EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 November 2025
EMADOC-1700519818-2419276
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Opsumit

macitentan

Procedure no: EMA/PAM/0000295189

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Abbreviation	Description of abbreviated term
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BDI	Borg Dyspnea Index
BSA	body surface area
CI	confidence interval
CO	cardiac output
COVID-19	Coronavirus Disease 2019
CR	category-ratio
CSR	Clinical Study Report
DBL	database lock
EC	Ethics Committee
ECG	electrocardiogram
EEA	European Economic Area
EOS	end of study
EOT	end-of-treatment
ERA	endothelin receptor antagonist
ET	endothelin
EU	European Union
FC	functional class
FMI	Final Market Image
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IP	prostacyclin receptor
IRB	Institutional Review Board
LAP	left atrium pressure
LVEDP	left ventricular end diastolic pressure
LVEI	left ventricular eccentricity index
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
NT-proBNP	N-terminal pro–brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PDE-5	phosphodiesterase type 5
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PT	preferred term
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
QoL	quality of life
QTc	corrected interval
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RHC	right heart catheterization
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF	short form
SOC	system organ class
SvO2	venous oxygen saturation
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment-emergent adverse event
TPR	total pulmonary resistance

US	United States
WHO	World Health Organization
WU	Wood units

1. Introduction

On 29 August 2025, the MAH submitted completed paediatric study for Opsumit (study 67896062PAH3001), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study 67896062PAH3001 was designed to support the macitentan clinical development program for the treatment of pediatric patients with PAH in Japan. The study population comprises 7 Japanese children with PAH. At baseline, 2 participants were under 2 years of age (21 and 22 months) and 5 participants were over 2 years of age (2.5, 3, 9, 11, and 13 years).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Macitentan (Opsumit) is an orally active endothelin receptor antagonist (ERA), active on both endothelin (ET) ETA and ETB receptors, approved for marketing in the EU through the centralised procedure on 20 December 2013.

The initial marketing authorization included only adult patients. Subsequently, in 2024, an extension of the marketing authorisation [procedure number EMEA/H/C/002697/X/0051/G] was approved to include children aged 2 years and older.

Currently, macitentan is approved by the European Commission as 2 formulations for oral use for the following indications:

-Film-coated tablets (containing 10 mg macitentan):

"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).

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)".

-Dispersible tablets (containing 2.5 mg macitentan):

"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)".

Pediatric development for macitentan was done in accordance with the agreed PIP (EMEA-001032-PIP01-10-M07); a positive opinion for the final compliance check was received on 23 February 2024 (EMEA-C-001032-PIP01). The following clinical studies were part of the pediatric clinical development program:

- Study AC-055-312 (TOMORROW): a multicenter, open-label, randomized, Phase 3 study to assess the PK, safety, and efficacy of macitentan versus standard of care in children with PAH from ≥1 month to <18 years of age. Data from the completed randomized Core Period supported the approval of the pediatric indication. The single-arm extension period of the study is ongoing.
- -Study 67896062PAH1013: a PK and safety study in children from ≥1 month to <2 years of age. This study was prematurely terminated, and no participants were enrolled.
- Study 67896062PAH3001: a PK, safety, and efficacy study in Japanese children with PAH from ≥3 months to <15 years of age. Interim PK, safety, and efficacy data for the 2 enrolled participants <2 years of age supported the approval of the pediatric indication.

Study 67896062PAH3001 has now been completed and final results have been provided within this procedure.

2.2. Information on the pharmaceutical formulation used in the study

In study 67896062PAH3001, macitentan was administered in the pharmaceutical form of dispersible tablets with unit dose strengths of 1 mg and 2.5 mg. It should be noted that within the EU, the 1 mg dose was not authorized (only the 10 mg dose in the form of film-coated tablets and the 2.5 mg dose as dispersible tablets are approved). Whole tablets were dispersed in water and administered orally (eg, via spoon, glass, syringe) once daily.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an abbreviated final CSR and the 2024 interim CSR for study number 67896062PAH3001: "A multicenter, open-label, phase III study to assess the efficacy, safety, and pharmacokinetics of macitentan in Japanese pediatric patients (≥3 months to <15 years) with pulmonary arterial hypertension".

Study 67896062PAH3001 was designed to support the macitentan clinical development program for the treatment of pediatric patients with PAH in Japan. The study population comprises 7 japanese children with PAH.

This study planned 3 DBLs:

- The first DBL occurred when 2 participants <2 years of age had completed evaluations at Week 24.
- The second DBL occurred when all participants completed evaluations at Week 24 and both primary endpoint measurements at baseline and at Week 24 were available for at least 5 participants.

- The third DBL occurred at the end of study (EOS) when all participants completed evaluations at Week 52 and consecutive safety follow-up. The dataset at third DBL was provided for the long-term safety evaluation

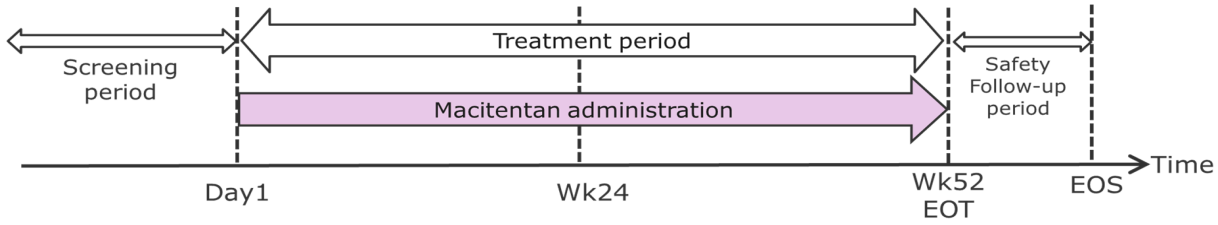
The analyses presented in the abbreviated final clinical study report (CSR) provided are based on the third database lock (DBL). Results of the primary efficacy endpoint (fold change at Week 24 in pulmonary vascular resistance index [PVRI]), secondary efficacy endpoint hemodynamic parameters/right heart catheterization, and PK endpoint were described in the 67896062PAH3001 Interim CSR dated 19 December 2024, which included all results up to the Week 24 (second DBL) with an interim cutoff date of 24 July 2024.

2.3.2. Clinical study

Study 67896062PAH3001: "A multicenter, open-label, phase III study to assess the efficacy, safety, and pharmacokinetics of macitentan in Japanese pediatric patients (≥3 months to <15 years) with pulmonary arterial hypertension".

This was a multicenter, open-label, single-arm, Phase 3 study. The study consisted of a screening period (Day -30 to Day -1), treatment period (Day 1 to Week 52 [EOT]), and posttreatment follow-up period (30 days after EOT) (Figure 1).

Figure 1: Schematic Overview of the Study



PE: fold change in PVRI at Week 24

Methods

Study participants

Main inclusion criteria:

The target population consisted of Japanese (defined as participants whose parents were Japanese [excluding naturalized Japanese] as verbally reported by the participant or his or her parent(s)/legally designated representative) males or females between ≥3 months and <15 years of age at the first administration of study intervention, participants with PAH belonging to the Nice 2013 Updated Classification Group 1 (including Down syndrome), WHO FC I to IV, PAH-specific treatment-naïve participants or participants on PAH-specific treatment, and PAH diagnosis confirmed by historical right heart catheterization (RHC) (characterized by mPAP ≥25 mm Hg, and pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, and PVRI >4 Wood Units [WU]×m2), where in the absence of pulmonary vein obstruction and/or significant lung disease, PAWP could be replaced by left atrium pressure (LAP) or left ventricular end diastolic pressure (LVEDP) (in absence of mitral stenosis) assessed by heart catheterization.

Main exclusion criteria:

- Participants with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease, and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.
- Participants with PAH associated with open shunt: a. Eisenmenger syndrome, b. Moderate to large left-to-right shunts as judged by the investigator
- Participants with certain 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 patients with Fontan-palliation
- Pulmonary hypertension due to lung disease (eg, bronchopulmonary dysplasia)
- Patients with the following diseases: a) Patients with pulmonary vein stenosis; b) Patients with bronchopulmonary dysplasia
- Haemoglobin or haematocrit <75% of the lower limit of normal range (LLN) at Screening.
- Serum AST and/or ALT >3 × ULN at Screening.
- Severe hepatic impairment, e.g., Child-Pugh Class C, at Screening.
- Clinical signs of hypotension which in the investigator’ s judgment would preclude
- initiation of a PAH-specific therapy at Screening.
- Severe renal dysfunction with an estimated Glomerular Filtration Rate (eGFR) 2 <30 mL/min/1.73 m2 at Screening.
- Known concomitant life-threatening disease with a life expectancy <12 months.
- Patients receiving PAH-specific treatments (excluding PDE-5 inhibitor) at the first administration of study intervention.
- Start or change of dose* with PDE-5 inhibitor within 90 days before RHC at Screening (* Dose adjustments are permitted based on patient body-weight change).
- Start or change of dose* of Calcium channel blockers and/or diuretics within 7 days before RHC (* Dose adjustments are permitted based on patient body-weight change).
- Previous treatment* with macitentan at any time.
- Any PAH-related surgical intervention planned, or patients listed for organ transplantation related to PAH.
- Treatment with strong inducers of CYP3A4 (e.g., rifabutin, rifampicin, carbamazepine, phenobarbital, phenytoin, St. John’ s wort), within 4 weeks prior to the first
- administration of study intervention.
- Systemic treatment with strong inhibitors of CYP3A4 (e.g., clarithromycin, itraconazole, ketoconazole, nelfinavir, posaconazole, ritonavir, and voriconazole) within 4 weeks prior to the first administration of study intervention.
- Systemic treatment with moderate dual CYP3A4/CYP2C9 inhibitor (e.g., fluconazole and amiodarone), or administration of a combination of a moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole) within 4 weeks prior to the first administration of study intervention.

Treatments

All participants received a once-daily dose of macitentan dispersed in water and administered orally. Study interventions, dose and mode of administration are detailed in table 1.

Table 1. Study Interventions, Dose, and Mode of Administration

<table>
<tr><td>Intervention Name</td><td>Macitentan</td></tr>
<tr><td>Dose Formulation</td><td>Dispersible Tablet</td></tr>
<tr><td>Unit Dose Strength(s)</td><td>Final Market Image (FMI) 1.0 mg and 2.5 mg</td></tr>
<tr><td>Dosage Level(s)</td><td>If a participant was ≥2 years of age,
<table>
<tr><th>Body weight</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td><15 kg</td><td>3.5 mg</td><td>1 tablet 1.0 mg + 1 tablet 2.5 mg</td></tr>
<tr><td>≥15 kg and <25 kg</td><td>5.0 mg</td><td>2 tablets 2.5 mg</td></tr>
<tr><td>≥25 kg and <50 kg</td><td>7.5 mg</td><td>3 tablets 2.5 mg</td></tr>
<tr><td>≥50 kg</td><td>10.0 mg</td><td>4 tablets 2.5 mg</td></tr>
</table>
If a participant was under 2 years of age,
<table>
<tr><th>Age</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td>≥3 months and <6 months</td><td>1.0 mg</td><td>1 tablet 1.0 mg</td></tr>
<tr><td>≥6 months and <2 years</td><td>2.5 mg</td><td>1 tablet 2.5 mg</td></tr>
</table></td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Delivery Instructions</td><td>Whole tablet(s) were dispersed in water and administered orally (eg, via spoon, glass, syringe). The full daily dose was taken at a single occasion. Macitentan was administered once daily and irrespective of time of food intake but at approximately the same time of the day. The same administration method was to be used as far as possible.</td></tr>
</table>

The macitentan dose was modified in 2 participants who had their dose increased based on increased age. One participant had a temporary interruption of macitentan treatment because of an SAE of bronchitis (refer to safety section).

Objectives

Primary Objective:

- To evaluate the effect of macitentan on hemodynamic measures at Week 24.

Secondary Objectives:

- To evaluate the effect of macitentan on pulmonary hemodynamic parameters other than PVRI at Week 24.
- To evaluate the effect of macitentan on WHO FC at Week 24 (for patients whose age was >4 years of age when initial informed consent.
- To evaluate the effect of macitentan on Panama FC at Week 24.
- To evaluate the effect of macitentan on exercise capacity at Week 24 (For patients who were developmentally able to understand and perform the 6MWT and whose age was ≥6 years of age when initial informed consent.
- To evaluate the effect of macitentan on (NT-proBNP) at Week 24.
- To evaluate the effect of macitentan on echocardiography at Week 24.
- To evaluate the effect of macitentan on quality of life at Week 24.
- To evaluate the effect of macitentan on physical activity at Week 24 (For patients whose age was ≥2 years of age when initial informed consent.

- To assess PK of macitentan and its active metabolite (aprocitentan) in pediatric participants with PAH.
- To evaluate the long-term effect of macitentan on exercise capacity in PAH children (for patients who were developmentally able to understand and perform 6MWT and whose age was ≥6 years of age when initial informed consent.
- To evaluate the long-term effect of macitentan on dyspnea on exertion (for patients who performed 6MWT.
- To evaluate the effect of macitentan on physical activity (for patients whose age was ≥2 years of age when initial informed consent.
- To evaluate the long-term effect of macitentan on WHO FC.
- To evaluate the long-term effect of macitentan on Panama FC.
- To evaluate the long-term effect of macitentan on NT-proBNP.
- To evaluate the long-term effect of macitentan on Echocardiography.
- To evaluate the effect of macitentan on quality of life.
- To evaluate the safety and tolerability of macitentan in pediatric participants with PAH.

Exploratory Objective

-To confirm the time to occurrence of the morbidity/mortality event.

Outcomes/endpoints

Primary Endpoint

The primary endpoint of the study was the fold change in PVRI at Week 24. The geometric mean of PVRI fold change at Week 24 was estimated with observed values. The success criterion was defined as the geometric mean of PVRI fold change at Week 24 ≤81.6%.

Secondary Endpoints

-Efficacy Endpoints

- Hemodynamic parameters/Right heart catheterization: PVR (Wood), mRAP (mm Hg), mPAP (mm Hg), cardiac index (L/min/m2), CO (L/min), TPR (dyn sec/cm5), SvO2 (%).
- Functional classification: WHO FC (I, II, III, IV), Panama FC (I, II, IIIa, IIIb, IV).
- Exercise capacity: 6-minute walking distance (6MWD), Borg Dyspnea Index (BDI)
- Biomarker: NT-proBNP.
- Echocardiography: Tricuspid annular plane systolic excursion (TAPSE), left ventricular
- eccentricity index (LVEI).
- QoL: PedsQLTM 4.0 Generic Core Scales Short Form (SF-15)
- Physical activity: Accelerometry

-Safety Endpoints

The Safety Analysis Set was used for analyses of the safety variables. AEs, SAEs, related AEs, AEs by severity and TEAEs were summarized by SOC and PT. Descriptive statistics were provided for all other safety assessments (clinical laboratory parameters, vital signs and ECG parameters).

Adverse Events:

The verbatim terms used by investigators in the electronic Case Report Form to identify AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days was considered to be treatment-emergent.

AEs of special interest included: anemia/decreased hemoglobin level, edema/fluid retention, hepatic impairment, and hypotension. Additional AEs of special interest included: symptomatic hypotension, menstrual disorders, ovarian cyst, pulmonary veno-occlusive disease with event of pulmonary edema, testicular disorders and male infertility, and pregnancy. All AEs of special interest were summarized by SOC and PT.

Clinical Laboratory Tests: Marked laboratory abnormalities and change from baseline in laboratory parameters over time were described.

Electrocardiogram: ECG parameters and change from baseline over time (the predose ECG was used as baseline) were described. Analyzed ECG variables were heart rate, PR interval, QRS interval, QT interval, and QTc interval using the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF).

Vital Signs: Change from baseline in vital signs (pulse/heart rate, and blood pressure [systolic and diastolic]), height and body weight were described over time.

-*Pharmacokinetics Endpoints (*results of PK analyses).

-*Exploratory Endpoints (morbidity/mortality):* time to morbidity/mortality, time to hospitalization or death due to PAH, time to hospitalization due to PAH, time to death due to PAH, and time to death.

Sample size

Planned: A target of 6 participants (aged ≥3 months and <15 years) were to be enrolled in this study, based on the probability to achieve the success criterion for the primary endpoint of the study (fold change in PVRI at Week 24) and assuming discontinuation of 1 participant.

Analysed: A total of 7 participants were enrolled and treated with study intervention. All 7 participants were included in the Safety and Efficacy Analysis Sets. All 7 participants completed the 52-week intervention period and consecutive safety follow-up.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The analyses presented in the final abbreviated CSR are based on the third database lock (DBL).

Results of the primary efficacy endpoint (fold change at Week 24 in PVRI), secondary efficacy endpoint hemodynamic parameters/right heart catheterization, and PK endpoint were described in the 67896062PAH3001 Interim CSR dated 19 December 2024, which included all results up to the Week 24 (second DBL) with an interim cutoff date of 24 July 2024.

Assuming the true PVRI fold change from baseline to Week 24 was 70% and the standard deviation (SD) of logarithmic PVRI fold change was 0.50, 5 participants would show a 75.4% probability to achieve success criterion. PVRI fold change at Week 24 could be calculated when both measurements, baseline

and Week 24, were available. Considering discontinuation of 1 participant without PVRI assessment of Week 24 during the study, a total of 6 participants were defined as the sample size for this study.

Efficacy endpoints were summarized over time by descriptive statistics. Descriptive summary statistics, such as n, mean, SD, median, geometric mean, inter quantile range, minimum, and maximum for continuous variables, and counts and proportions for discrete variables, were used to summarize data. No statistical test was performed due to the small sample size and insufficient statistical power. Unless otherwise specified, no imputation was applied to the analysis. The efficacy endpoints were analyzed using the Efficacy Analysis Set.

The following secondary efficacy endpoints were estimated at Week 52: exercise capacity (6MWD and Borg Dyspnea Index [BDI]), FC (WHO and Panama FC), biomarker (NT-proBNP), echocardiography (TAPSE and LVEI), QoL (PedsQLTM 4.0 Generic Core Scales Short Form [SF-15]), and physical activity (accelerometry).

The Safety Analysis Set was used for analyses of the safety variables. AEs, SAEs, related AEs, AEs by severity and treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC)and preferred term (PT). Descriptive statistics were provided for all other safety assessments (clinical laboratory parameters, vital signs and ECG parameters).

The PK Analysis Set was used for the analyses of macitentan and aprocitentan PK. Trough (predose) concentrations of macitentan and its metabolite, aprocitentan, were evaluated at steady state at Week 12 in participants aged 2 years or older, and at Week 4 and Week 8 in participants aged under 2 years. Plasma PK Profile and Parameters of Macitentan and Aprocitentan Over 24 Hours: in participants aged 2 years or older, steady state plasma PK profiles and parameters of macitentan and aprocitentan over 24 hours were evaluated by various age groups and weight groups.

The populations for purposes of analysis are defined in Table 2.

Table 2. Analysis sets

Population	Description
Screened Analysis set	All participants who were screened and had a participant identification number.
Efficacy Analysis Set	All participants who have received at least 1 dose of study intervention.
PK Analysis Set	All participants who have received at least 1 administration of macitentan and whose measured plasma or blood concentration after macitentan administration for PK analysis was available.
Safety Analysis Set	All participants who have received at least 1 dose of study intervention.

Results

Participant flow

The final CSR submitted by the MAH includes the results up to the EOS when all participants completed evaluations at Week 52 and consecutive safety follow-up.

Disposition of participants is presented in Table 3. The data includes all screened participants. A total of 8 participants were screened across 6 study centers in Japan. Out of the 7 participants treated with study intervention, all 7 participants completed the 52-week intervention period and completed the study. The duration of the study was approximately 2 years.

None of the participants discontinued study intervention.

Table 3. Study disposition; Screened Analysis set (study 67896062PAH3001)

	Total
Analysis set: Screened	8
Participants who signed informed consent form	8 (100.0%)
Patients who withdrew after signing informed consent but before the first administration of Macitentan	1 (12.5%)
Patients who received the first administration of Macitentan after informed consent	7 (87.5%)
Patients who completed the 24 week treatment period after the first administration of Macitentan	7 (87.5%)
Patients who completed the 52 week treatment period after the first administration of Macitentan	7 (87.5%)
Patients who completed the study	7 (87.5%)
Patients who discontinued Macitentan before completing the 24 week treatment period after the first administration of Macitentan	0
Patients who discontinued from the study after receiving the first administration of Macitentan and before completing the 24 week treatment period	0
Patients who discontinued after completing the 24 week treatment period but before completing the safety follow-up period	0

Major protocol deviations were reported for 3 out of 7 participants treated with study intervention by the data cutoff date (24 July 2024). These included the following: 'Received wrong treatment or incorrect dose' in 1 participant who received clarithromycin after the first administration of macitentan without an interruption of macitentan (ie, a moderate CYP3A4/CYP2C9 inhibitor), 'Received a disallowed concomitant treatment' in 1 participant who received a disallowed PAH-specific therapy other than PDE-5 inhibitor from the first administration of study intervention for the purpose other than PAH worsening (selexipag), and 'Other' in 1 participant who had RHC assessments not done per protocol schedule at Week 24.

In addition to major protocol deviations reported in 3 participants described in the 67896062PAH3001 Interim CSR (CSR 67896062PAH3001 2024), 1 additional participant was reported with major protocol deviation of "Received a disallowed concomitant treatment" (ie, disallowed PAH specific therapy other than PDE-5 inhibitor from the first administration of study intervention for the purpose other than PAH worsening). In total, 2 participants received a disallowed PAH specific therapy other than PDE-5 inhibitor from the first administration of study intervention for the purpose other than PAH worsening, ie, selexipag and epoprostenol sodium, both administered after RHC assessment at Week 24 (selexipag at Day 197, and epoprostenol sodium at Day 255).

Baseline data

All 7 participants treated with study intervention were Asian (Japanese) with a median (range) weight of 13.00 (8.2; 78.5) kg and a median (range) height of 87.10 (76.0; 164.9) cm. None were of Hispanic or Latino ethnicity. Of 7 treated participants, 4 participants were male. The median (range) age at Day 1 (baseline) was 3.0 (1;13) years, with 2 participants aged <2 years (21 and 22 months) and 5 participants aged ≥2 years (Table 4).

Table 4. Baseline Disease Characteristics

	Total
Analysis set: Safety	7
Age, years	
N	7
Mean (SD)	5.7 (5.12)
Median	3.0
Range	(1; 13)
IQ range	(1.0; 11.0)
< 2 years	2 (28.6%)
≥ 2 years	5 (71.4%)
Sex	
N	7
Female	3 (42.9%)
Male	4 (57.1%)
Undifferentiated	0
Unknown	0

	Total
Race	
N	7
Asian (Japanese)	7 (100.0%)
Other	0
Ethnicity	
N	7
Hispanic or Latino	0
Not Hispanic or Latino	7 (100.0%)
Weight, kg	
N	7
Mean (SD)	26.53 (25.222)
Median	13.00
Range	(8.2; 78.5)
IQ range	(11.10; 38.50)
< 15 kg	4 (57.1%)
≥ 15 to < 25 kg	1 (14.3%)
≥ 25 to < 50 kg	1 (14.3%)
≥ 50 kg	1 (14.3%)
Height, cm	
N	7
Mean (SD)	108.14 (34.839)
Median	87.10
Range	(76.0; 164.9)
IQ range	(80.30; 137.60)

Key: IQ = interquartile, SD=Standard deviation
Note: N's for each parameter reflect non-missing values.

Three out of 7 treated participants were of iPAH etiology, while other 4 participants were of PAH associated with congenital heart disease (CHD), ie, post-operative PAH etiology. WHO FC was assessed in participants of >4 years of age at baseline, and there were 3 participants for whom this assessment was done, with all assessed participants being of WHO FC II. Two out of 7 treated participants were of Panama FC I, and other 5 participants were of Panama FC II. None of the participants were of Panama FC III or IV. 6MWT was performed in participants ≥6 years of age, and there were 3 participants for whom this assessment was done, with a median (range) 6MWD of 420.000 (378.88; 455.00) m (table 5).

Table 5. Summary of Disease Characteristics at Baseline; Safety Analysis Set

	Total
Analysis set: Safety	7
Pulmonary arterial hypertension etiology	
N	7
iPAH	3 (42.9%)
hPAH	0
PAH associated with CHD	4 (57.1%)
PAH with co-incidental CHD	0
Post-operative PAH	4 (57.1%)
Drug or toxin induced PAH	0
PAH associated with HIV	0
PAH-aCTD	0
Time from PAH diagnosis to randomization, years	
N	7
Mean (SD)	0.705 (0.9629)
Median	0.356
Range	(0.11; 2.82)
IQ range	(0.115; 0.843)
Concomitant use of drugs for PAH	
N	7
Sildenafil and/or Tadalafil (PDE-5 inhibitor)	6 (85.7%)
Beraprost	0
Ambrisentan	0
Other	1 (14.3%)
None	0
WHO FC (I, II, III, IV)	
N	3
I	0
II	3 (100.0%)
III	0
IV	0
Panama FC (I, II, IIIa, IIIb, IV)	
N	7
I	2 (28.6%)
II	5 (71.4%)
IIIa	0
IIIb	0
IV	0
mPAP, mmHg	
N	7
Mean (SD)	45.4 (17.09)
Median	42.0
Range	(25; 68)
IQ range	(30.0; 67.0)

	Total
PAWP, mmHg	
N	6
Mean (SD)	7.8 (1.94)
Median	7.5
Range	(6; 11)
IQ range	(6.0; 9.0)
PVRI, Wood m^2	
N	7
Mean (SD)	9.503 (5.4309)
Median	6.739
Range	(4.51; 17.71)
IQ range	(4.872; 15.000)
6MWD, m	
N	3
Mean (SD)	417.960 (38.1010)
Median	420.000
Range	(378.88; 455.00)
IQ range	(378.880; 455.000)

Key: IQ = interquartile, SD=Standard deviation, mPAP = mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure, PVRI = pulmonary vascular resistance index, 6MWD = 6-minute walk distance, PAH = Pulmonary arterial hypertension, WHO FC = World Health Organization Functional Classification, PDE-5i=Phosphodiesterase type-5 inhibitor, iPAH = idiopathic pulmonary arterial hypertension, hPAH = hereditary pulmonary arterial hypertension, CTD = connective tissue disease, HIV = human immunodeficiency virus, aCTD = autoimmune connective tissue disease
Note: N's for each parameter reflect non-missing values.

Concomitant therapy of special interest included ERA monotherapy, PDE-5 inhibitor monotherapy, and ERA and PDE-5 inhibitor combination therapy. Overall, 6 out of 7 treated participants received a concomitant therapy of special interest, and all these participants received PDE-5 inhibitor monotherapy tadalafil

Number analysed

Out of the 7 participants treated with study intervention, all 7 participants completed the 52-week intervention period, and completed the study. The duration of the study was approximately 2 years.

Pk results

Pharmacokinetics results were provided in Interim CSR date. All 7 treated participants were included in the PK Analysis Set.

For participants of ≥2 years of age:

- Individual macitentan Cmax and AUC τ values appeared to be similar for all age and weight groups, except for the Cmax and AUC τ values of 1 participant in the ≥10 to <15 kg weight group and ≥2 to <6 years age group that appeared to be higher, but due to the limited data this should be interpreted with caution.

- For aprocitentan, individual Cmax and AUC τ values were highest for the youngest age group and lowest body weight group, and individual Cmax appeared to decrease with increasing age and body weight, but due to the limited data this should be interpreted with caution.

- The mean (SD) plasma concentration of macitenan and aprocitentan were 85.6 (37.3) and 917 (266) ng/mL, respectively, at Week 12 (Visit 6; predose).

Table 6. Steady-state Pharmacokinetic Parameters of Macitentan and Aprocitentan in Japanese Children with PAH, Stratified by Age Group, After Administration of 3.5, 5.0, 7.5, or 10 mg Macitentan Once Daily (QD), Based on Body Weight (Study 67896062PAH3001: Pharmacokinetics Analysis Set)

		Macitentan		
	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng.h/mL)
≥2 - <6 years	2	230 - 352	4.33 - 7.48	3151 - 5714
≥6 - <12 years	2	184 - 250	3.80 - 4.02	2855 - 2886
≥12 - <18 years	1	193	3.80	2897
		Aprocitentan		
≥2 - <6 years	2	1170 - 1340	0.00 - 23.33	23246 - 28313
≥6 - <12 years	2	929 - 1000	0.00 - 24.12	14768 - 18521
≥12 - <18 years	1	764	23.50	15288

Individual values are shown.

Table 7. Steady-state Pharmacokinetic Parameters of Macitentan and Aprocitentan in Japanese Children with PAH, Stratified by Weight Group, After Administration of 3.5, 5.0, 7.5, or 10 mg Macitentan Once Daily (QD), Based on Body Weight (Study 67896062PAH3001: Pharmacokinetics Analysis Set)

		Macitentan		
	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng.h/mL)
≥10 kg - <15 kg (3.5 mg QD)	2	230 - 352	4.33 - 7.48	3151 - 5714
≥15 kg - <25 kg (5.0 mg QD)	1	184	3.80	2855
≥25 kg - <50 kg (7.5 mg QD)	1	250	4.02	2886
≥50 kg (10 mg QD)	1	193	3.80	2897
		Aprocitentan		
≥10 kg - <15 kg (3.5 mg QD)	2	1170 - 1340	0.00 - 23.33	23246 - 28313
≥15 kg - <25 kg (5.0 mg QD)	1	1000	0.00	14768
≥25 kg - <50 kg (7.5 mg QD)	1	929	24.12	18521
≥50 kg (10 mg QD)	1	764	23.50	15288

Individual values are shown.

For 2 participants of <2 years of age
Plasma concentrations of macitentan and aprocitentan at steady state were:

- At Visit 4 (Week 4), 55.1 and 143 ng/mL for macitentan, 864 and 662 ng/mL for aprocitentan, respectively.
- At Visit 5 (Week 8), 59.4 and 83.5 ng/mL for macitentan, and 982 and 648 ng/mL for aprocitentan, respectively.

Efficacy results

Efficacy results were provided in the Interim CSR dated 19 December 2024, which included all results up to the Week 24 (second DBL) with an interim cutoff date of 24 July 2024. At week 52 (abbreviated final CSR), the conclusions of the efficacy results remain unchanged from the interim analysis at Week 24.-

Primary Efficacy Endpoint

The primary endpoint of this study was the fold change at Week 24 in PVRI (Wood m^2). The geometric mean of fold change of PVRI at Week 24 was 59.4% (95% CI: 32.0%, 110.3%), which met the prespecified success criterion of ≤81.6% (Table 8).

This success criterion was based on an exploratory analysis of data from Study AC-055-302 (SERAPHIN), the pivotal Phase 3 study of macitentan in participants aged 12 to 85 years with PAH. Given that macitentan 10 mg was shown to be effective in reducing the risk of morbidity/mortality events and the PVRI geometric mean of fold change (Week 24 to baseline) was 71.4% (95% CI: 62.5%, 81.6%), it would be clinically meaningful if the point estimate of PVRI fold change (Week 24 to baseline) was equal to or less than 81.6% in this pediatric study.

Five out of 7 treated participants had a decrease in PVRI from baseline to Week 24, with 4 participants showing a decrease of ≥2 Wood m2. For 1 participant RHC assessment was not performed per protocol schedule at Week 24: PVRI assessment was done at Day 279 and not during Week 24 as planned. This was reported as a major protocol deviation.

Table 8. PVRI (Wood m2) Fold Change at Week 24; Efficacy Analysis Set (Study 67896062PAH3001)

	Total
Analysis set: Efficacy	7
Fold change at Week 24 (%)[a]	
N	7
Mean (SD)	70.14 (38.112)
Median	66.67
IQ range	(31.58; 107.87)
Range	(20.0; 116.0)
95% CI for Mean	(34.894, 105.389)
Geometric Mean	59.43
Geometric CV (%)	75.1
95% CI for Geometric Mean	(32.019, 110.303)

[a] Fold change is calculated as: PVRI at Week 24 / PVRI at Baseline *100
Key: SD=Standard deviation, IQ = interquartile, CV = coefficient of variance, CI = confidence interval

-Secondary Endpoints

Hemodynamic Parameters/Right Heart Catheterization

Hemodynamic parameters for secondary endpoints were measured in all participants and changes from baseline to Week 24 were estimated.

Improvements in pulmonary hemodynamic variables other than PVRI, including mPAP, mRAP and TPR were observed: the mean (SD) and geometric mean fold change from baseline to Week 24 were 79.44 (23.874)% and 76.59% for mPAP, 93.96 (47.421)% and 75.71% for mRAP, and 79.35 (31.828)% and 73.69% for TPR, respectively.

The mean (SD) and geometric mean fold change from baseline to Week 24 was 101.03 (22.623)% and 98.71% for cardiac index, respectively. For 1 participant RHC assessment was not performed per protocol schedule at Week 24: PVRI assessment was done at Day 279 and not during Week 24 as planned. This was reported as a major protocol deviation.

Fold change from baseline to Week 24 and change from baseline to Week 24 in RHC parameters are shown in Table 9 and Table 10, respectively.

Table 9. Fold Change from Baseline to Week 24 in Hemodynamic parameters / Right heart catheterization; Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Fold Change From Baseline								
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max	Geom Mean	% CV
Analysis set: Efficacy	7																
PVR (Wood)																	
Baseline	7	11.524	2.8021	1.0591	12.110	7.92	15.12										
Week 24	7	7.790	5.1496	1.9464	5.910	2.59	16.09	11.524	7	66.66	35.491	13.415	67.80	18.4	106.4	56.46	76.11
mRAP (mm Hg)																	
Baseline	7	8.4	7.66	2.89	5.0	3	25										
Week 24	7	5.6	2.94	1.11	6.0	3	11	8.4	7	93.96	47.421	17.924	100.00	12.0	150.0	75.71	106.10
mPAP (mm Hg)																	
Baseline	7	45.4	17.09	6.46	42.0	25	68										
Week 24	7	37.4	22.65	8.56	36.0	17	83	45.4	7	79.44	23.874	9.024	73.33	50.0	122.1	76.59	29.46
Cardiac Index ($L/min/m^2$)																	
Baseline	7	4.13	0.789	0.298	4.30	2.8	5.1										
Week 24	7	4.10	0.949	0.359	3.70	2.9	5.2	4.13	7	101.03	22.623	8.551	103.57	70.2	133.3	98.71	24.10
CO (L/min)																	
Baseline	7	3.21	1.357	0.513	2.50	1.9	5.3										
Week 24	7	3.29	1.258	0.475	3.00	2.0	5.4	3.21	7	106.56	24.922	9.420	112.20	70.5	142.9	103.91	25.09
TPR ($dyn\ sec/cm^5$)																	
Baseline	7	1170.6	252.69	95.51	1218.0	755	1527										
Week 24	7	927.6	423.18	159.95	800.0	453	1443	1170.6	7	79.35	31.828	12.030	72.58	40.7	125.0	73.69	44.29
SvO_2 (%)																	
Baseline	7	74.7	9.64	3.64	72.0	65	95										
Week 24	7	71.9	4.02	1.52	72.0	66	77	74.7	7	97.19	10.325	3.903	100.00	75.8	107.1	96.67	11.55

Key: PVR = pulmonary vascular resistance, mRAP = mean right atrial pressure, mPAP = mean pulmonary artery pressure, CO = cardiac output, TPR = total pulmonary resistance, SvO_2 = mixed venous oxygen saturation, SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum, CV = geometric coefficient of variance, Geom = geometric

Table 10. Change from Baseline to Week 24 in Hemodynamic parameters / Right heart catheterization; Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Change From Baseline							
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
PVR (Wood)															
Baseline	7	11.524	2.8021	1.0591	12.110	7.92	15.12								
Week 24	7	7.790	5.1496	1.9464	5.910	2.59	16.09	11.524	7	-3.734	4.4971	1.6997	-2.550	-11.50	0.97
mRAP (mm Hg)															
Baseline	7	8.4	7.66	2.89	5.0	3	25								
Week 24	7	5.6	2.94	1.11	6.0	3	11	8.4	7	-2.9	8.57	3.24	0.0	-22	2
mPAP (mm Hg)															
Baseline	7	45.4	17.09	6.46	42.0	25	68								
Week 24	7	37.4	22.65	8.56	36.0	17	83	45.4	7	-8.0	12.62	4.77	-8.0	-21	15
Cardiac Index ($L/min/m^2$)															
Baseline	7	4.13	0.789	0.298	4.30	2.8	5.1								
Week 24	7	4.10	0.949	0.359	3.70	2.9	5.2	4.13	7	-0.03	1.019	0.385	0.10	-1.4	1.3
CO (L/min)															
Baseline	7	3.21	1.357	0.513	2.50	1.9	5.3								
Week 24	7	3.29	1.258	0.475	3.00	2.0	5.4	3.21	7	0.07	0.743	0.281	0.30	-1.3	0.9
TPR ($dyn\ sec/cm^5$)															
Baseline	7	1170.6	252.69	95.51	1218.0	755	1527								
Week 24	7	927.6	423.18	159.95	800.0	453	1443	1170.6	7	-243.0	410.13	155.02	-207.0	-905	288
SvO_2 (%)															
Baseline	7	74.7	9.64	3.64	72.0	65	95								
Week 24	7	71.9	4.02	1.52	72.0	66	77	74.7	7	-2.9	9.37	3.54	0.0	-23	5

Key: PVR = pulmonary vascular resistance, mRAP = mean right atrial pressure, mPAP = mean pulmonary artery pressure, CO = cardiac output, TPR = total pulmonary resistance, SvO_2 = mixed venous oxygen saturation, SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum

Exercise Capacity

Change from baseline to Week 24 and Week 52 in 6MWD was assessed in participants aged 6 years or older (at the time of initial informed consent). Results must be interpreted with caution due to small sample size (N=3 at Week 24 and N=2 at Week 52). At Week 24, the change in 6MWD from baseline ranged from -44.00 to 40.00 meters, and at Week 52 it was -50.00 meters for 1 participant and 99.42 meters for the other participant (table 11).

Table 11. Change from Baseline to Week 24 and Week 52 in 6-minute Walk Test (6MWT); Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Change From Baseline							
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
Subgroup: ≥ 6 years of age	3														
Total Distance Walked in 6 Minutes (m)															
Baseline	3	417.960	38.1010	21.9976	420.000	378.88	455.00								
Week 24	3	422.857	32.8605	18.9720	411.000	397.57	460.00	417.960	3	4.897	43.6657	25.2104	18.690	-44.00	40.00
Week 52	2	441.650	51.8309	36.6500	441.650	405.00	478.30	416.940	2	24.710	105.6559	74.7100	24.710	-50.00	99.42

Dyspnea on exertion was evaluated with the Borg Dyspnea Index (BDI) just before and after the 6MWT. A lower score indicated less breathlessness. At Week 24, the change from baseline in BDI after the 6MWT ranged from -2.0 to -0.5, and at Week 52 it was -1.5 in 1 participant and -0.5 in the other participant (table 12).

Table 12. Change from Baseline to Week 24 and Week 52 in Borg Dyspnea Index; Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Change From Baseline							
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
Subgroup: ≥ 6 years of age	3														
Borg Dyspnea Index (Before 6MWT)															
Baseline	3	0.00	0.000	0.000	0.00	0.0	0.0								
Week 24	3	0.00	0.000	0.000	0.00	0.0	0.0	0.00	3	0.00	0.000	0.000	0.00	0.0	0.0
Week 52	2	0.00	0.000	0.000	0.00	0.0	0.0	0.00	2	0.00	0.000	0.000	0.00	0.0	0.0
Borg Dyspnea Index (After 6MWT)															
Baseline	3	3.50	2.784	1.607	4.00	0.5	6.0								
Week 24	3	2.33	2.082	1.202	3.00	0.0	4.0	3.50	3	-1.17	0.764	0.441	-1.00	-2.0	-0.5
Week 52	2	1.25	1.768	1.250	1.25	0.0	2.5	2.25	2	-1.00	0.707	0.500	-1.00	-1.5	-0.5

Key: SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum

Functional Classification

The WHO Functional Class was assessed in participants aged over 4 years and the Panama Functional Class was assessed in children aged up to 16 years. There were no changes from baseline to Week 24 or Week 52 in either the WHO Functional Class (N=3) or the Panama Functional Class (N=7) (table 13).

Table 13. Summary of WHO FC (I, II, III, IV) at baseline and Weeks 24 and 52; Efficacy Analysis Set (Study 67896062PAH3001)

		Baseline				
	N	I	II	III	IV	Total
Analysis set: Efficacy	7					
Subgroup: > 4 years of age	3					
N	3					
Class I		0	0	0	0	0
Class II		0	3	0	0	3
Class III		0	0	0	0	0
Class IV		0	0	0	0	0
Total		0	3	0	0	3
Proportion of Participants with Improvement	0.0					
95% CI	(NE, NE)					
Proportion of Participants with Worsening	0.0					
95% CI	(NE, NE)					

Note: N is the number of participants with non-missing values for WHO functional class at baseline and timepoint.
Key: CI = confidence interval, WHO = World Health Organization

NT-proBNP

A small but persistent reduction in NT-proBNP levels over time was observed. The mean (SD) change in plasma NT-proBNP from baseline to Week 24 (N=7) was -3.7423 (7.79983) pg/mL and to Week 52 (N=6) was -0.2360 (10.15074) pg/mL. The geometric mean fold change in plasma NT-proBNP from baseline to Week 24 was 100.96%, and to Week 52 was 102.71%.

Echocardiography

Change from baseline at each timepoint in LVEI and TAPSE is shown in Table 14 and Table 15.

The median (range) fold change from baseline in diastolic LVEI was 96.51% (64.1%; 116.8%) at Week 24 (N=7), and 90.17% (81.6%; 109.2%) at Week 52 (N=7). The median (range) fold change from baseline in systolic LVEI was 92.38% (52.2%; 134.2%) at Week 24 and 86.88% (70.3%; 91.3%) at Week 52. The median (range) fold change from baseline in BSA-normalized TAPSE was 102.17% (87.4%; 124.2%) at Week 24 (N=7) and 104.86% (74.2%; 127.6%) at Week 52 (N=6).

Table 14. Absolute Change from Baseline at each Analysis Time Point in Left Ventricular Eccentricity Index (LVEI); Efficacy Analysis Set(Study 67896062PAH3001)

	Measured Value							Absolute Change From Baseline						
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
Diastolic LVEI															
Baseline	7	1.158	0.0915	0.0346	1.180	1.00	1.27								
Week 12	7	1.084	0.1411	0.0533	1.088	0.95	1.33	1.158	7	0.116	0.1241	0.0469	0.064	0.01	0.32
Week 24	7	1.099	0.1882	0.0711	1.175	0.77	1.28	1.158	7	0.125	0.1491	0.0564	0.042	0.01	0.43
Week 52	7	1.062	0.1137	0.0430	1.051	0.90	1.19	1.158	7	0.128	0.0762	0.0288	0.099	0.01	0.22
Systolic LVEI															
Baseline	7	1.373	0.2121	0.0802	1.438	1.03	1.61								
Week 12	7	1.272	0.3299	0.1247	1.145	0.95	1.92	1.373	7	0.237	0.1519	0.0574	0.288	0.02	0.43
Week 24	7	1.257	0.2942	0.1112	1.338	0.75	1.57	1.373	7	0.229	0.2396	0.0906	0.128	0.02	0.69
Week 52	7	1.136	0.1742	0.0658	1.192	0.90	1.42	1.373	7	0.237	0.1225	0.0463	0.188	0.12	0.43

Key: LVEI = left ventricular eccentricity index, SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum

Table 15. Absolute Change from Baseline at each Analysis Time Point in Tricuspid Annular Plane Systolic Excursion (TAPSE); Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Absolute Change From Baseline						
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
BSA-normalized TAPSE															
Baseline	7	19.285	6.7085	2.5356	18.169	9.47	28.09								
Week 12	7	21.726	6.9546	2.6286	21.165	13.16	33.79	19.285	7	2.766	1.6763	0.6336	2.996	1.13	5.69
Week 24	7	19.182	5.4788	2.0708	20.630	11.77	25.31	19.285	7	1.873	1.0379	0.3923	2.296	0.54	3.07
Week 52	6	17.717	4.7406	1.9353	17.224	12.08	23.91	17.817	6	2.412	1.3666	0.5579	2.412	0.45	4.69

Key: BSA = body surface area, TAPSE = tricuspid annular plane systolic excursion, SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum

Quality of Life

QoL was assessed using the PedsQL in participants aged 2 years and older. Higher scores indicated better QoL. Although no change from baseline was observed in QoL at Week 24, it improved at Week 52. At Week 52, the median (range) change from baseline was 15.000 (6.67; 26.67) in the parent/caregiver total score (N=5), and 26.667 (-6.67; 30.00) in the participant total score (N=3) (table 16).

Table 16. Summary of Change from Baseline in Quality of Life (QOL); Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Change From Baseline						
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
Subgroup: ≥ 2 years of age	5														
Total score - parent(s)/caregiver(s) report															
Baseline	5	65.214	9.5863	4.2871	66.667	50.00	76.67								
Week 12	5	74.119	12.6189	5.6434	73.333	56.67	88.33	65.214	5	8.905	6.1274	2.7403	6.667	1.67	17.86
Week 24	5	73.405	16.1965	7.2433	73.333	56.67	96.67	65.214	5	8.190	11.3259	5.0651	10.000	-10.00	20.00
Week 52	5	81.024	9.2358	4.1304	76.786	73.33	96.67	65.214	5	15.810	7.8366	3.5046	15.000	6.67	26.67
Total score - subject report															
Baseline	3	70.556	12.5093	7.2222	63.333	63.33	85.00								
Week 12	3	79.444	13.8778	8.0123	75.000	68.33	95.00	70.556	3	8.889	3.4694	2.0031	10.000	5.00	11.67
Week 24	3	68.333	7.2648	4.1944	65.000	63.33	76.67	70.556	3	-2.222	17.8211	10.2890	1.667	-21.67	13.33
Week 52	3	87.222	7.8764	4.5474	90.000	78.33	93.33	70.556	3	16.667	20.2759	11.7063	26.667	-6.67	30.00

Key: SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum

Physical Activity

Physical activity was evaluated by accelerometry for participants aged 2 years and older at the time of initial informed consent. An improvement in mean daily time spent in light physical activity was observed at Week 52 (N=5). The median (range) change from baseline was 11.500 (-2.23; 136.98) minutes. A slight improvement in mean count per minute of daily activity was also observed at Week 52 (median [range] 56.650 [16.69; 396.70]) (Table 17).

Table 17. Change from Baseline at each Analysis Time Point in Physical Activity; Efficacy Analysis Set (Study 67896062PAH3001)

	Measured Value							Change From Baseline						
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Efficacy	7														
Subgroup: ≥ 2 years of age	5														
Number of hours of daytime activity															
Baseline	5	12.604	0.8561	0.3829	12.793	11.22	13.40								
Week 12	5	11.675	1.1024	0.4930	11.419	10.82	13.59	12.604	5	-0.929	0.9741	0.4356	-0.965	-1.98	0.42
Week 24	5	12.323	0.9289	0.4154	12.575	11.18	13.56	12.604	5	-0.280	1.3553	0.6061	-0.218	-2.22	1.42
Week 52	5	12.748	0.5673	0.2537	12.467	12.16	13.42	12.604	5	0.144	0.4985	0.2229	0.038	-0.39	0.94
Mean count per minute of daily activity															
Baseline	5	726.237	356.9011	159.6110	863.511	324.78	1165.24								
Week 12	5	800.183	503.5261	225.1837	917.451	216.14	1301.13	726.237	5	73.946	205.4249	91.8688	53.940	-108.63	415.83
Week 24	5	838.970	557.3239	249.2428	959.128	267.00	1633.58	726.237	5	112.733	219.3168	98.0815	95.617	-125.36	468.33
Week 52	5	851.664	420.6238	188.1087	1012.774	381.42	1260.21	726.237	5	125.427	157.5824	70.4730	56.650	16.69	396.70
Mean daily time spent in light physical activity[a]															
Baseline	5	223.150	117.1039	52.3705	217.182	99.50	393.15								
Week 12	5	224.750	157.3040	70.3485	234.071	45.80	421.43	223.150	5	1.600	46.5857	20.8338	16.890	-53.70	56.17
Week 24	5	258.310	198.5840	88.8095	257.833	76.86	572.71	223.150	5	35.159	92.2011	41.2336	-0.143	-56.06	179.56
Week 52	5	262.002	127.9625	57.2266	313.917	111.00	390.93	223.150	5	38.852	57.1818	25.5725	11.500	-2.23	136.98
Mean daily time spent in moderate to vigorous physical activity															
Baseline	5	0.545	0.7627	0.3411	0.000	0.00	1.58								
Week 12	5	0.577	0.9898	0.4427	0.000	0.00	2.29	0.545	5	0.032	0.4424	0.1979	0.000	-0.54	0.70
Week 24	5	0.714	1.0583	0.4733	0.000	0.00	2.36	0.545	5	0.169	0.6058	0.2709	0.000	-0.37	1.21
Week 52	5	1.038	1.8514	0.8280	0.000	0.00	4.27	0.545	5	0.493	1.5023	0.6718	0.000	-0.67	3.13

[a] Based on a threshold from 800 to 3199 activity counts per minute
Key: SD = standard deviation, SE = standard error, Med = median, Min = minimum, Max = maximum
Note: Data collected for 10 to 14 consecutive complete days before respective visits with a complete day defined as a record of at least 7 hours of data.

-Exploratory Endpoints

Exploratory endpoints included time to disease progression, time to first hospitalization/death due to PAH, time to first hospitalization for PAH, and time to death (due to PAH or all causes). None of the 7 participants experienced any disease progression event during the study.

Safety results

Safety results were provided in the Abbreviated Final Clinical Study Report, which include data results up to the EOS when all participants completed evaluations at Week 52 and consecutive safety follow-up.

-Exposure

The median (range) total duration of treatment was 361.0 (351; 374) days, and the median (range) total dose of study agent was 1,281.0 (1,200; 3,740) mg (table 18).

Table 18. Number of Participants Who Received Macitentan at Each Dosage Levels by Visit; Safety Analysis Set (Study 67896062PAH3001)

	Macitentan						
	1.0 mg	2.5 mg	3.5 mg	5.0 mg	7.5 mg	10.0 mg	Total
Analysis set: Safety	0	2	4	2	1	1	7
Baseline	0	2 (100.0%)	2 (50.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 4	0	2 (100.0%)	2 (50.0%)	2 (100.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 8	0	1 (50.0%)	3 (75.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 12	0	1 (50.0%)	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 16	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 20	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 24	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 28	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 40	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)
Week 52	0	0	4 (100.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	7 (100.0%)

All administered doses were counted (eg, if the dose was adjusted based on the patient's weight changes, both doses counted).

The mean compliance was 99.76% (99.4; 100.0%). through Week 52. The macitentan dose was modified in 2 participants who had their dose increased based on increased age, and 1 participant had a temporary interruption of macitentan treatment because of an SAE of bronchitis.

-Adverse Events

An overall summary of TEAEs is presented in Table 19.

All 7 participants treated with macitentan reported at least 1 AE. Five SAEs were reported in 2 participants and an AE of special interest was reported in 1 participant. No AEs related to study intervention, leading to discontinuation of study intervention, termination of study participation, or related to COVID-19 were reported.

Table 19. Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 67896062PAH3001)

	Total
Analysis set: Safety	7
Subjects with 1 or more:	
AEs	7 (100.0%)
Related AEs[a]	0
AEs leading to death[b]	0
Serious AEs	2 (28.6%)
AEs of special interest	1 (14.3%)
AEs leading to discontinuation of study treatment	0
AEs leading to termination of study participation	0
AEs Related to COVID-19	0

Key: AE = adverse event
[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.

The most frequently reported TEAEs (≥4 participants) by SOC were 'Infections and infestations' (7 [100%] participants), 'Gastrointestinal disorders' (5 [71.4%] participants), and 'General disorders and administration site conditions' (4 [57.1%] participants) of which the majority were non-serious. All 5 reported SAEs were in the 'Infections and infestations' SOC (2 participants), with 1 participant experiencing multiple SAEs.

The most frequently reported TEAEs (≥2 participants) by PT were nasopharyngitis (6 [85.7%] participants), pyrexia (4 [57.1%] participants), adenovirus infection, streptococcal infection and diarrhoea (3 [42.9%] participants each), and conjunctivitis, abdominal pain, conjunctivitis allergic and arthropod bite (2 [28.6%] participants each).

One TEAE of severe intensity occurred (bronchitis), which was reported as an SAE that led to study intervention interruption. Other TEAEs were of mild or moderate intensity.

There were no deaths reported during the study.

A total of 5 SAEs were reported in 2 participants, described as follows:

- One participant experienced 4 SAEs (metapneumovirus infection, bacteremia, and pneumonia bacterial [2 events]), which were all moderate in intensity and resolved.

  This participant also experienced an adverse event of especial interest (AESI) of iron deficiency anemia (Day 176), which was of mild intensity and resolved. This was the only AESI reported during the study and was not considered related to study intervention by the investigator.The participant had low hemoglobin at baseline and at each following assessment except for Week 20 (range: 103-118 g/L; normal range: 118-147 g/L) until Week 52 when hemoglobin value was reported within the normal range.

- One participant experienced an SAE of bronchitis of severe intensity, which led to interruption of study intervention for 1 day. The SAE led to interruption of study intervention for 1 day from Day 15 to Day 16, after which study intervention was resumed. The SAE resolved.

No AEs related to study intervention, or AEs leading to premature discontinuation of study intervention or termination of study participation were reported during the study. There were no dose modifications because of AEs.

-Evaluation of Clinical Laboratory Tests

There were no clinically meaningful changes from baseline in hematology or clinical chemistry values during the study, nor trends over time observed.

Hematology:

Hemoglobin decreased, leukopenia, and thrombocytopenia are listed as macitentan ADRs. None of the 7 participants had a hemoglobin value of <80 g/L postbaseline. At Week 52, only 1 participant was reported with markedly abnormal hematology laboratory value post-baseline, ie, abnormal levels of leukocytes of $<3.0\times10^9$/L.

A single hematological laboratory abnormality of neutropenia on Day 145 (1.04×109/L, normal range: 1.35-8.65×109/L) was reported as a TEAE. Neutropenia was reported as a non-serious TEAE of mild intensity. Neutropenia was resolved and deemed not related to study intervention by the investigator.

One participant experienced an AESI of iron deficiency anemia, as previously mentioned.

Clinical Chemistry

One participant who was reported with a non-serious TEAE of crystal urine present (reported term: urine calcium oxalate crystal) on Day 141 (calcium at baseline: 2.52 mmol/L, Day 141 [Week 20]: 2.2455 mmol/L, and Day 173 [Week 24]: 2.3204 mmol/L; normal range: 8.4-10.3 mg/dL [2 to 18 years]).
TEAE of crystal urine present was resolved and deemed not related to study intervention by the investigator.

At Week 52, no markedly abnormal clinical chemistry values post-baseline were reported.

-Other Safety Evaluations

There were no clinically meaningful findings in vital signs, ECGs, or physical examinations during the study

2.3.3. Discussion on clinical aspects

Macitentan (Opsumit) is an orally active endothelin receptor antagonist (ERA) targeting both ETA and ETB receptors. It was initially authorized on December 2013 for the treatment of adult patients with pulmonary arterial hypertension (PAH). In 2024, the marketing authorization was extended to include pediatric patients aged 2 years and older. This extension of indication to the paediatric population largely relied on extrapolation from the established efficacy results in adult patients [procedure number EMEA/H/C/002697/X/0051/G].

Currently, macitentan is approved in two oral formulations: a) 10 mg film-coated tablets: indicated for long-term treatment of PAH in adults and pediatric patients under 18 years weighing ≥40 kg, both with WHO Functional Class II to III; and b) 2.5 mg dispersible tablets: indicated for long-term treatment of PAH in pediatric patients aged 2 to less than 18 years with WHO Functional Class II to III. In all cases, macitentan can be used as monotherapy or in combination.

This Article 46 procedure of Regulation (EC) No 1901/2006 concerns the submission of a stand-alone study, 67896062PAH3001 study titled "A multicenter, open-label, phase III study to assess the efficacy, safety, and pharmacokinetics of macitentan in Japanese pediatric patients (≥3 months to <15 years) with pulmonary arterial hypertension". The study was designed to support the macitentan clinical development program for the treatment of pediatric patients with PAH in Japan and is part of the European pediatric clinical development program, in accordance with the agreed PIP, EMEA-001032-PIP01-10-M07. During the procedure for the extension of indication to the paediatric population [EMEA/H/C/002697/X/0051/G], preliminary data from 2 patients were submitted and information was reflected in the Summary of Product Characteristics (SmPC) (sections 4.8 and 5.1). Final results of Study 67896062PAH3001 have now been provided within this procedure.

The 67896062PAH3001 study, is a multicenter, open-label, single-arm, phase 3 study. It consisted of a screening period (Day -30 to Day -1), treatment period (Day 1 to Week 52 [EOT]), and posttreatment follow-up period (30 days after EOT).

A total of 8 participants were screened across 6 study centers in Japan, and 7 participants were treated. Out of the 7 participants treated with study intervention, all 7 participants completed the 52-week intervention period, completed the study (the intervention period and consecutive safety follow up) and were included in the safety and efficacy analysis sets. The duration of the study was approximately 2 years and none of the participants discontinued study intervention.

At baseline, 2 participants were under 2 years of age (21 and 22 months) and 5 participants were over 2 years of age (2.5, 3, 9, 11, and 13 years). All 7 participants treated with study intervention were Asian (Japanese) with a median (range) weight of 13.00 (8.2; 78.5) kg and a median (range) height of 87.10 (76.0; 164.9) cm. Four participants were male. Three out of 7 treated participants were of iPAH etiology, while other 4 participants were of PAH associated with congenital heart disease (CHD), ie, post-operative PAH etiology. WHO FC was assessed in participants of >4 years of age at baseline, and there were 3 participants for whom this assessment was done, with all assessed participants being of WHO FC II. Two out of 7 treated participants were of Panama FC I, and other 5 participants were of Panama FC II.

All participants received a once-daily dose of macitentan dispersed in water and administered orally. Patients 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]. The formulations of macitentan used in the study consisted of dispersible tablets with unit dose strengths of 1 mg and 2.5 mg. It should be noted that within the EU, the 1 mg dose was not authorized, as the paediatric indication was restricted to children ≥ 2 years (only the 10 mg dose in the form of film-coated tablets and the 2.5 mg dose as dispersible tablets are approved).

Concerning efficacy results, the small sample size and the uncontrolled nature of the study prevent any definitive conclusions from being drawn; the results should therefore be considered purely descriptive.

A reduction in pulmonary vascular resistance was observed. The primary hemodynamic endpoint of this study (the fold change at Week 24 in PVRI) was achieved. At Week 24, the geometric mean fold change of PVRI was 59.43% (95% CI: 32.0%, 110.3%), fulfilling the predefined success criterion by the MAH of ≤81.6%. This threshold was established based on an exploratory analysis of data from the pivotal phase III study AC-055-302 (SERAPHIN) conducted in adult population, where macitentan 10 mg demonstrated efficacy in reducing morbidity/mortality risk and achieved a geometric mean PVRI fold change of 71.4% (95% CI: 62.5%, 81.6%). Therefore, in the context of pediatric study, a fold

change equal to or below 81.6% was assumed to be considered clinically meaningful. However, although the result can be view as reassuring it should be taken into account that the value of hemodynamic measurements in the evaluation of medicinal products for HAP is not as clear and the place of these measurements is currently limited diagnosis and a secondary endpoint.

Additional improvements were noted in other pulmonary hemodynamic parameters beyond PVRI, including mPAP, mRAP, and TPR at week 24, as well as in echocardiography parameters (LVEI, LVEI and TAPSE) at week 24 and 52.

Effect on exercise capacity was explored by the 6-minute walk test in participants aged 6 years or older (only N=3 at Week 24 and N=2 at Week 52). At Week 24, the change in 6MWD from baseline ranged from -44.00 to 40.00 meters, and at Week 52 it was -50.00 meters for 1 participant and 99.42 meters for the other participant).

No changes were observed in WHO Functional Class or Panama Functional Class at week 24 or 52 and only a small reduction in NT-proBNP levels over time was observed (mean (SD) change in plasma NT-proBNP from baseline to Week 24 (N=7) was -3.7423 (7.79983) pg/mL and to Week 52 (N=6) was -0.2360 (10.15074) pg/mL.

None of the 7 participants experienced any disease progression event during the study (week 52), which was assessed as an exploratory endpoint (time to disease progression, time to first hospitalization/death due to PAH, time to first hospitalization for PAH, and time to death (due to PAH or all causes).

With respect to safety, no safety concerns were observed among the 7 participants enrolled in the study. All TEAEs were classified as mild to moderate, except for one severe TEAE that was reported as a serious adverse event (bronchitis). None of the TEAEs were considered related to study intervention by the investigator.

No deaths were reported during the study. A total of 5 SAEs occurred. One participant suffered from metapneumovirus infection, bacteraemia, and bacterial pneumonia (2events), all of moderate intensity and resolved successfully. Additionally, one participant experienced severe bronchitis, which led to a one-day interruption of the study treatment, but this event was also resolved. None of them were considered related to the drug as per the investigator.

Decreases in hemoglobin levels have been associated with endothelin receptor antagonists (ERAs), including macitentan, and a warning is already included in SmPC. In this context, one participant in study 67896062PAH3001 experienced an adverse event of iron deficiency anemia. Nonetheless, the event was of mild intensity, resolved completely and was not considered related to macitentan as per the investigator. Importantly, this was the only AESI reported during the study, which is reassuring.

Therefore, although the very small sample size (only 7 children) warrants a cautious interpretation of the data, it is reassuring that the provided data do not raise any significant safety concerns in this population, in line with what was concluded during the paediatric indication extension procedure.

The MAH states that no regulatory consequences arise from the final results of this study. In this regard, although it is acknowledged that the data provided do not alter the conclusion adopted during the assessment of the pediatric indication (efficacy determination considered to be primarily based on extrapolation, supported by pharmacokinetic data and the similarity of the disease between adults and children), it is important to consider the nature of pulmonary arterial hypertension (PAH), which is classified as a rare disease. In this context, all available pediatric data are considered valuable and should be thoroughly assessed and reflected in the SmPC, where appropriate, as established in

European Commission SmPC guideline, 2009 (London, 20 November 2008) . Moreover, since current approved SmPC for Opsumit (sections 4.8 and 5.1) already contains information related to study 67896062PAH3001, based on data from two patients assessed during the pediatric extension procedure (procedure number EMEA/H/C/002697/X/0051/G), it is considered that SmPC should be updated to reflect the final paediatric study population (n=7) and complete study results.

Finally, it should be taken into account that 2 patients from Study PAH3001 were included in the Population PK Analysis, which served as basis for the dosage of macitentan in the pediatric population (procedure number EMEA/H/C/002697/X/0051/G). The initial PK/PD model that was supportive for the paediatric indication granted for the product (in children aged 2 years and above) was robust and the new scarce PK data submitted do not change this conclusion. No new PK data are provided in children < 2 years, but this population is already outside the approved indication.

3. CHMP overall conclusion and recommendation

Final results from 67896062PAH3001 study have been submitted within this procedure. This is a multicenter, open-label, phase III study to assess the efficacy, safety, and pharmacokinetics of macitentan in Japanese pediatric patients (≥3 months to <15 years) with pulmonary arterial hypertension (PAH). The study population comprises 7 Japanese children with PAH. At baseline, 2 participants were under 2 years of age (21 and 22 months) and 5 participants were over 2 years of age (2.5, 3, 9, 11, and 13 years).

Due to the small sample size and the uncontrolled design of the study, the efficacy results are considered **only** purely descriptive. Safety findings were in line with the known safety profile of macientan. New data do not raise any significant safety concerns in this population, in line with what was concluded during the paediatric indication extension procedure.

Recommendation

Since current approved SmPC for Opsumit (sections 4.8 and 5.1) already contains information related to study 67896062PAH3001, based on data from two patients assessed during the pediatric extension procedure (procedure number EMEA/H/C/002697/X/0051/G), it is considered that SmPC should be updated to reflect the final paediatric study population (n=7) and complete study results.

☒ **Fulfilled:**

In view of the available data regarding the final study results available from 67896062PAH3001 study included in the PIP for Opsumit, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 to update the product information (description of the study in sections 4.8 and 5.1) or provide a justification for not doing so. This should be provided without any delay and <***no later than 60 days after the receipt*** of these conclusions.> or <by date>.