15 September 2022
EMA/953202/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Opsumit

macitentan

Procedure no.: EMEA/H/C/002697/P46/011

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☒	Start of procedure	18/07/2022	18/07/2022
☒	CHMP Rapporteur Assessment Report	22/08/2022	22/08/2022
☒	CHMP members comments	05/09/2022	n/a
☒	Updated CHMP Rapporteur Assessment Report	08/09/2022	n/a
☒	CHMP adoption of conclusions:	15/09/2022	15/09/2022

1. Introduction

On 01 July 2022, the MAH submitted a completed study including a subset of paediatric patients (Study No./acronym: AC-055H302/RUBATO OL) for Opsumit (macitentan), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

Of the 111 patients (age range: 13 to 49 years) enrolled, 12 (10.8%) were paediatric subjects (age range: 13 to less than 18 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. 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)".

Pursuant to Article 7 of Regulation (EC) No 1901/2006, as amended, the initial marketing authorisation application included an EMA Decision (P/0087/2012) on the agreement of an EU Paediatric Investigation Plan (PIP; EMEA-001032-PIP01-10-M01) for oral use of macitentan as dispersible tablet and film-coated tablet for the treatment of Pulmonary Arterial Hypertension (PAH) indication. The last EMA Decision (P/0480/2021) corresponding to the acceptance of a modification of an agreed PIP for macitentan for the treatment of PAH (EMEA-001032-PIP01-10-M04) was issued by December 2021.

In accordance with Article 46 of the regulation (EC) No 1901/2006, Janssen-Cilag International NV hereby submits to the EMA a final study report for the study number AC-055H302 (acronym: RUBATO open-label [OL]).

The MAH stated that study number AC-055H302 (RUBATO OL) "Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects" is a standalone study. As such, a line listing is not provided.

AC-055H302 (RUBATO OL) was a Phase 3 extension of the AC-055H301 (RUBATO double-blind [DB]) study. The results of Study AC-055H301/RUBATO DB, which did not meet the primary and secondary efficacy endpoints, were already submitted to the EMA for Opsumit (EMEA/H/C/002697/P46/010) in accordance with Article 46 of Regulation (EC) No. 1901/2006.

Both AC-055H301/RUBATO DB and AC-055H302/RUBATO OL studies are part of the PIP for oral use of macitentan as dispersible tablet and film-coated tablet agreed upon for the treatment of functional single ventricle heart disease with total cavo-pulmonary connection indication (EMEA-001032-PIP03-19; [Decision P/0242/2021]), but not for the PIP agreed to the treatment of PAH indication (EMEA-001032-PIP01-M04; [Decision P/0480/2021]).

2.2. Information on the pharmaceutical formulation used in the study

The formulation of macitentan used in the study was the same as the product approved in the EU (*i.e.*, 10 mg film-coated tablets), which is intended to treat adult patients with PAH from World Health Organization FC II and III.

No paediatric formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study number AC-055H302 (RUBATO OL): "Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects".

AC-055H302 (RUBATO OL) was a Phase 3 extension of the AC-055H301 (RUBATO double-blind [DB]) study. The OL study was stopped prematurely because the main DB study did not meet the primary and secondary efficacy endpoints.

Only 12/111 (10.8%) participants were paediatric subjects (age range: 13 to less than 18 years).

2.3.2. Clinical study

Clinical study number AC-055H302 (RUBATO OL): Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects

Description

The RUBATO open-label (OL) study was a prospective, multicenter, single-arm, Phase 3 extension of the RUBATO double-blind (DB) study to assess the long-term use of macitentan 10 mg in Fontan-palliated adult and adolescent participants beyond the 52 weeks of treatment (macitentan 10 mg or placebo) in the RUBATO DB study. Participants were rolled over from the DB study to this OL study without knowledge of their previous study treatment. The RUBATO OL analyses included safety endpoints and exploratory efficacy endpoints.

The study comprised the following 4 consecutive periods:

- *Enrollment period*:

The enrollment period for a participant began with the visit at Week 52 in the RUBATO DB study and signing of the informed consent form and lasted until the administration of the first dose in the RUBATO OL study (Visit 1).

- *Treatment period*:

The treatment period started with the administration of the first dose of macitentan 10 mg in the OL study and lasted until whichever of the following occurred first:

- 104 weeks (2 years) of study treatment for each participant after the last participant completed the RUBATO DB treatment period.
- The participant or investigator decided to discontinue the study intervention.
- The sponsor decided to stop the RUBATO OL study.

- *Safety follow-up (S-FU) period*:

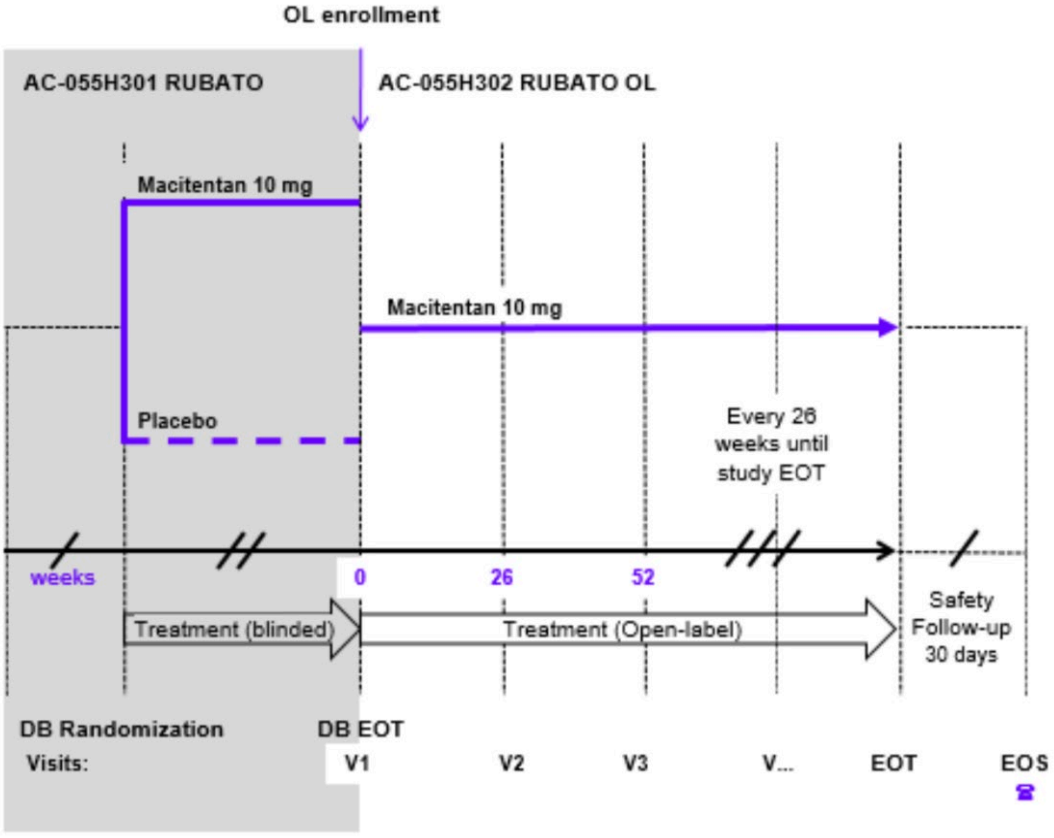
For an individual participant, S-FU started on the day after the last dose of OL study intervention and ended 30 to 35 days thereafter with the EOS visit.

- *End-Of-Study*:

For an individual participant, the study was completed with the EOS visit. For all participants, EOS corresponded to the last visit performed in this RUBATO OL study.

A diagrammatic representation of the study design is presented in Figure 1.

Figure 1: Study Design



DB=double-blind (study); EOS=End-of-Study; EOT=End-of-Treatment; OL=open-label (extension); V=visit; ☎=telephone call (for visit)

Where administration of RUBATO OL study intervention did not immediately follow End-of-Treatment (EOT) in the RUBATO DB study, the participant was to enter the normal DB S-FU period until administration of the first dose of the OL study intervention occurred.

Methods

Study participants

The target population consisted of adolescent (>12 years) and adult male and female participants who had previously participated in the RUBATO DB study and completed Week 52 of the RUBATO DB study. Treatment with endothelin receptor antagonists (other than macitentan as the study treatment) was not permitted during the study.

Inclusion/Exclusion Criteria

For inclusion in the study, all of the following inclusion criteria were to be fulfilled. It was not permitted to waive any of the criteria for any participant.

1. Written informed consent/assent from the participant and/or legal representative prior to initiation of any study-mandated procedures.

2. Participants who had completed Week 52 of the RUBATO DB study.

3. Women of childbearing potential were eligible if they:

   - had a negative serum pregnancy test prior to first intake of OL study intervention.
   - agreed to perform monthly pregnancy tests up to the end of S-FU period.
   - used reliable methods of contraception from enrollment up to at least 30 days after study intervention discontinuation.

Key exclusion criteria included the following:

1. Clinical worsening leading to medical interventions including reoperation of Fontan circulation (Fontan take-down) during the enrollment period.

2. Criteria related to macitentan use:
   - Hemoglobin <75% of the lower limit of normal assessed by central laboratory at enrollment.
   - Known or suspected pulmonary veno-occlusive disease.
   - Known and documented severe hepatic impairment defined as Child-Pugh Score C, based on measurement of total bilirubin, serum albumin, International normalized ratio, or prothrombin time (except for participants under non-Vitamin K antagonists) and based also on presence/absence and severity of ascites and hepatic encephalopathy.
   - Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) range assessed by central laboratory at enrollment.
   - Severe renal impairment (estimated creatinine clearance <30 mL/min/1.73 m2) assessed by central laboratory at enrollment.
   - Pregnancy, breastfeeding, or intention to become pregnant during the study, or women of childbearing potential not using a reliable method of contraception.
   - Hypersensitivity to any active substance or excipient of any of the study drugs.
   - Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer such as carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort, within 1 month prior to enrollment (Visit 1).
   - Treatment with a strong CYP3A4 inhibitor such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir, within 1 month prior to enrollment (Visit 1).
   - Treatment with a moderate dual CYP3A4/CYP2C9 inhibitor (eg, fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors within 1 month prior to enrollment (Visit 1). Please note that his was a criterion modified per Amendment 2.

3. Any known factor or disease that could interfere with treatment compliance or full participation in the study (eg, chemotherapy treatment for cancer) or illness with an anticipated life expectancy of less than 12 months.

Treatments

The study intervention used in the OL study was macitentan 10 mg, orally administered as film-coated tablets once daily with or without food.

The treatment period started with the administration of the first dose of macitentan 10 mg in the OL study and lasted until whichever of the following occurred first:

- 104 weeks (2 years) of study treatment for each participant after the last participant completed the RUBATO DB treatment period.
- The participant or investigator decided to discontinue the study intervention.
- The sponsor decided to stop the RUBATO OL study.

Objectives

Primary Objective:

- To assess the long-term safety and tolerability of macitentan in Fontan-palliated adult and adolescent participants.

Secondary Objectives:

- To assess the effect of macitentan on exercise capacity (measured by peak oxygen uptake/consumption [VO2]).
- To assess the effect of macitentan on daily Physical Activity measured by Accelerometer (PA-Ac).

Other Objectives:

- To assess the effect of macitentan on time to first occurrence of clinical worsening (or morbidity) events and VO2 at ventilatory anaerobic threshold (VAT). Due to the early termination of the study, other objectives (efficacy on other endpoints related to exercise capacity, effect on N-terminal prohormone of brain natriuretic peptide, and effect on pharmacoeconomic endpoints related to hospitalization) were not assessed.

Outcomes/endpoints

Primary Endpoint

- The primary endpoint for this study was safety and tolerability.

Safety Endpoints

- Treatment-emergent adverse events (AEs) and serious adverse events (SAEs) up to 30 days after study intervention discontinuation and AEs leading to death.
- Adverse events leading to premature discontinuation of study intervention.
- Change in vital signs (systolic and arterial diastolic blood pressure and pulse rate), including peripheral oxygen saturation and body weight over time.

- Treatment-emergent marked laboratory abnormalities up to 30 days after study intervention discontinuation.
- Change in laboratory parameters over time.

Exploratory Efficacy Endpoints

Efficacy endpoints were assessed in an exploratory manner.

- Change in peak VO2 from baseline to each scheduled timepoint.
- Change in VO2 at VAT from baseline to each scheduled timepoint.
- Change from baseline to each scheduled timepoint in mean count per minute of daily PA-Ac.
- Composite endpoint of event related to Fontan-palliated clinical worsening time to first occurrence of clinical worsening up to End-of-Study (EOS), defined as one or more of the following:
    - Unscheduled hospitalization for Fontan-palliated morbidity event.
    - Signs and symptoms of heart failure, requiring change in diuretic therapy.
    - Clinical worsening leading to interventions related to Fontan-palliated condition.
    - Worsening to New York Heart Association (NYHA) functional class (FC) III, investigator assessed using the Specific Activity Scale.
    - Signs and symptoms requiring the addition of a new class of cardiovascular medication (eg, nitrates, alpha-blockers, or endothelin receptor antagonists), or insertion of a pacemaker.
    - Failing-Fontan defined as one or more of the following:
        - Enlisted on the active list for heart transplantation or effective heart transplantation.
        - Reoperation (eg., mechanical circulatory support, Fontan take-down, Fontan revision/conversion, atrioventricular [AV] valve repair/replacement).
        - Worsening of NYHA FC IV, investigator assessed using the Specific Activity Scale.
        - Protein-losing enteropathy.
        - Plastic bronchitis/chyloptysis.
        - Peritoneal, pleural, mediastinal, or pericardial effusions.
        - Severe hepatic impairment.
        - Severe renal impairment.
        - Death related to Failing-Fontan.
- Events related to Fontan-palliated morbidity, time to first occurrence up to EOS of one or more of the following:
- Ventricular tachyarrhythmia or supraventricular tachyarrhythmia.
- Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis).

Sample size

Only participants from the AC-055H301/RUBATO DB study who had previously completed the 52-weeks treatment period were rolled over to RUBATO OL study. The planned total sample size was approximately 134 participants.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The RUBATO OL analyses included exploratory efficacy endpoints and safety endpoints. No formal hypothesis testing was performed.

No sample size statistical considerations were made for the RUBATO OL study as this was dependent on the number of randomized participants in the RUBATO DB study.

Data were listed and summarized by appropriate descriptive statistics.

Following population analysis sets were used in the study.

Table 1: Analysis Set Definition

Analysis Set	Period definition	Treatment Arms
RUBATO Open-label Extension Set (OLES)	The RUBATO Open-label Extension Set (OLES) included all participants treated with macitentan in RUBATO OL study. Only data from the OL period were considered with the exception of baseline data (including demographic data, medical and disease history data, prior medication) which could origin from the double-blind (DB) period. Treatment arms "DB-Macitentan 10 mg" and "DB-Placebo" followed the treatment arm from RUBATO DB safety set (SS), ie, were based on actual treatment received in the RUBATO DB study.	DB-Placebo DB-Macitentan 10 mg OL Macitentan 10 mg (All OLES participants)
RUBATO pool (Full Analysis Set [FAS] and SS)	Pool of all RUBATO DB and RUBATO OL data. Data from the same participants randomized in DB were concatenated with their data from the OL extension study. Baseline was defined relative to first intake of study medication in the RUBATO DB study, as defined in the RUBATO DB study Statistical Analysis Plan. Treatment arms for FAS followed the treatment arm assignment from RUBATO DB FAS analyses, ie, treatment as randomized. Treatment arms for SS followed the treatment arm assignment from RUBATO DB SS analyses, ie, were based on actual treatment received in the RUBATO DB study.	Placebo/Macitentan 10 mg (Plc/Maci) Macitentan 10 mg /Macitentan 10 mg (Maci/Maci)
RUBATO Total Macitentan Analysis Set (TMAS) (SS)	Only participants receiving at least 1 dose of macitentan (either in RUBATO DB or RUBATO OL) were included. Only participants from the macitentan arm in the RUBATO DB SS analyses were considered to have received macitentan in the RUBATO DB, their data were concatenated with their data from the OL extension. For participants from the DB study SS placebo arm, only data with assessment dates during the OL period were considered, with the exception of baseline data (including demographic data, medical and disease history data, prior medication) which could origin from the DB period. Baseline was defined relative to first intake of macitentan study treatment (either in RUBATO DB or RUBATO OL).	Macitentan 10 mg Pool

Results

Participant flow

In this OL extension study (Study Period: 03 May 2019 [first participant first visit] to 18 January 2022 [last participant last visit]), 111 participants from de RUBATO DB study (54 participants from the placebo group [hereafter, DB-placebo] and 57 participants from the macitentan group [hereafter, DB-macitentan]) were enrolled and received macitentan 10 mg once daily. Of these, 110 (99.1%) participants prematurely discontinued study intervention (Table 2) and study (Table 3).

The main reason for premature study intervention discontinuation and study discontinuation was sponsor's decision to terminate the OL study because the main DB study did not meet the primary and secondary efficacy endpoints (93/111 [83.8%] participants). Other reasons included death (1 participant in the DB-placebo group) and COVID-19 related other non-medical reasons (1 participant in the in the DB-macitentan group).

Table 2: Treatment Disposition; RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Completed study treatment[a]	1 (1.9%)	0	1 (0.9%)	6 (4.9%)
Terminated treatment prematurely	53 (98.1%)	57 (100%)	110 (99.1%)	116 (95.1%)
Reason for termination				
Death	1 (1.9%)	0	1 (0.9%)	1 (0.8%)
Lost to Follow-up	1 (1.9%)	1 (1.8%)	2 (1.8%)	2 (1.6%)
AE ^	1 (1.9%)	0	1 (0.9%)	4 (3.3%)
Lack of efficacy ^	0	0	0	0
Other	50 (92.6%)	56 (98.2%)	106 (95.5%)	109 (89.3%)
Other medical reasons ^	0	1 (1.8%)	1 (0.9%)	2 (1.6%)
COVID-19 related	0	0	0	0
Other non medical reasons ^	2 (3.7%)	9 (15.8%)	11 (9.9%)	13 (10.7%)
COVID-19 related	0	1 (1.8%)	1 (0.9%)	2 (1.6%)
Sponsor decision	48 (88.9%)	46 (80.7%)	94 (84.7%)	94 (77.0%)
Study termination	48 (88.9%)	45 (78.9%)	93 (83.8%)	93 (76.2%)
Other	0	1 (1.8%)	1 (0.9%)	1 (0.8%)
No reason provided	0	0	0	0

Key: AE = Adverse event; COVID-19=Coronavirus Disease-2019; DB=double-blind; OL=open-label; S-FU=safety follow-up

^ This combines reports of subject and physician decision.

[a] Per protocol amendment 3 (protocol version 4), RUBATO OL was planned to continue for each subject until the last subject globally completed 104 weeks (2 years) of treatment. Subjects who enrolled into RUBATO OL (ie, were treated with OL treatment) and who did not consent to protocol version 4, but completed 104 weeks of OL treatment and the corresponding S-FU period under protocol version 3, were considered treatment and study completers in the OL period.

For subjects in Open Label Extension Set, disposition corresponds to disposition in OL study.

For subjects in the Total Macitentan Analysis Set, disposition corresponds to disposition in DB study for subjects not enrolled to OL, and to OL study disposition for subjects enrolled into OL study.

All subjects received Macitentan 10 mg in the Open Label (OL) study.

Cross-reference: Modified from Attachment TSIDS03

Table 3: Study Disposition; RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Completed the study participation[a]	1 (1.9%)	0	1 (0.9%)	8 (6.6%)
Terminated study participation prematurely	53 (98.1%)	57 (100%)	110 (99.1%)	114 (93.4%)
Reason for termination				
Death	1 (1.9%)	0	1 (0.9%)	1 (0.8%)
Lost to Follow-up	1 (1.9%)	1 (1.8%)	2 (1.8%)	2 (1.6%)
AE ^	1 (1.9%)	0	1 (0.9%)	3 (2.5%)
Lack of efficacy ^	0	2 (3.5%)	2 (1.8%)	2 (1.6%)
Other	50 (92.6%)	54 (94.7%)	104 (93.7%)	106 (86.9%)
Other medical reasons ^	0	0	0	0
COVID-19 related	0	0	0	0
Other non medical reasons ^	2 (3.7%)	8 (14.0%)	10 (9.0%)	12 (9.8%)
COVID-19 related	0	1 (1.8%)	1 (0.9%)	2 (1.6%)
Sponsor decision	48 (88.9%)	46 (80.7%)	94 (84.7%)	94 (77.0%)
Study termination	48 (88.9%)	45 (78.9%)	93 (83.8%)	93 (76.2%)
Other	0	1 (1.8%)	1 (0.9%)	1 (0.8%)
No reason provided	0	0	0	0

Key: AE=adverse event; COVID-19=Coronavirus Disease-2019; DB=double-blind; OL=open-label
^ This combines reports of subject and physician decision.
[a] Per protocol amendment 3 (protocol version 4), RUBATO OL was planned to continue for each subject until the last subject globally completed 104 weeks (2 years) of treatment. Subjects who enrolled into RUBATO OL (ie, were treated with OL treatment) and who did not consent to protocol version 4, but completed 104 weeks of OL treatment and the corresponding S-FU period under protocol version 3, were considered treatment and study completers in the OL period.
For subjects in Open Label Extension Set, disposition corresponds to disposition in OL study.
For subjects in the Total Macitentan Analysis Set, disposition corresponds to disposition in DB study for subjects not enrolled to OL, and to OL study disposition for subjects enrolled into OL study.
All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Modified from Attachment TSIDS01

Study and study intervention disposition in paediatric patients (12 to <18 years) in the RUBATO OL Extension and Total Macitentan Analysis Sets are provided in Table 4 and Table 5, respectively.

Table 4: Study Disposition in paediatric patients (adolescents); RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Age: 12 - < 18	6	6	12	14
Completed the study participation	0	0	0	1 (7.1%)
Terminated study participation prematurely	6 (100.0%)	6 (100.0%)	12 (100.0%)	13 (92.9%)
Reason for termination				
Death	0	0	0	0
Lost to Follow-up	0	0	0	0
AE ^	0	0	0	0
Lack of efficacy ^	0	1 (16.7%)	1 (8.3%)	1 (7.1%)
Other	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Other medical reasons ^	0	0	0	0
COVID-19 related	0	0	0	0
Other non medical reasons ^	0	0	0	0
COVID-19 related	0	0	0	0
Sponsor decision	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Study termination	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Other	0	0	0	0
No reason provided	0	0	0	0

Key: AE = Adverse event.
^ This combines reports of subject and physician decision.
For subjects in Open Label Extension Set, disposition corresponds to disposition in OL study.

For subjects in the Total Macitentan Analysis Set, disposition corresponds to disposition in DB study for subjects not enrolled to OL, and to OL study disposition for subjects enrolled into OL study.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

Table 5: Treatment Disposition in paediatric patients (adolescents); RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Age: 12 - < 18	6	6	12	14
Completed study treatment	0	0	0	1 (7.1%)
Terminated treatment prematurely	6 (100.0%)	6 (100.0%)	12 (100.0%)	13 (92.9%)
Reason for termination				
Death	0	0	0	0
Lost to Follow-up	0	0	0	0
AE ^	0	0	0	0
Lack of efficacy ^	0	0	0	0
Other	6 (100.0%)	6 (100.0%)	12 (100.0%)	13 (92.9%)
Other medical reasons ^	0	1 (16.7%)	1 (8.3%)	1 (7.1%)
COVID-19 related	0	0	0	0
Other non medical reasons ^	0	0	0	0
COVID-19 related	0	0	0	0
Sponsor decision	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Study termination	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Other	0	0	0	0
No reason provided	0	0	0	0

Key: AE = Adverse event.
^ This combines reports of subject and physician decision.
For subjects in Open Label Extension Set, disposition corresponds to disposition in OL study.
For subjects in the Total Macitentan Analysis Set, disposition corresponds to disposition in DB study for subjects not enrolled to OL, and to OL study disposition for subjects enrolled into OL study.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

Recruitment

A total of 111 participants, who had previously completed Week 52 of the RUBATO DB study and met the inclusion/exclusion criteria for OL study, were enrolled in Australia, Canada , China, Czechia, Denmark, France, New Zealand, Poland, Taiwan, United Kingdom of Great Britain and Northern Ireland and the United States.

Of the 111 participants enrolled, 10.8% of participants were adolescents (12 to <18 years).

Baseline data

Demographic Characteristics

In the RUBATO OL Extension Set, the majority of participants were white (87/111; 78.4%) and male (77/111; 69.4%). The median age at OL study start was 23.0 years (range 13 to 49 years). Of the 111 participants enrolled, 10.8% of participants (12/111) were adolescents (12 to <18 years). The median body mass index at OL study start was 22.90 kg/m2 (range: 15.6 to 35.7 kg/m2). Most participants were enrolled at sites in Europe (59.5%) and by region most participants were non-United States based (83.8%) (Table 6).

Table 6: Summary of Demographic Characteristics; RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Age, years				
N	54	57	111	122
Mean (SD)	26.0 (7.93)	24.3 (6.03)	25.1 (7.04)	24.4 (6.94)
Median	24.5	23.0	23.0	23.0
Range	(13; 49)	(13; 37)	(13; 49)	(12; 49)
IQ Range	(21.0; 29.0)	(20.0; 28.0)	(21.0; 29.0)	(20.0; 28.0)
12 - < 18	6 (11.1%)	6 (10.5%)	12 (10.8%)	14 (11.5%)
18 - < 30	36 (66.7%)	39 (68.4%)	75 (67.6%)	85 (69.7%)
30 - < 40	8 (14.8%)	12 (21.1%)	20 (18.0%)	19 (15.6%)
40 - < 65	4 (7.4%)	0	4 (3.6%)	4 (3.3%)
>= 65	0	0	0	0
Sex				
N	54	57	111	122
Female	16 (29.6%)	18 (31.6%)	34 (30.6%)	39 (32.0%)
Male	38 (70.4%)	39 (68.4%)	77 (69.4%)	83 (68.0%)
Race				
N	54	57	111	122
Asian	8 (14.8%)	5 (8.8%)	13 (11.7%)	14 (11.5%)
White	41 (75.9%)	46 (80.7%)	87 (78.4%)	96 (78.7%)
Other	5 (9.3%)	6 (10.5%)	11 (9.9%)	12 (9.8%)
Ethnicity				
N	50	54	104	114
Hispanic or Latino	1 (2.0%)	2 (3.7%)	3 (2.9%)	3 (2.6%)
Not Hispanic or Latino	46 (92.0%)	50 (92.6%)	96 (92.3%)	104 (91.2%)
Unknown	3 (6.0%)	2 (3.7%)	5 (4.8%)	7 (6.1%)
Geographical region[a]				
N	54	57	111	122
America	8 (14.8%)	14 (24.6%)	22 (19.8%)	22 (18.0%)
Europe	35 (64.8%)	31 (54.4%)	66 (59.5%)	75 (61.5%)
Asia	6 (11.1%)	5 (8.8%)	11 (9.9%)	11 (9.0%)
Oceania	5 (9.3%)	7 (12.3%)	12 (10.8%)	14 (11.5%)
Region				
N	54	57	111	122
US	7 (13.0%)	11 (19.3%)	18 (16.2%)	18 (14.8%)
Non-US	47 (87.0%)	46 (80.7%)	93 (83.8%)	104 (85.2%)
Body mass index, kg/m^2 [b]				
N	54	57	111	122
Mean (SD)	24.15 (5.148)	23.47 (3.999)	23.80 (4.586)	23.71 (4.636)
Median	23.15	22.90	22.90	22.65
Range	(15.6; 35.7)	(15.6; 33.7)	(15.6; 35.7)	(15.4; 37.0)
IQ Range	(20.40; 27.20)	(20.90; 25.40)	(20.70; 26.10)	(20.50; 26.30)
Underweight	5 (9.3%)	2 (3.5%)	7 (6.3%)	8 (6.6%)
Normal	31 (57.4%)	38 (66.7%)	69 (62.2%)	73 (59.8%)
Overweight	10 (18.5%)	12 (21.1%)	22 (19.8%)	28 (23.0%)
Obese class I	6 (11.1%)	5 (8.8%)	11 (9.9%)	10 (8.2%)
Obese class II	2 (3.7%)	0	2 (1.8%)	3 (2.5%)
Obese class III	0	0	0	0

Key: DB=double-blind; BMI=body mass index; IQ=Interquartile; OL=open-label; SD=standard deviation.
Note: N's for each parameter reflect non-missing values.
[a] Each market is assigned to a geographical region based on the Standard Country or Area Codes for Statistical Use (M49).
[b] For adults, BMI cutoffs defined as: underweight (<18.5), normal weight (18.5-<25), overweight (25-<30), obese class I (30-<35), obese class II (35-<40), obese class III (>=40). For adolescents, BMI-for-age cutoffs equivalent to BMI cutoffs for adults are calculated from the WHO Child Growth Standards (2007).
Age and BMI are derived from analysis set baseline. Other parameters were assessed at enrollment into DB study.
All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Modified from Attachment TSIDEM01

A summary of demographic characteristics in paediatric patients (12 to <18 years) in the RUBATO OL Extension and Total Macitentan Analysis Sets is provided in Table 7.

Table 7: Summary of Demographic Characteristics in paediatric patients (adolescents); RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Age: 12 - < 18	6	6	12	14
Age, years				
N	6	6	12	14
Mean (SD)	15.5 (1.52)	14.8 (1.60)	15.2 (1.53)	14.9 (1.86)
Median	15.5	15.0	15.0	15.0
Range	(13; 17)	(13; 17)	(13; 17)	(12; 17)
IQ Range	(15.0; 17.0)	(13.0; 16.0)	(14.0; 16.5)	(13.0; 17.0)
Sex				
N	6	6	12	14
Female	2 (33.3%)	2 (33.3%)	4 (33.3%)	5 (35.7%)
Male	4 (66.7%)	4 (66.7%)	8 (66.7%)	9 (64.3%)
Race				
N	6	6	12	14
Asian	2 (33.3%)	3 (50.0%)	5 (41.7%)	5 (35.7%)
White	4 (66.7%)	3 (50.0%)	7 (58.3%)	9 (64.3%)
Ethnicity				
N	6	6	12	14
Not Hispanic or Latino	5 (83.3%)	6 (100.0%)	11 (91.7%)	13 (92.9%)
Unknown	1 (16.7%)	0	1 (8.3%)	1 (7.1%)
Geographical region[a]				
N	6	6	12	14
America	0	1 (16.7%)	1 (8.3%)	2 (14.3%)
Europe	2 (33.3%)	1 (16.7%)	3 (25.0%)	4 (28.6%)
Asia	2 (33.3%)	3 (50.0%)	5 (41.7%)	5 (35.7%)
Oceania	2 (33.3%)	1 (16.7%)	3 (25.0%)	3 (21.4%)
Region				
N	6	6	12	14
US	0	1 (16.7%)	1 (8.3%)	2 (14.3%)
Non-US	6 (100.0%)	5 (83.3%)	11 (91.7%)	12 (85.7%)
Weight, kg				
N	6	6	12	14
Mean (SD)	59.47 (16.405)	58.98 (16.264)	59.23 (15.577)	60.93 (20.110)
Median	60.50	52.05	56.35	57.10
Range	(42.8; 87.4)	(46.0; 88.0)	(42.8; 88.0)	(40.0; 110.8)
IQ Range	(43.00; 62.60)	(47.70; 68.10)	(46.85; 65.35)	(43.00; 73.80)
Height, cm				
N	6	6	12	14
Mean (SD)	165.12 (8.287)	163.58 (3.878)	164.35 (6.221)	161.88 (7.512)
Median	164.35	163.25	164.10	161.80
Range	(152.0; 174.0)	(160.0; 170.0)	(152.0; 174.0)	(152.0; 174.0)
IQ Range	(162.00; 174.00)	(160.00; 165.00)	(160.75; 167.75)	(157.00; 165.50)
Body mass index, kg/m^2 [b]				
N	6	6	12	14
Mean (SD)	21.82 (6.018)	21.92 (5.231)	21.87 (5.376)	23.04 (6.484)
Median	20.00	19.75	20.00	21.00
Range	(15.6; 32.8)	(17.5; 30.4)	(15.6; 32.8)	(15.6; 37.0)
IQ Range	(18.60; 23.90)	(18.00; 26.10)	(18.25; 25.00)	(18.10; 28.30)
Underweight	1 (16.7%)	0	1 (8.3%)	1 (7.1%)
Normal	4 (66.7%)	4 (66.7%)	8 (66.7%)	8 (57.1%)
Overweight	0	1 (16.7%)	1 (8.3%)	2 (14.3%)
Obese class I	1 (16.7%)	1 (16.7%)	2 (16.7%)	2 (14.3%)
Obese class II	0	0	0	1 (7.1%)
Obese class III	0	0	0	0

Key: BMI = Body mass index, IQ = Interquartile, SD = Standard deviation
Note: N's for each parameter reflect non-missing values.
a Each market is assigned to a geographical region based on the Standard Country or Area Codes for Statistical Use (M49).
b For adults, BMI cutoffs defined as: underweight (<18.5), normal weight (18.5-<25), overweight (25-<30), obese class I (30-<35), obese class II (35-<40), obese class III (>=40). For adolescents, BMI-for-age cutoffs equivalent to BMI cutoffs foradults are calculated from the WHO Child Growth Standards (2007).

Age, body weight, height, and BMI, are derived from analysis set baseline. Other parameters were assessed at enrollment into DB study.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

Other Baseline Characteristics

At OL study start, only 2/111 participants (1.8%) were receiving any pulmonary arterial hypertension specific concomitant therapies (*i.e.*, sildenafil citrate/sildenafil). At OL baseline, the majority of participants were in NYHA Class II (100/111 [90.1%]). The median (IQ range) peak VO2 at OL baseline was 22.90 (19.00, 27.00) mL/kg/min. The mean (SD) count per minute of daily PA-Ac at OL baseline was 262.95 (124.244) in the DB-placebo group (n=35) and 296.47 (123.433) in the DB-macitentan group (n=38).

At OL study start, the median (IQ range) time since Fontan-palliation completion was 19.46 (15.00; 23.32) years and 69/111 participants (62.2%) had lateral tunnel total cavopulmonary connection. A higher proportion of participants had an associated dominant left ventricular morphology (55.9% [62/111 participants]) compared with right/mixed morphology (44.1% [49/111 participants]).

A summary of baseline characteristics in paediatric patients (12 to <18 years) in the RUBATO OL Extension and Total Macitentan Analysis Sets is provided in Table 8.

Table 8: Summary of Baseline Characteristics in paediatric patients (adolescents); RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	54	57	111	122
Age: 12 - < 18	6	6	12	14
PAH specific therapies concomitant at start of study treatment in analysis set [a]				
N	6	6	12	14
No	6 (100.0%)	6 (100.0%)	12 (100.0%)	14 (100.0%)
Yes	0	0	0	0
Sildenafil	0	0	0	0
Sildenafil Citrate	0	0	0	0
NYHA FC at analysis set baseline				
N	6	6	12	14
Class I	0	1 (16.7%)	1 (8.3%)	0
Class II	6 (100.0%)	5 (83.3%)	11 (91.7%)	14 (100.0%)
Class III	0	0	0	0
Class IV	0	0	0	0
Peak VO_2 (mL/kg/min) at analysis set baseline				
N	6	6	12	14
Mean (SD)	23.83 (5.638)	25.48 (9.490)	24.66 (7.492)	23.78 (6.433)
Median	24.20	24.50	24.20	20.65
Range	(17.5; 29.2)	(14.9; 39.3)	(14.9; 39.3)	(15.7; 36.5)
IQ range	(18.90; 29.00)	(18.20; 31.50)	(18.55; 29.50)	(18.90; 29.20)
VO_2 at VAT at analysis set baseline				
N	6	6	12	13
Mean (SD)	15.98 (3.706)	18.02 (7.600)	17.00 (5.799)	16.62 (4.639)
Median	15.35	18.35	15.60	17.20
Range	(12.4; 21.7)	(9.6; 27.5)	(9.6; 27.5)	(10.1; 24.8)
IQ range	(12.80; 18.30)	(10.50; 23.80)	(12.60; 22.20)	(12.80; 20.50)
Mean count per minute of daily PA-Ac at analysis set baseline				
N	4	6	10	11
Mean (SD)	288.69 (63.986)	305.35 (146.667)	298.69 (115.712)	332.58 (112.906)
Median	282.59	299.96	282.59	330.72
Range	(227.4; 362.2)	(152.5; 492.8)	(152.5; 492.8)	(157.3; 546.7)
IQ range	(235.46; 341.92)	(167.69; 419.25)	(207.53; 392.38)	(243.49; 362.16)
NT-proBNP (pmol/L) at analysis set baseline				
N	6	6	12	14
Mean (SD)	10.72 (5.394)	10.81 (3.352)	10.76 (4.282)	20.12 (32.450)
Median	8.78	11.06	10.58	10.00
Range	(6.0; 17.9)	(6.0; 15.2)	(6.0; 17.9)	(6.0; 131.0)
IQ range	(6.00; 16.91)	(8.10; 13.41)	(6.69; 14.30)	(6.00; 17.72)

Key: IQ = Interquartile, NYHA FC = New York heart association functional class, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, PA-Ac = Physical activity measured by accelerometer, PAH = Pulmonary arterial hypertension, SD = Standard deviation, VO_2 = Oxygen uptake/consumption, VAT = Ventilatory anaerobic threshold.
Note: N's for each parameter reflect non-missing values.
[a] PAH specific medications are based on latest implemented WHO-DRUG dictionary version WHODrug Global B3 202103.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

Concomitant Medications

In the RUBATO OL Extension Set, 97.3% of participants (108/111) received at least 1 or more concomitant medications. The most frequently reported concomitant medication by Anatomical Therapeutic Chemical Class (≥25.0%) were platelet aggregation inhibitor excluding heparin (58.6%), other viral vaccines (41.4%), plain ACE inhibitors (28.8%), and vitamin K antagonists (27.9%). The most frequently reported concomitant medications (≥10.0%) by standardized medication name were acetylsalicylic acid (55.9%), tozinameran (34.2%), warfarin (17.1%), amoxicillin (14.4%), lisinopril (12.6%), furosemide (11.7%), and paracetamol (10.8%).

Number analysed

A total of 111 participants from the DB study (placebo group: 54, macitentan group: 57) were enrolled and received macitentan 10 mg in the OL study.

Populations Analyzed

The definitions of the analysis sets used in the OL extension study are described in Table 1.

The RUBATO Pool Full Analysis Set included all 137 participants who were randomized in the DB study, irrespective of their enrollment in the OL extension study (Table 9).

The RUBATO OL Extension Set included 111 participants from the DB study who enrolled in the OL extension study and received at least 1 dose of OL study treatment, i.e., macitentan 10 mg. The treatment group placebo/macitentan 10 mg corresponds to DB-placebo and macitentan 10 mg/macitentan 10 mg corresponds to DB-macitentan 10 mg (Table 9).

The Total Macitentan Analysis Set (Macitentan 10 mg pool) included 122 participants who received macitentan 10 mg in the DB study but did not enroll into the OL study (n=11), participants who received macitentan 10 mg in the DB as well as OL study (n=57), and participants who received macitentan 10 mg only in the OL study (n=54) (Table 9).

Table 9. Number of Subjects in Each Analysis Set; RUBATO Pool Full Analysis Set (Studies AC-055H301/AC-055H302)

	Placebo/ Macitentan 10 mg	Macitentan 10 mg/ Macitentan 10 mg	Total (in Analysis Set)
RUBATO pool (FAS)	69	68	137
RUBATO pool (SS)	69	68	137
RUBATO Open-label Extension Set (OLES)	54	57	111
RUBATO Total Macitentan Analysis Set (TMAS)	54	68	122

For OLES, treatment group Placebo/Macitentan 10 mg corresponds to DB-Placebo and Macitentan 10 mg/Macitentan 10 mg corresponds to DB-Macitentan 10 mg.
For TMAS, all subjects who received at least 1 dose of Macitentan 10 mg in the DB and/or OL study are included (Pool).
Column header is based on treatment randomized (received) during the DB/OL studies
All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Attachment TSIDEM03

Efficacy results

- Data Sets Analyzed

The exploratory efficacy variables were analyzed on the RUBATO Pool Full Analysis Set and RUBATO OL Extension Set (Table 9).

- Fontan-palliated Morbidity and Fontan-palliated Clinical Worsening

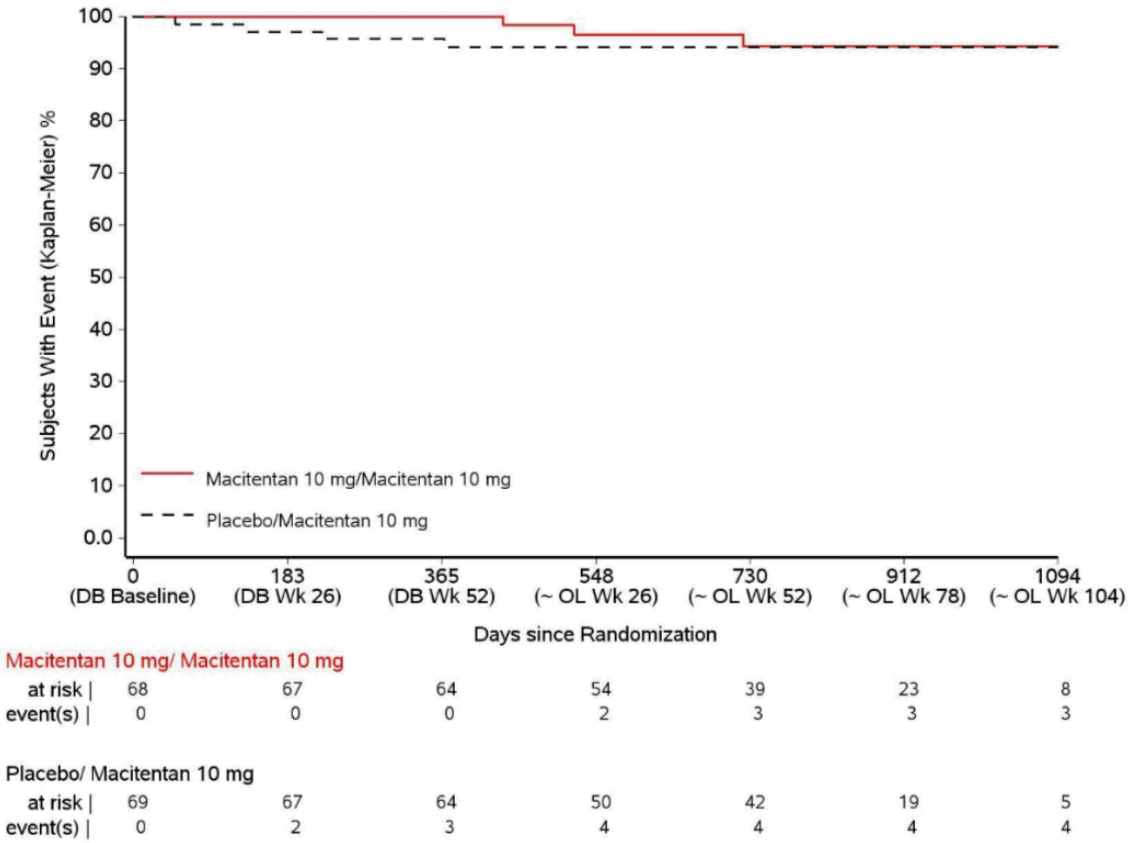
Time to event analyses were conducted in the RUBATO Pool Full Analysis Set over the combined DB + OL studies.

Five participants in the placebo/macitentan 10 mg group and 3 participants in the macitentan 10 mg/macitentan 10 mg group had clinical events related to Fontan-palliated morbidity.

Three participants in the placebo/macitentan 10 mg group and 6 participants in the macitentan 10 mg/macitentan 10 mg group had clinical events related to Fontan-palliated clinical worsening.

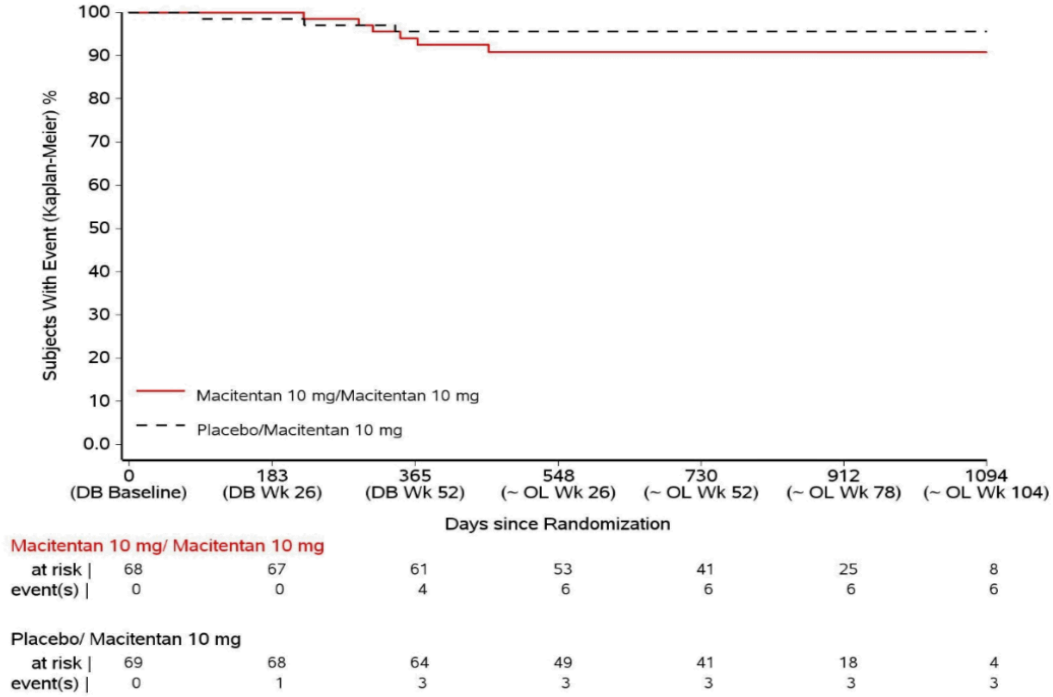
For both analyses, the Kaplan-Meier estimates were similar between the 2 groups (Figure 2 and Figure 3).

Figure 2: Kaplan-Meier Curves of Time to Clinical Events Related to Fontan palliated Morbidity; RUBATO Pool Full Analysis Set (Studies AC-055H301/AC-055H302)



All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Attachment GEFMOR01

Figure 3: Kaplan-Meier Curves of Time to Clinical Events Related to Fontan palliated Clinical Worsening; RUBATO Pool Full Analysis Set (Studies AC-055H301/AC-055H302)



All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Attachment GEFWOR01

The clinical study report (CSR) of study AC-055H302/RUBATO OL included a mix of adolescents and adults with no disaggregated efficacy results included by age subset.

- Physical Activity Measure by Accelerometer

In the RUBATO OL Extension Set, at OL baseline (n=73), the mean (SD) of mean count per minute of daily PA-Ac was 280.40 (124.110) (DB-placebo: 262.95 [124.244], DB-macitentan: 296.47 [123.433]). The mean (SD) change from OL baseline to OL Week 26 (n=42) was 19.74 (131.622) (DB-placebo: 24.19 [86.001], DB-macitentan: 15.70 [164.609]) and from OL baseline to OL Week 52 (n=20) was 44.58 (153.196) (DB-placebo: 97.51 [159.620], DB-macitentan: -8.36 [133.565]).

- Cardiopulmonary Exercise Testing - Change in Peak VO2 and VO2 at VAT

In the RUBATO OL Extension Set, at OL baseline (N=111), the mean (SD) peak VO2 was 23.33 (6.055) mL/kg/min (DB-placebo: 22.70 [5.923] mL/kg/min, DB-macitentan: 23.93 [6.170] mL/kg/min). The mean (SD) change from OL baseline to OL Week 52 (n=71) was -0.82 (2.724) mL/kg/min (DB-placebo: -0.69 [2.569] mL/kg/min, DB-macitentan: -0.93 [2.873] mL/kg/min).

At OL baseline (N=111), the mean (SD) VO2 at VAT was 14.60 (3.725) mL/kg/min (DB-placebo: 14.71 [3.547] mL/kg/min, DB-macitentan: 14.48 [3.914] mL/kg/min). The mean (SD) change from OL baseline to OL Week 52 (n=65) was -0.12 (2.643) mL/kg/min (DB-placebo: -0.45 [2.181] mL/kg/min, DB-macitentan: 0.16 [2.986] mL/kg/min).

Safety results

- Data Sets Analyzed

For the OL extension study, safety data were analyzed using the RUBATO OL Extension Set including 111 participants who enrolled in the OL study and received at least 1 dose of OL study intervention, *i.e.*, macitentan 10 mg.

To analyze safety data during the macitentan treatment-emergent period (DB+OL periods), safety endpoints were analyzed using Total Macitentan Analysis Set (macitentan 10 mg pool) which included 122 participants who received macitentan 10 mg in the DB study but did not enroll into the OL study (n=11), participants who received macitentan 10 mg in the DB as well as OL study (n=57), and participants who received macitentan 10 mg only in the OL study (n=54) (Table 9).

- Extent of Exposure

RUBATO OL Extension Set (N=111)

The median (IQ range) study intervention duration and total exposure to study intervention (with/without interruptions) was 53.86 (45.71 to 76.57/76.0) weeks.

Total Macitentan Analysis Set (N=122)

The median (IQ range) study intervention duration (regardless of interruption) and total exposure to study intervention (excluding interruptions) was 84.29 (52.14 to 110.86) weeks and 80.29 (52.14 to 107.29) weeks, respectively.

A summary of Study Treatment Exposure in paediatric patients (12 to <18 years) in the RUBATO OL Extension and Total Macitentan Analysis Sets are provided in Table 10.

Table 10: Summary of Study Treatment Exposure in paediatric patients (adolescents); RUBATO Pool Safety Set, RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Pool (Safety Analysis Set)		RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	Placebo/ Macitentan 10 mg[c]	Macitentan 10 mg/ Macitentan 10 mg	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	69	68	54	57	111	122
Age: 12 - < 18	10	8	6	6	12	14
Study treatment duration (weeks) [a]						
N	10	8	6	6	12	14
Mean (SD)	111.66 (40.066)	115.86 (29.758)	79.45 (30.468)	66.57 (15.632)	73.01 (24.047)	100.26 (34.401)
Median	105.14	128.07	79.36	69.36	70.29	105.00
Range	(53.1; 176.7)	(52.6; 143.0)	(45.7; 120.6)	(48.1; 90.9)	(45.7; 120.6)	(45.7; 143.0)
IQ Range	(91.00; 136.43)	(102.43; 135.14)	(46.43; 105.29)	(50.57; 71.14)	(49.36; 87.71)	(74.14; 130.71)
Study treatment duration (weeks) [a]						
< 24	0	0	0	0	0	0
24 - < 48	0	0	2 (33.3%)	0	2 (16.7%)	2 (14.3%)
48 - < 72	2 (20.0%)	1 (12.5%)	0	5 (83.3%)	5 (41.7%)	1 (7.1%)
72 - < 96	1 (10.0%)	0	2 (33.3%)	1 (16.7%)	3 (25.0%)	2 (14.3%)
96 - < 120	3 (30.0%)	2 (25.0%)	1 (16.7%)	0	1 (8.3%)	3 (21.4%)
120 - < 144	2 (20.0%)	5 (62.5%)	1 (16.7%)	0	1 (8.3%)	6 (42.9%)
>= 144	2 (20.0%)	0	0	0	0	0
Cumulative study treatment duration (weeks)[a]						
< 24	0	0	0	0	0	0
>= 24	10 (100.0%)	8 (100.0%)	6 (100.0%)	6 (100.0%)	12 (100.0%)	14 (100.0%)
>= 48	10 (100.0%)	8 (100.0%)	4 (66.7%)	6 (100.0%)	10 (83.3%)	12 (85.7%)
>= 72	8 (80.0%)	7 (87.5%)	4 (66.7%)	1 (16.7%)	5 (41.7%)	11 (78.6%)
>= 96	7 (70.0%)	7 (87.5%)	2 (33.3%)	0	2 (16.7%)	9 (64.3%)
>= 120	4 (40.0%)	5 (62.5%)	1 (16.7%)	0	1 (8.3%)	6 (42.9%)
>= 144	2 (20.0%)	0	0	0	0	0
Total exposure to treatment (weeks) [b]						
N	10	8	6	6	12	14
Mean (SD)	110.59 (39.760)	112.02 (28.173)	79.40 (30.478)	66.57 (15.632)	72.99 (24.046)	98.04 (32.637)
Median	103.29	118.00	79.21	69.36	70.29	103.86
Range	(53.1; 173.6)	(52.6; 143.0)	(45.7; 120.6)	(48.1; 90.9)	(45.7; 120.6)	(45.7; 143.0)
IQ Range	(87.43; 136.43)	(101.29; 131.00)	(46.43; 105.29)	(50.57; 71.14)	(49.36; 87.71)	(73.86; 122.29)
Number of treatment interruptions of >30 days						
0	10 (100.0%)	7 (87.5%)	6 (100.0%)	6 (100.0%)	12 (100.0%)	13 (92.9%)
1	0	1 (12.5%)	0	0	0	1 (7.1%)

Key: SD = Standard deviation, IQ = Interquartile
[a] Study treatment duration (weeks) is defined as [(treatment end date - treatment start date + 1)/7], regardless of treatment interruptions.
[b] Total exposure to treatment (weeks) is defined as the [study treatment duration (days) - the sum of all treatment interruptions (days)]/7.
[c] In the treatment arm, overall study treatment in the analysis set, i.e. comprising placebo and macitentan 10 mg is summarized.
Gaps between DB EOT and OL treatment start date are considered as interruption
All subjects received Macitentan 10 mg in the Open Label (OL) study.

- *Adverse Events*

RUBATO OL Extension Set (N=111)

The proportion of participants with at least 1 treatment-emergent AE was 61.3% (68 participants; DB-placebo: 36/54 [66.7%], DB-macitentan: 32/57 [56.1%]).

The most frequently reported treatment-emergent AEs (≥5% all participants) were COVID-19 (14 [12.6%] participants; DB-placebo: 6/54 [11.1%], DB-macitentan: 8/57 [14.0%]), headache (8 [7.2%] participants; DB-placebo: 4/54 [7.4%], DB-macitentan: 4/57 [7.0%]), fatigue (7 [6.3%] participants; DB-placebo: 3/54 [5.6%], DB-macitentan: 4/57 [7.0%], and palpitations (7 [6.3%] participants; DB-placebo: 2/54 [3.7%], DB-macitentan: 5/57 [8.8%]).

An overview of treatment-emergent AEs during the OL extension study (RUBATO OL Extension Set) and macitentan treatment-emergent period (Total Macitentan Analysis Set) is provided in Table 11.

Total Macitentan Analysis Set (N=122)

The proportion of participants with at least 1 treatment-emergent AE during the macitentan treatment-emergent period was 75.4% (92/122 participants).

The most frequently reported treatment-emergent AEs (≥5%) were COVID-19 (17/122 [13.9%]), headache (13/122 participants [10.7%]), fatigue (9/122 participants [7.4%]), dyspnea (8/122 participants [6.6%]), palpitations and pyrexia (7/122 participants [5.7%] each).

An overview of treatment-emergent AEs during the OL extension study (RUBATO OL Extension Set) and macitentan treatment-emergent period (Total Macitentan Analysis Set) is provided in Table 11.

Table 11. Overall Summary of Treatment-emergent Adverse Events; RUBATO Pool Safety Set, RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Pool (Safety Set)	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	Macitentan 10 mg / Macitentan 10 mg	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	68	54	57	111	122
Subjects with 1 or more:					
AEs	56 (82.4%)	36 (66.7%)	32 (56.1%)	68 (61.3%)	92 (75.4%)
Severe AEs[a]	9 (13.2%)	4 (7.4%)	2 (3.5%)	6 (5.4%)	13 (10.7%)
Related AEs[b]	15 (22.1%)	8 (14.8%)	6 (10.5%)	14 (12.6%)	23 (18.9%)
AEs leading to death[c]	0	1 (1.9%)	0	1 (0.9%)	1 (0.8%)
Serious AEs[d]	19 (27.9%)	10 (18.5%)	8 (14.0%)	18 (16.2%)	29 (23.8%)
Related serious AEs	1 (1.5%)	1 (1.9%)	0	1 (0.9%)	2 (1.6%)
AEs leading to discontinuation of study treatment	3 (4.4%)	2 (3.7%)	0	2 (1.8%)	5 (4.1%)
Incidence rate adjusted by observation time					
Serious AEs[d]					
Subject-Years of Observation[e]	117.5	59.2	59.6	118.8	176.7
Incidence Rate per 100 subject-years of observation[f]	16.2	16.9	13.4	15.2	16.4
AEs leading to discontinuation of study treatment					
Subject-Years of Observation[e]	138.9	64.5	67.5	132.0	203.3
Incidence Rate per 100 subject-years of observation[f]	2.2	3.1	0.0	1.5	2.5

Key: AE=adverse event; DB=double-blind; OL=open-label
[a] If the intensity is missing, the event is considered severe.
[b] An AE is categorized as related if assessed by the investigator as related to study treatment or in case the relationship is missing.
[c] AEs leading to death are based on AE outcome of Fatal.
[d] An AE is categorized as serious as assessed by the investigator or in case the information of seriousness is missing.
[e] Subject-years of observation is calculated as (sum of subject-observation time for all subjects / 365.25 days). For each subject, the subject-observation time is calculated by considering the study treatment duration for subjects without event or by considering the study treatment duration up to the date of first event (or up to the study treatment end date, if earlier) for subjects with event.
[f] Adjusted incidence rate is calculated as 100 * (number of subjects with at least one treatment-emergent event/subject-years of observation).
All subjects received Macitentan 10 mg in the Open Label (OL) study.
Cross-reference: Attachment TSFAE01

A summary of Treatment-emergent Adverse Events in paediatric patients (12 to <18 years) group in the RUBATO OL Extension and Total Macitentan Analysis Sets are provided in Table 12.

Table 12: Overall Summary of Treatment-emergent Adverse Events in paediatric patients (adolescents); RUBATO Pool Safety Set, RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-55H301/AC-055H302)

	RUBATO Pool (Safety Set)	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	Macitentan 10 mg / Macitentan 10 mg	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	68	54	57	111	122
Age: 12 - < 18	8	6	6	12	14
Subjects with 1 or more:					
AEs	6 (75.0%)	5 (83.3%)	3 (50.0%)	8 (66.7%)	11 (78.6%)
Severe AEs[a]	2 (25.0%)	0	2 (33.3%)	2 (16.7%)	2 (14.3%)
Related AEs[b]	2 (25.0%)	1 (16.7%)	0	1 (8.3%)	3 (21.4%)
AEs leading to death[c]	0	0	0	0	0
Serious AEs[d]	2 (25.0%)	1 (16.7%)	2 (33.3%)	3 (25.0%)	3 (21.4%)
Related serious AEs	0	0	0	0	0
AEs leading to discontinuation of study treatment	0	0	0	0	0
Incidence rate adjusted by observation time					
Serious AEs[d]					
Subject-Years of Observation[e]	16.4	9.1	6.6	15.7	25.5
Incidence Rate per 100 subject-years of observation[f]	12.2	10.9	30.5	19.1	11.7
AEs leading to discontinuation of study treatment					
Subject-Years of Observation[e]	17.8	9.1	7.7	16.8	26.9
Incidence Rate per 100 subject-years of observation[f]	0.0	0.0	0.0	0.0	0.0

Key: AE = Adverse event
a If the intensity is missing, the event is considered severe.
b An AE is categorized as related if assessed by the investigator as related to study treatment or in case the relationship is missing.
c AEs leading to death are based on AE outcome of Fatal.
d An AE is categorized as serious as assessed by the investigator or in case the information of seriouness is missing.
e Subject-years of observation is calculated as (sum of subject-observation time for all subjects / 365.25 days). For each subject, the subject-observation time is calculated by considering the study treatment duration for subjects without event or by considering the study treatment duration up to the date of first event (or up to the study treatment end date, if earlier) for subjects with event.
f Adjusted incidence rate is calculated as 100 * (number of subjects with at least one treatment-emergent event/subject-years of observation).
All subjects received Macitentan 10 mg in the Open Label (OL) study.

- *Deaths and Adverse Events with Fatal Outcome*

RUBATO OL Extension Set (N=111)

One adult participant (DB-placebo) died due to an "unknown" cause.

Total Macitentan Analysis Set (N=122)

One adult participant died due to an unknown cause during the OL study.

- *Serious Adverse Events*

RUBATO OL Extension Set (N=111)

The proportion of participants who had at least 1 treatment-emergent SAE was 16.2% (18 participants; DB-placebo: 10/54 [18.5%], DB-macitentan: 8/57 [14.0%]). One participant had an SAE of decreased sperm concentration during the OL study. The participant had a medical history of fertility disorders.

One participant (DB-placebo group) had an SAE of COVID-19.

No treatment-emergent SAEs were reported in more than 1 participant.

Total Macitentan Analysis Set (N=122)

The proportion of participants with at least 1 treatment-emergent SAE was 23.8% (29 participants). Atrial flutter was reported in 2 participants and all other SAEs were reported 1 participant each.

One participant had an SAE of COVID-19.

- *Discontinuations Due to Adverse Events*

RUBATO OL Extension Set (N=111)

Adverse events leading to discontinuation of study interventionwere reported in 2 (1.8%) participants in the DB-placebo group and these were death and decreased spermatozoa progressive motility.

No COVID-19 related AEs led to study intervention discontinuation.

Total Macitentan Analysis Set (N=122)

Adverse events leading to discontinuation of study intervention were reported in 5 (4.1%) participants.

These were increased AST (1 participant), increased ALT and AST (1 participant), and changes in mental status (1 participant), during the DB study. The OL study AEs leading to study intervention discontinuation were death and decreased spermatozoa progressive motility.

No COVID-19 related AEs led to study intervention discontinuation.

- *Adverse Events of Special Interest*

RUBATO OL Extension Set (N=111)

Five (4.5%) participants had at least 1 Hepatic adverse events of special interest (AESI) (DB-placebo: 4/54 participants [7.4%], DB-macitentan: 1/57 participant [1.8%]), corresponding to an incidence rate of 4.0/100 participant-years (PY) of observation. Two (1.8%) participants (both DB-placebo) had serious Hepatic AESI (hepatic mass and hepatocellular carcinoma). No Hepatic AESI led to discontinuation of study intervention. A treatment-emergent increase in aspartate aminotransferase (AST) ≥3 x upper limit of normal (ULN) (HH) was reported in 1 (0.9%) participant and bilirubin ≥2 x ULN (HH) was reported in 1 (0.9%) participant.

Two (1.8%) participants (1 in each group) had at least 1 Edema and fluid retention AESI (preferred term: peripheral edema), corresponding to an incidence rate of 1.5/100 PY of observation.

One (0.9%) participant (DB-macitentan) had an Anemia/hemoglobin decrease AESI (preferred term: microcytic anemia) corresponding to an incidence rate of 0.8/100 PY of observation.

Two (1.8%) participants (DB-placebo) had at least 1 Hypotension AESI (preferred term: decreased blood pressure) corresponding to an incidence rate of 1.5/100 PY of observation. None of these events were reported as serious or led to discontinuation of the study intervention.

Total Macitentan Analysis Set (N=122)

Ten (8.2%) participants had at least 1 Hepatic AESI corresponding to an incidence rate of 5.1/100 PY of observation. By preferred term, these included increased alanine aminotransferase (ALT) (3 participants), increased AST, and increased transaminase (2 participants each). Three (2.5%)

participants had serious Hepatic AESI (increased ALT and increased AST; hepatic mass; and hepatocellular carcinoma) and 2 (1.6%) participants had Hepatic AESI which led to discontinuation of study intervention (increased ALT and AST; increased AST). Treatment-emergent increases in AST ≥3 x ULN (HH) were reported in 2 (1.7%) participants, ALT ≥3 x ULN (HH) were reported in 3 (2.5%) participants, and bilirubin ≥2 x ULN (HH) were reported in 3 (2.5%) participants. No participant had ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN (at the same sample date and/or at any post-baseline time point up to 30 days after EOT).

Seven (5.7%) participants had at least 1 Edema and fluid retention AESI corresponding to an incidence rate of 3.6/100 PY of observation. The most frequent AESI was peripheral edema (4 participants). One (0.8%) participant had a serious Edema and fluid retention AESI (preferred term: pleural effusion). No participant discontinued study intervention due to Edema and fluid retention AESI.

One (0.8%) participant had an Anemia/hemoglobin decrease AESI (preferred term: microcytic anemia) corresponding to an incidence rate of 0.5/100 PY of observation. No Anemia/hemoglobin decrease AESI were reported as serious or led to discontinuation of the study intervention.

Three (2.5%) participants had at least 1 Hypotension AESI corresponding to an incidence rate of 1.5/100 PY of observation. By preferred term, these were decreased blood pressure (2 participants) and orthostatic hypotension (1 participant). No Hypotension AESI were reported as serious or led to discontinuation of the study intervention.

The number of paediatric patients (12 to <18 years) with treatment-emergent adverse events of special interest - hepatic events in the RUBATO OL Extension and Total Macitentan Analysis Sets are provided in Table 13 and Table 14.

Table 13: Number of paediatric patients (adolescents) With Treatment-emergent Adverse Events of Special Interest - Hepatic Events by Preferred Term; RUBATO Pool Safety Set, RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Pool (Safety Analysis Set)	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	Macitentan 10 mg / Macitentan 10 mg	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	68	54	57	111	122
Hepatic adverse events of special interest					
Age: 12 - < 18	8	6	6	12	14
Subjects with 1 or more AESIs	2 (25.0%)	0	1 (16.7%)	1 (8.3%)	2 (14.3%)
Preferred term					
Alanine aminotransferase increased	1 (12.5%)	0	0	0	1 (7.1%)
Aspartate aminotransferase increased	0	0	0	0	0
Transaminases increased	0	0	0	0	0
Blood alkaline phosphatase increased	1 (12.5%)	0	1 (16.7%)	1 (8.3%)	1 (7.1%)
Hepatomegaly	0	0	0	0	0
Gamma-glutamyltransferase increased	0	0	0	0	0
Hepatic cirrhosis	0	0	0	0	0
Hepatic mass	0	0	0	0	0
Hepatocellular carcinoma	0	0	0	0	0

Key: AESI = Adverse event of special interest
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 24.0.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

Table 14: Number of paediatric patients (adolescents) With Treatment-emergent Adverse Events of Special Interest - Edema and Fluid Retention, by Preferred Term; RUBATO Pool Safety Set, RUBATO Open-label Extension Set and RUBATO Total Macitentan Analysis Set (Studies AC-055H301/AC-055H302)

	RUBATO Pool (Safety Analysis Set)	RUBATO Open Label Extension Set			Total Macitentan Analysis Set
	Macitentan 10 mg / Macitentan 10 mg	DB-Placebo	DB-Macitentan 10 mg	OL Macitentan 10 mg (All subjects)	Macitentan 10 mg (Pool)
Analysis set:	68	54	57	111	122
Edema and fluid retention					
Age: 12 - < 18	8	6	6	12	14
Subjects with 1 or more AESIs	1 (12.5%)	1 (16.7%)	0	1 (8.3%)	2 (14.3%)
Preferred term					
Oedema peripheral	0	1 (16.7%)	0	1 (8.3%)	1 (7.1%)
Pleural effusion	1 (12.5%)	0	0	0	1 (7.1%)
Joint swelling	0	0	0	0	0

Key: AESI = Adverse event of special interest
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 24.0.
All subjects received Macitentan 10 mg in the Open Label (OL) study.

- *Clinical Laboratory Evaluation*

RUBATO OL Extension Set (N=111)

A treatment-emergent hemoglobin decrease ≥80 g/L and <100 g/L was reported in 1 (0.9%) participant.

Treatment-emergent leukocyte decreases <3.0 x 10^9/L (LL) and <1.9 x 10^9/L (LLL) were observed in 10 (9.3%) participants and 2 (1.9%) participants, respectively. Treatment-emergent decreases in platelet <75 x 10^9/L were observed in 3 (2.8%) participants.

Total Macitentan Analysis Set (N=122)

A treatment-emergent hemoglobin decrease ≥80 g/L and <100 g/L was reported in 1 (0.8%) participant.

Treatment-emergent leukocyte decreases <3.0 x 10^9/L (LL) and <1.9 x 10^9/L (LLL) were observed in 14 (11.6%) participants and 2 (1.7%) participants, respectively. Treatment-emergent decreases in platelet <75 x 10^9/L were observed in 4 (3.3%) participants.

- *Other Safety Evaluations*

RUBATO OL Extension Set (N=111)

Three (2.7%) participants had systolic blood pressure abnormality (<90 mmHg for adults or <85 mmHg for adolescents who were <150 cm in height).

Total Macitentan Analysis Set (N=122)

Three (2.5%) participants had treatment-emergent systolic blood pressure abnormality (<90 mmHg for adults or <85 mmHg for adolescents who were <150 cm in height).

2.3.3. Discussion on clinical aspects

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 with 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".

This Article 46 procedure of Regulation (EC) No 1901/2006, concerns the submission of a stand-alone study, which is the AC-055H302 (RUBATO open-label [OL]) study named: "Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects".

AC-055H302/RUBATO OL study, was a Phase 3 extension of the already sumitted AC-055H301/RUBATO double-blind (DB) study (Procedure No EMEA/H/C/002697/P46/010.1) to assess the long-term use of macitentan 10 mg for up to 104 weeks (2 years) in Fontan-palliated participants beyond 52 weeks (1 year) of treatment in the RUBATO DB study. Adult and adolescent participants were rolled over from the DB study to this OL study to receive macitentan 10 mg without knowledge of their previous study treatment (macitentan 10 mg or placebo, randomized in a 1:1 ratio). Both DB and OL RUBATO studies are part of an agreed PIP for macitentan for the treatment of functional single ventricle heart disease with total cavo-pulmonary connection indication (EMEA-001032-PIP03-19 [Decision P/0242/2021]; PIP study 1 and PIP study 2, respectively). The primary objective of the hereby submitted study was to assess the long-term safety and tolerability whereas the secondary and other objectives were to assess efficacy endpoints in an exploratory manner. The efficacy exploratory endpoints were the effect of macitentan on exercise capacity (change in Peak VO2) and on daily Physical Activity measured by Accelerometer (PA-Ac) as well as the effect on endpoints related to clinical events (time to first occurrence of clinical worsening or morbidity) and on change in VO2 at ventilatory anaerobic threshold [VAT]). The study design as well as the proposed objectives seem adequate for an OL extension study to describe the long-term effects of macitentan 10 mg in a target population where there are no approved medications for treatment.

In this OL extension study (03 may 2019 [first participant first visit] to 18 January 2022 [last participant last visit]), 111 participants from de RUBATO DB study (54 participants from the placebo group [hereafter, DB-placebo group] and 57 participants from the macitentan group [hereafter, DB-macitentan group]) were enrolled and received macitentan 10 mg film-coated tablets administered orally once-daily. Of the 111 participants enrolled, 10.8% of participants (12/111; DB-placebo group: 6, DB-macitentan group: 6) were adolescents (12 to <18 years). All enrolled participants except 1 (110/111 [99.1%]) prematurely discontinued the study intervention as well as the study. The main reason for premature study intervention discontinuation and study discontinuation was sponsor's decision to terminate the OL study because the main DB study did not meet the primary and secondary efficacy endpoints (93/111 [83.8%] participants). With the exception of 1 adolescent participant (DB-macitentan) who terminated study participation prematurely because of lack of efficacy, 11/12 (91.7%) adolescent participants discontinued the study intervention and the study because of the sponsor's decision.

The majority of participants were white (87/111 [78.4%]) and male (77/111 [69.4%]). The median age at OL study start was 23.0 years (age range: 13 to 49 years). At OL study start, the median time since Fontan palliation completion was 19.46 years and 69/111 (62.2%) participants had lateral tunnel total cavopulmonary connection. A higher proportion of participants had an associated dominant left ventricular morphology (62/111 [55.9%]) compared with right/mixed morphology (49/111[44.1%]).

At OL baseline, the majority of adolescent participants were in NYHA Class II (11/12 [91.7%]; DB-macitentan group included the only subject in FC I) and the median (IQ range) peak VO2 at OL baseline was 24.20 (18.55, 29.50) mL/kg/min. The mean (SD) count per minute of daily PA-Ac at OL baseline was 288.69 (63.986) in the DB-placebo group (n=4) and 305.35 (146.667) in the DB-macitentan group (n=6). No adolescent patients were on PAH specific therapies at baseline. The applicant has not provided information for the OL study in adolescents with respect to baseline characteristics such as time since Fontan palliation completion, type of primary TCPC Fontan completion or associated dominant ventricular morphology. However, it has to be kept on mind that as it was stated in the EMEA/H/C/002697/P46/010.1 assessment report for the completed rubato DB study, differences as regards baseline characteristics between paediatric and adult studied populations, which not only include the age, but also the type of TCPC or the type of functional ventricular heart among others, could still interfere with the interpretation of the treatment response. Therefore, it is considered that no further information is required.

The exploratory efficacy variables were analyzed on the RUBATO Pool Full Analysis Set (N=137; participants enrolled in the OL study who received at least 1 dose of OL study intervention [i.e., macitentan 10 mg]) and RUBATO OL Extension Set (N=111; data from the same participants randomized in DB were concatenated with their data from the OL extension study). For the analyses of the effect of macitentan on efficacy endpoints, obtained data were similar between the DB-placebo and DB-macitentan. These results are in line with those observed in the main DB study where the primary and secondary efficacy endpoints were not met.

Safety data were analyzed using the RUBATO OL Extension Set (N=111) and the Total Macitentan Analysis Set (macitentan 10 mg pool; included 122 participants who received macitentan 10 mg in the DB study but did not enroll into the OL study [n=11], participants who received macitentan 10 mg in both DB and OL studies [n=57], and participants who received macitentan 10 mg only in the OL study ([n=54]). The median (IQ range) study intervention duration (regardless of interruption) and total exposure to study intervention (excluding interruptions) was 84.29 (52.14 to 110.86) weeks and 80.29 (52.14 to 107.29) weeks, respectively. For adolescent participants, the median (IQ range) study intervention duration (regardless of interruption) Study treatment duration (weeks) and total exposure to study intervention (excluding interruptions) Total exposure to treatment was 105.00 (74.14 to 130.71) weeks and 103.86 (73.86 to 122.29) weeks, respectively. Although RUBATO OL study did not last enough to be considered a purely long-term study, the obtained data are considered relevant to support data obtained from the RUBATO DB study.

For RUBATO OL Extension Set, the proportion of participants with at least 1 treatment-emergent AE was 61.3% (68 participants; DB-placebo: 36/54 [66.7%], DB-macitentan: 32/57 [56.1%]). The most frequently reported treatment-emergent AEs (≥5% all participants) were COVID-19 (14 [12.6%] participants; DB-placebo: 6/54 [11.1%], DB-macitentan: 8/57 [14.0%]), headache (8 [7.2%] participants; DB-placebo: 4/54 [7.4%], DB-macitentan: 4/57 [7.0%]), fatigue (7 [6.3%] participants; DB-placebo: 3/54 [5.6%], DB-macitentan: 4/57 [7.0%], and palpitations (7 [6.3%] participants; DB-placebo: 2/54 [3.7%], DB-macitentan: 5/57 [8.8%]). When adolescent particpants were assessed, the proportion of participants with at least 1 treatment-emergent AE was 66.7% (8/12 participants; DB-placebo: 5, DB-macitentan: 3). The proportion of adolescent participants who had at least 1 treatment-emergent SAE was 25.0% (3/12 participants; DB-placebo: 1, DB-macitentan: 2). No adolescent patients experienced AEs leading to death, related serious AEs or AEs leading to discontinuation of study treatment. Overall, no unexpected or new safety findings were observed during the OL extension study.

According to the submitted data, the AC-055H302 (RUBATO OL) study results confirmed no clinically meaningful difference favouring macitentan that would provide treatment benefit to Fontan-palliated

patients. Moreover, safety findings were consistent with the known safety profile of macitentan, with no new safety findings reported/observed during the study.

Since the MAH does not claim for use of macitentan in Fontan-palliated patients on the basis of the lack of benefit versus placebo shown in the AC-055H301 (RUBATO DB) study and given that safety data reported in the RUBATO study are in line with the approved EU summary product characteristics (SmPC) for macitentan, it is considered that no further regulatory action is required.

3. CHMP Overall conclusion and recommendation

The AC-055H302 (RUBATO OL) study submitted within this procedure was a Phase 3 extension of the AC-055H301 (RUBATO double-blind [DB]) study that was prematurely stopped because the main DB study did not meet the primary and secondary efficacy endpoints. Safety findings were in line with the known safety profile of macientan.

Of the 111 patients (age range: 13 to 49 years) enrolled, 12 (10.8%) participants were paediatric subjects (age range: 13 to less than 18 years).

Recommendation

Since the MAH does not claim for use of macitentan in Fontan-palliated patients on the basis of the lack of benefit versus placebo shown in the AC-055H301 (RUBATO) study and given that safety data reported in the RUBATO study are in line with the approved EU summary product characteristics (SmPC) for macitentan, it is considered that no further regulatory action is required.

☒ Fulfilled:

No regulatory action required.