mean daily time spent in moderate to vigorous physical [measured by accelerometry] and quality of Life (measured by the PedsQL™ 4.0 Generic Core Scales Short Form [SF15]). Exploratory efficacy measurements in the study included Panama FC, physical activity as measured by accelerometery and 6MWD.

Eligible patients were from 1 months to less than 18 years of age with PAH, evidenced by a mPAP ≥ 25 mmHg, PAWP ≤15 mm Hg, and pulmonary vascular resistance index (PVRi) >3 Wood Units x m^2) via RHC, weighting ≥3.5 kg classified as WHO functional Class I, II or III. In this regard, it should be remarked that, contrary to SERAPHIN study in adults, where only patients with WHO FC II-IV were included, patients with WHO FC I were included in TOMORROW study, suggesting that the paediatric population was less severe than the adult population included in SERAPHIN. Patients with WHO FC I are normally asymptomatic. None of current authorized PAH-specific therapy is indicated for FC I patients.

PAH-specific treatment-naïve participants, or participants who are already treated with PAH specific monotherapy or double combination therapy excluding macitentan and IV/SC prostanoids were included in the study, which concurs with the approved indication in adults (monotherapy and combination).

The study consisted of two parts, the core period and the single-arm extension period. In the core period, subjects ≥ 2 years who were confirmed eligible at Visit 2 were randomized in a 1:1 ratio to either receive macitentan or initiate/continue standard of care (SoC), which include PAH non-specific treatment and/or up to 2 PAH-specific medications as per local practice. Participants treated with a PDE-5i and/or other PAH-specific therapy (such as an ERA or inhaled/oral prostanoids) at randomization could continue these medications if randomized to SoC treatment. However, participants taking these medications who were randomized to macitentan could only continue taking PDE-5i (i.e participants with no PAH-specific therapy at randomization received macitentan monotherapy, participants on a PDE-5i monotherapy at randomization received macitentan as add-on therapy, participants on an ERA or oral/inhaled prostanoids monotherapy at randomization received macitentan monotherapy instead and participants a PDE-5i in combination with another PAH-specific therapy at randomization received the combination of macitentan and the PDE-5i). For participants randomized to SoC, additional PAH-specific therapy (excluding macitentan and intravenous/subcutaneous prostanoids) could be prescribed and initiated during the screening period. No placebo arm was included. In subjects < 2 years old, oral/ inhaled prostanoids treatment were also allowed PAH-specific background therapy in all study periods.

Randomization was stratified by ongoing/planned ERA (yes/no) treatment and by WHO FC (FC I/II vs FC III). The proportion of participants with ERA treatment, as a component of the planned SoC, is limited to a maximum of 40% of the overall number of participants randomized. Subjects < 2 years of age were assigned as a cohort to the macitentan group without randomization (and without ERA cap in this cohort). Enrolment of children <2 years of age was only initiated once

sufficient PK data for macitentan were obtained in older children. The single-arm extension period (SAEP) starts when the end of the core period has been announced. The core period ends at analysis 2, a cut-off date. Therefore, individual duration depends on time of enrolment. Site visits occur every 12 weeks and the overall study duration is minimum 7 years.

The used study design, although in line with the PIP, is not considered appropriate and could only be considered supportive in terms of efficacy. As results of the pivotal study efficacy results are considered only exploratory and demonstration of efficacy relies mainly on extrapolation exercise from adults (refer to section 3.2: '*Extrapolation of adult data*' and Section 3.4: '*Uncertainties and limitations about favourable effects*').

3.1.3.2. Extrapolation of adult data

Due to the inconclusive efficacy results of the TOMORROW study, the totality of evidence included in this submission supporting the efficacy of macitentan for paediatric patients should be based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will results in similar efficacy in children. There are several considerations that justify the overall approach to extrapolate efficacy from adults, which are expressed in the *EMA reflection paper on extrapolation (EMA 2018)* as well as in the current draft *ICH E11A guideline on paediatric extrapolation (EMA 2022).* Development of a paediatric extrapolation concept requires an understanding of the factors that influence the similarity of disease, the pharmacology of the drug and the response to therapy as well as the safety of use in all the relevant populations.

Disease similarity

Regarding disease similarity, it is considered that the pathophysiology of PAH is similar among children enrolled in TOMORROW (⩾2 to <18 years of age) and adults. Historically, the definition of PAH in children has been the same as in adults, i.e. mPAP ⩾25 mmHg and PVR ⩾ 240 dyn s cm-5 (3 Wood units). However, the distribution of PAH aetiologies in children is different from that in adults, with a larger proportion of PAH associated with CHD in children, whereas in both populations, the majority of patients have IPAH.

Similar drug pharmacology

It is expected that the hemodynamic mechanism of action of macitentan is responsible for PAH efficacy which is expected to be similar in adults and children. However, this does not automatically mean that there is similar drug pharmacology, which besides mechanism of action also refers to absorption, distribution, metabolism, and excretion (ADME) properties. Nevertheless, PK modelling showed that the mean exposure obtained in the paediatric population of ⩾2 to <18 years of age in the TOMORROW study was comparable with that observed in the adult PAH patients, as the GMR point estimates were within the 0.8 to 1.25 reference range for this age category. For children between ⩾6 months to <2 years, the GMR point estimates were outside the 0.8 to 1.25 reference range with values of 0.69 (CI 0.57; 0.83) and 0.71 (CI 0.59; 0.85) for AUC, combo, ss and Cmax, combo, ss with the proposed dosing regimen. In this age group, 72.7% of the participants were already older than 20 months at randomization. Based on this, it is considered that there is insufficient PK data available in children aged ⩾6 months to <2 years group in order to support posology in this age group. Furthermore, no pharmacokinetic data is available for children ⩾1 month and <6 months of age, and the proposed posology is based on in silico simulations. Considering this, the proposed dose recommendation was not accepted for children <2 years months of age.

On the other hand, a stochastic simulation considering a random distribution of virtual paediatric patients from 2 years of age for each body-weight cohort were performed to derivate the exposure parameter (AUCu,combo,ss) following the current proposed dosing regimen. The results showed a slight lower exposure in paediatric patients compared to adult patients for all body-weight cohorts except for the ⩾50 kg body-weight cohort. Then, an update in body-weight cohorts was conducted to better match the adult exposure range. The alternative cohorts in patients >2 years of age (10-20kg, 20-40kg, >40kg) provided more similar exposure compared to the adult population, therefore, the dose recommendation in the SmPC was updated.

Similar exposure response

According to the *Reflection Paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018)* the primary focus will usually be to establish a line of reasoning about the relation between dose, exposure, pharmacodynamic (PD) effects and clinical responses. However, in the current application there was no proof that similar exposures result in similar pharmacodynamic effects since no PK/PD analysis for both the paediatric population and the adult population was provided.

The Applicant provided the results of PIP study 10, in which the observed treatment effects of macitentan in the adult, adolescent and pediatric populations were compared in a pharmacodynamic and efficacy similarity assessment using data from the adult SERAPHIN study and the pediatric TOMORROW study (only children ≥2 to <18 years of age). Since in the SERAPHIN study the comparator was placebo, while in the TOMORROW study the controlled group was SoC (including any treatment other than macitentan or IV/SC prostanoids) and the data is presented in comparison to placebo or SoC in specific forest plots, the comparisons were difficult to interpret and firm conclusions on a consistent effect size cannot be made.

Consequently, the Applicant was requested to also expand the extrapolation concept based on literature data and pharmacological principles to justify the extrapolation of efficacy based on similar exposure.

The provided literature on the safe and efficacious use of macitentan in children also supports the extrapolation of data from the adult population to the paediatric population aged ≥ 2 years, which is therefore considered acceptable.

However, considering that in the provided publications the median age was ≥ 8.5 years or above, that the paediatric patients aged < 2 years in the TOMORROW study did not provide additional relevant information on efficacy and that the PK of children aged < 2 was not established which precludes a recommendation for an appropriated dose for these patients, there is still insufficient evidence for children aged < 2 that similar exposures results in similar pharmacodynamic effects. Consequently, the indication has been limited to children aged ≥ 2 years.

3.2. Favourable effects

Efficacy in paediatric population aged ≥2 years to <18 years is mainly based in an extrapolation exercise based upon exposure-matching to the adult efficacious dose range given the similarity of the disease in children and adults, as well as on supportive exploratory efficacy and safety data from the TOMORROW phase 3 study.

Exploratory results for benefits

The main efficacy data of macitentan in children with PAH derived from TOMORROW study (AC-055-312).

In patients aged ≥2 years to <18 years, macitentan showed a non-statistically significant numerical trend for time to first CEC-confirmed disease progression compared to SOC (28.8% (n=21 events) vs 32.0% (n=24 events); adjusted HR of 0.828, 95% CI] = [0.460; 1.492], 2-sided stratified p=0.567). Positive numerical trends were also observed in other secondary endpoints, like NT-proBNP, WHO FC and also in parent report and child report of QoL, measured using the SF15 questionnaire. Four hierarchical composite endpoints (HCE) were conducted as exploratory efficacy analyses, which suggest positive trends of macitentan, mainly driven by results on CEC-confirmed clinical worsening and in the SF25 questionnaire.

However, this evidence cannot be viewed as confirmatory evidence due to the inappropriate study design of TOMORROW study (see uncertainties below).

In addition, in section 4.1 for the treatment in adults the information regarding PAH etiologies was removed as this information was already included in section 5.1 and the extension of the indication to the paediatric population relies mainly on the extrapolation from adult patients with PAH.

3.3. Uncertainties and limitations about favourable effects

The design of the TOMORROW study, although in line with the PIP, is not considered appropriate to adequately evaluate the efficacy of macitentan in paediatric subjects. The open-label study design is acceptable for naïve patients. However, it makes the interpretation of results only descriptive/exploratory in the add-on setting. The no inclusion of a placebo in the SoC arm and allowing ERA treatment in the SoC group arm makes impossible to discern the effect of macitentan as combination therapy. As advised in previous scientific advice, in the add-on setting a blinded comparison macitentan vs. placebo on top of the specific PAH agents (excluding ERA users), could have been done, which would have been more clinically relevant and it would have allowed a better comparison with adult data, as in the SERAPHIN study in adults, a doubled blind design was performed.

Moreover, contrary to what is stated in *EMA Guideline on Clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension [EMEA/CHMP/EWP/356954/2008],* patients were not sufficiently stable on their background medications, as switching at time of randomization was allowed. Importantly, using ongoing/planned ERA treatment (yes/no) as stratification factor no distinction is made between ERA treatment naïve patients planning to receive ERA treatment and patients already receiving ERA treatment at randomization, which may have a large impact on the efficacy results and makes interpretation of the results within a treatment arm and between both treatment arms even more difficult.

Therefore, due to TOMORROW study design limitations, efficacy results in patients aged ≥2 years to <18 years are only considered exploratory, and efficacy of the paediatric indication mainly rely on an extrapolation exercise (ICH guideline E11A).

Provided data in patients <2 years were very scarce. The main uncertainty was that none of the subjects enrolled was less than 1 year. In fact, almost all subjects were near to 2 years [range:1.2-1.9]. Therefore, no sufficient PK data for the entire age subset of 1 months to < 2 years were available and consequently an accurate posology for paediatric patients aged 1 to < 2 year cannot be estimated. Therefore, the small sample size, the limited duration of exposure and the impossibility of establishing a posology in this subset, do not allow to establish the

efficacy/safety in children <2 years. Paediatric therapeutic indication has been limited to patients aged ≥2 years.

The initially requested paediatric indication was broader than the one approved for adults. Authorized adult therapeutic indication for macitentan is restricted to WHO FC II/III, while proposed paediatric indication also included FC WHO FC I. In this regard, TOMORROW study included 37 patients [25%] who had WHO FC I at baseline. Although the rationale of intervening early rather that awaiting progression events could be followed and it cannot be ruled out that certain PAH patients with WHO FC I could benefit from an early treatment with PAH specific therapies, TOMORROW study does not provide the adequate evidence to clearly discern the benefit of macitentan in FC WHO FC I patients. Since due to study design, demonstration of efficacy mainly relies on extrapolation exercise from adults, the inclusion of WHO FC I in therapeutic indication was supported. Consequently, the indication of the paediatric population has been reworded in line with the currently approved indication for adult patients i.e. 'WHO FC I to III" changed into "with WHO FC II to III.

Key efficacy endpoint in TOMORROW study (time to first CEC-confirmed disease progression) deviates from the one proposed in the relevant CHMP guideline [EMA/CHMP/213972/2010] and the one that was investigated in SERAPHIN study, making it more difficult to bridge results from adults and children. The composite primary endpoint of the TOMORROW study includes a "soft" component of "Clinical worsening of PAH" based on a subjective assessment of "Need for, or initiation of new PAH-specific therapy, or IV diuretics or continuous oxygen use" that is not in line with the definition used in the SERAPHIN study. Investigating deterioration in 6-MWD in developmentally able patients, would have provided greater objectivity to the endpoint.

Six minutes walking distance test (in children ≥ 6 years developmentally able) was only included as an exploratory endpoint in TOMORROW study. However, 6MWT criteria was only implemented with the approval of TOMORROW study protocol version 8.0, at which point, the majority of patients had been already recruited. As a result, change from baseline in 6MWD were only available for assessment at EOCP for a reduced number of participants (n=11; 8 macitentan vs. 3 SoC). Although it is accepted that the utility of the measurement of 6MWD is more limited in children, as it is only reliable in developmentally able children >6 years of age, it is considered that measuring this endpoint, at least as secondary (as previously advised) in a larger number of patients, would have allowed to have a clearer insight into effect of macitentan in the improvement of symptoms and would have facilitated a comparison with the observed effect in adults and with other PAH specific therapies.

The change from baseline 6MWD was lower in the macitentan arm (n=8) compared with the SoC arm (n=3) at Week 12 (19.64 vs 29.22 m), Week 24 (8.55 vs. 94.54 m), and Week 48 (47.47 vs. 71.89 m). Results must be interpreted with caution due to the small sample size.

There were some disbalances in baseline characteristics between arms related to baseline severity of patients, which could influence the interpretation of results. Baseline mean NT-proBNP was higher in the macitentan arm (145.33 pmol/L) versus SoC (77.12 pmol/L); however, the median NT-proBNP levels at baseline were lower in the macitentan arm compared with the SoC arm (18.23 vs. 21.18 pmol/L, respectively). NT-proBNP levels were in general low for this specific PAH population. The Applicant justified that for the paediatric population in the TOMORROW study and for the adult population in the SERAPHIN study different assays were used resulting in an approximately 50-fold difference in baseline median NT-proBNP values.

With respect to the clinical and PD comparison [Study 10] between adults (SERAPHIN study) and paediatrics (TOMORROW study) provided, differences in baseline characteristics and differences in

study design, particularly since in the SERAPHIN study the comparator was placebo, while in the TOMORROW study the controlled group was SoC (including any treatment other than macitentan or IV/SC prostanoids), make the comparison challenging. The comparative PD and clinical analysis performed yielded results subject to high variability and wide confidence interval, providing limited evidence. Thus, extrapolation exercise is mainly based in matching a similar systemic exposure in paediatrics to those observed in adults at the proposed doses, supported by TOMORROW study results, in conjunction with the similar mechanism of action of macitentan in both populations, the pharmacological principles and the literature data.

3.4. Unfavourable effects

The safety database supporting this application in children and adolescents ≥ 2 years old is based on 72 patients included in the pivotal ongoing paediatric study TOMORROW and data from patients between 12 and 18 y.o. included in the supportive studies SERAPHIN (n=6), MAESTRO (n=13) and RUBATO (n=8). In study TOMORROW ≥2 y.o., 58 patients (80.6%) completed the 24-month follow up, and data from 29 patients are available at month 54.

The median duration of exposure in the macitentan arm (TOMORROW study) was 168.43 (12.9;312.4) weeks (115.00 (0.1;316.4) in the SoC group). The macitentan exposure in the adult studies was shorter than in the paediatric studies, with median exposures in the SERAPHIN, MAESTRO, and RUBATO studies of 98.7 (3.7; 149.0), 16.14 (16.0; 17.0), and 52.71 (51.6; 63.1) weeks, respectively.

Adverse events reported as related to macitentan during the TOMORROW study in the ≥2 years subset included nasopharyngitis, epistaxis, nasal congestion, wheezing, diarrhea, abdominal pain, paraesthesia, alanine aminotransferase increased, heart rate increased, transaminases increased, intermenstrual bleeding, priapism, palpitations, urticaria, vascular skin disorder, flushing, headache, anemia, insomnia, and haemoglobin decreased. No patients below 2 years had an AE assessed as related to macitentan. Most of the reported AEs are generally in line with the known safety profile of macitentan in adults.

Additionally, based on data provided by the Applicant, there was an imbalance in menstrual bleeding between macitentan and control arms in adult and adolescent females treated with macitentan. Therefore, the event increased uterine bleeding was added as a common ADR in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

In TOMORROW study in children >2 years old there were several new ADRs considered pediatric-specific identified (upper respiratory tract infection, rhinitis and gastroenteritis). No specific causes or other plausible explanations for any of them were identified and no relationship between the discussed ADRs and the COVID-19 pandemic could be identified.

In patients < 2 years, safety data come from patients from the pivotal study TOMORROW (n=9), and from 2 children from the 67896062PAH3001 phase 3 study. The low number of enrolled patients < 2 years in clinical trials is considered an important limitation, as very limited clinical safety data are available to establish a robust safety conclusion in this subgroup. This subgroup was not accepted as part of the approved indication.

3.6. Effects Table

Table 1. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Time to CEC-confirmed disease progression	Total number of disease progression events [1]	N (%)	21/73 (28.8)	24/75 (32.0)	**Unc:** - HR 0.828 (95% CI: 0.46, 1.49); p=0. 0.567 - Study design inappropriate due to SoC arm and due to the definition "planned/ongoing" for any specific PAH therapy	Module 5.3.5. Summary of main efficacy results
Time to confirmed hospitalization for PAH	Total number of hospitalisations for PAH	N (%)	11/73 (15.06)	11/75 (14.)	**Unc:** - HR 0. 0.912 (95% CI: 0.393, 2.12); p=0.882 - Study design inappropriate due to SoC arm and due to the definition "planned/ongoing" for any specific PAH therapy	Module 5.3.5. Summary of main efficacy results
Time to confirmed death due to PAH	Total number of death due to PAH	N (%)	6 (6.5)	4 (6.3)	**Unc:** - HR 1.530 (95% CI: 0.429, 5.457); p=0.529 - Study design inappropriate due to SoC arm and due to the definition "planned/ongoing" for any specific PAH therapy	Module 5.3.5. Summary of main efficacy results
Unfavourable Effects						
TEAEs, all	Subjects with 1 or more Treatment-emergent adverse events, related or not related	n (%)	67/72 (93.1%)	51/75 (68.0%)	Difference in exposure between randomized treatments (253.0 subject-year in macitentan versus 187.7 subject-year in SoC) due to a higher discontinuation rate in the SoC arm.	Module 2.7.4. Summary of Clinical Safety
SAES	Serious adverse events	n (%)	26/72 (36.1%)	16/75 (21.3%)	SAEs considered related to macitentan were anaemia and alanine aminotransferase increased (1 participant [1.4%] each)	Module 2.7.4. Summary of Clinical Safety

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AEs leading to premature discontinuation	Adverse events leading to premature discontinuation	n (%)	4/72 (5.6%)	2 (2.7%)		Module 2.7.4. Summary of Clinical Safety
ADR	Upper respiratory tract infection	N (%)	23 (31.9)	12 (16.0)	**Unc:** - not identified in adult population - comparison with SoC arm	Module 2.7.4. Summary of Clinical Safety
	Rhinitis	N (%)	6 (8.3)	2 (2.7)		
	Gastroenteritis	N (%)	8 (11.1)	1 (1.3)		
AEs of Special interest	Anaemia	N (%)	11 (15.3)	2 (2.7)	**SoE**: - known ADR - safety results consistent with the adult population **Unc**: - comparison with SoC arm	Module 2.7.4. Summary of Clinical Safety
	Hepatic disorders	N (%)	3 (4.2)	3 (4.0)		
	Hypotension	N (%)	3 (4.2)	1 (1.3)		
	Oedema/fluid retention	N (%)	4 (5.6)	1 (1.3)		

Abbreviations: AEs = adverse events; CEC = Clinical Event Committee; HR = Hazard Ratio; SAEs = Serious Adverse Events; TEAEs = treatment-emergent adverse events;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy data of macitentan in children with PAH is mainly based on TOMORROW study that was coupled with an extrapolation exercise from adults (ICH guideline E11A).

For the paediatric population aged ≥2 years to <18 years, in the pivotal trial, there was a non-statistically significant numerical trend for time to first CEC-confirmed disease progression compared to SOC (28.8% (n=21 events) vs 32.0% (n=24 events); adjusted HR of 0.828, 95% CI] = [0.460; 1.492], 2-sided stratified p=0.567). Positive numerical trends were also observed in other secondary endpoints, like NT-proBNP, WHO FC and also in parent report and child report of QoL, measured using the SF15 questionnaire. Four hierarchical composite endpoints (HCE) were conducted as exploratory efficacy analyses, which also suggest positive trends of macitentan, mainly driven by results on CEC-confirmed clinical worsening and in the SF25 questionnaire.

However, although this study showed favorable trends in several efficacy endpoints for the age category of ⩾ 2 to 18 years, the design of this study, despite in line with the PIP, is not considered appropriate to draw firm conclusions due to comparison with a SoC arm and by using the definition of "ongoing/planned" PAH therapy at baseline, including the stratification factor of

"ongoing/planned ERA treatment''. As such, these results can only be considered supportive to the extrapolation exercise.

The risks observed in the paediatric population were similar to those found in adults. These events are usually mild to moderate and manageable in standard practice.

Regarding the age category of < 2 years old, small sample size, the limited duration of exposure and the impossibility of establishing a posology in this subset, do not allow to establish the efficacy/safety in children <2 years. Consequently, paediatric therapeutic indication has been limited to patients aged ≥2 years.

3.7.2. Balance of benefits and risks

As commented in previous section, the efficacy data of macitentan in children with PAH is mainly based on exploratory data from the TOMORROW study, and mainly for children ≥ 2 years to > 18 years.

The positive trend towards a benefit with respect to the delay in clinical worsening is somewhat consistent with that observed in the SERAPHIN study in adults. The risks observed in the paediatric population were also similar to those found in adults.

Although the efficacy outcomes of the TOMORROW study suggest favourable trends, the study design is considered inappropriate in order to draw firm conclusions. Therefore, the totality of evidence included in this submission supporting the efficacy of macitentan for paediatric patients should be based on the assumption that similar exposures and pharmacodynamic effects in children compared to adults will results in similar efficacy in children as expressed in the *EMA reflection paper on extrapolation (EMA 2018)* as well as in the current draft *ICH E11A guideline on paediatric extrapolation (EMA 2022)*.

The risks observed in the paediatric population were similar to those found in adults. These events are usually mild to moderate and manageable in standard practice.

In children < 2 years efficacy and safety data are quite limited and the exposure at the doses proposed in children < 2 years did not match the exposure obtained in the adult population, thus making the extrapolation from adults in this age subset unfeasible. In children ≥ 2 years extrapolation from the adult population has been shown.

3.8. Conclusions

The overall benefit/risk balance of Opsumit is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP consensus is of the opinion that Opsumit is not similar to 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 and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Opsumit 2.5 mg, dispersible tablets is favourable in the following indication:

Paediatric population
Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years with WHO Functional Class (FC) II to III (see section 5.1).

For the existing 10 mg, film-coated tablets strength, the CHMP considers by consensus that the indication should be amended as follow:

Adults

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III (see section 5.1).

~~Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease~~ (see section 5.1).
Paediatric population

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Opsumit 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).

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.

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 Opsumit is marketed, all patients who are expected to use Opsumit are provided with the following educational material:

- Patient Card

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0457/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension application to introduce a new pharmaceutical form associated with a new strength (2.5 mg dispersible tablet) grouped with an extension of indication (C.I.6.a) to include, as monotherapy or in combination, the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 2 years to less than 18 years of age of WHO Functional Class (FC) II to III for OPSUMIT. In addition, the indication of the 10 mg coated tablet is extended, as monotherapy or in combination, for the long-term treatment of PAH in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III. This is based on an extrapolation exercise with exposure matching to the adult efficacious dose range given the similarity of the disease in children and adults, as well as on supportive efficacy and safety data from the phase 3 AC-055-312 study (TOMORROW). TOMORROW is a multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC for the film-coated tablets are updated. The Package Leaflet and Labelling are updated in accordance. Version 14.4 of the RMP has also been submitted.

5. References

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