20 September 2018
EMA/687037/2018
Human Medicines Evaluation 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/P46/008

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

On 9 July 2018, the MAH submitted the final study report for the clinical study AC-055-308 (MAESTRO OL) for macitentan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that AC-055-308 (MAESTRO OL) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study was conducted in Eisenmenger syndrome (ES) subjects with macitentan 10 mg film-coated tablets. No pediatric formulation was used, as all subjects in this study received the commercially available adult formulation.

2.3. Clinical aspects

2.3.1. Introduction

Macitentan is an orally active potent endothelin receptor antagonist (ERA), active on both endothelin (ET) ETA and ETB receptors and approximately 100-fold more selective for ETA as compared to ETB in vitro. Pulmonary arterial hypertension (PAH) is associated with an activation of the ET system. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents the ET-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

Macitentan was approved under the brand name Opsumit® for the treatment of PAH in adult subjects in December 2013, based on data generated in a long-term Phase 3 study (AC-055-302/SERAPHIN) with a morbidity/mortality primary endpoint [Pulido 2013].

In the EU, macitentan is approved in the following indication:

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of 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).

Eisenmenger syndrome (ES) is part of the WHO Group 1 of pulmonary hypertension (PH) and is a progressive, multi-organ disorder with high morbidity and mortality that represents the most advanced form and end-stage of congenital heart disease (CHD)-associated PAH. In general, ES is characterized by the complete or partial reversal of an initial long-standing systemic-to-pulmonary cardiac shunt that induces an increase in pulmonary vascular resistance and eventually progresses into a cyanotic pulmonary-to-systemic shunt [Beghetti 2009]. As such, although the cardiac defect is present at birth, ES usually presents later in life, either before puberty or in

early adulthood, as the existing alterations of the normal physiology of the heart lead to maladaptive responses that develop over time. The risk for developing ES appears to be determined by the size of the initial systemic-to-pulmonary shunt and the volume of pulmonary blood flow, as well as the type of cardiac defect. ES is a heterogeneous disease, resulting from a range of congenital heart defects characterized by elevated pulmonary arterial pressure and right-to-left shunting with cyanosis [Gatzoulis 2014].

Subjects with ES were excluded from the SERAPHIN study in PAH, which only allowed simple congenital systemic-to-pulmonary shunts at least 1 year post-surgical repair. In order to demonstrate that macitentan improves exercise capacity in an ES population, a dedicated Phase 3 study, AC-055-305/MAESTRO [D-16.551], was conducted in subjects with ES.

CHD accounts for nearly one third of all major congenital anomalies and is the most common congenital condition diagnosed in newborns [Hoffman 2002, Reller 2008]. As the underlying congenital heart lesion(s) drive the progression of ES, the study was open to subjects aged 12 years of age and older to allow for the inclusion of these subjects when ES physiology first manifests, or early in the course of their disease. Patients with Down Syndrome (DS) represent an important subset of the ES population. These subjects tend to have a higher incidence of complex cardiac defects that are most commonly associated with PAH, and in particular, ES. Despite this, there is a lack of clinical trials in subjects with both ES and DS, with significant therapeutic implications in the management of these subjects as a consequence. In an effort to address the high unmet need in this population, the MAESTRO study was the first randomized clinical trial in ES to include subjects with DS.

Following participation in the MAESTRO study, subjects were invited to enroll in the open-label (OL), non-comparative, multicenter, long-term, extension study AC-055-308/MAESTRO OL. MAESTRO OL was aimed at assessing the long-term safety and tolerability of macitentan in subjects with ES, including ES patients with DS, beyond the treatment period of the MAESTRO study, and the long-term effect of macitentan on exercise capacity in this patient population. 14 adolescents (aged 12–17 years) were enrolled into the MAESTRO OL study. The study data are therefore being submitted for review to the European Medicines Agency (EMA), in accordance with Article 46 of Regulation (EC) No. 1901/2006 (the 'Paediatric Regulation').

The MAESTRO OL study was not part of the macitentan Paediatric Investigation Plan agreed upon for the PAH indication.

The purpose of this addendum is to provide a summary of the data from the MAESTRO OL study with emphasis on the pediatric sub-set, focusing on long-term safety and effect on exercise capacity. A previous addendum was written to summarize the data from pediatric subjects in the MAESTRO study only [D-17.321] and submitted to EMA under the Article 46 procedure (EMEA/H/C/002697/P46/0006).

The MAESTRO OL study was prematurely terminated after the MAESTRO study did not demonstrate a statistically significant effect of macitentan on the primary efficacy endpoint of exercise capacity as measured by 6-minute walk distance (6MWD).

2.3.2. Clinical study

Study AC-055-308/MAESTRO OL

Description

Long-term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome.

Methods

Objectives

The AC-055-308 / MAESTRO open-label (OL) study aimed to assess the long-term safety and tolerability of macitentan in subjects with ES beyond the treatment of the AC-055-305 / MAESTRO double-blind (DB) study, and to assess the long-term effect of macitentan on exercise capacity in this subject population.

Study design

AC-055-308/MAESTRO OL was a multi-center, OL, non-comparative, Phase 3 extension study following the AC-055-305/MAESTRO study to assess the long-term safety, tolerability and efficacy of macitentan in subjects with ES [D-16.551]. The study was conducted in 51 centers in 19 countries. It was planned to enroll up to 220 subjects (males or females) from the MAESTRO study. Subjects were enrolled into the OL study without knowledge of their previous study treatment (macitentan or placebo).

A total of 217 subjects were enrolled into the OL study. The enrollment visit in the MAESTRO OL study (OL Visit 1) was combined with the end-of-treatment (EOT) or premature EOT visit of the MAESTRO study.

The MAESTRO OL study was conducted in accordance with Good Clinical Practice guidelines.

The main features of the MAESTRO OL study are summarized in Table 1, below.

Table 1 AC-055-308/MAESTRO OL study characteristics

	Study objectives	Patients enrolled/evaluable	Demographic characteristics	Treatment/dose	Design/type of control/blinding
AC-055-308 (MAESTRO OL)	**Primary objective:** To assess the long-term safety, tolerability, and efficacy of macitentan in subjects with Eisenmenger Syndrome	**Enrolled:** 217 **Treated:** 217	**Sex:** 74 male / 143 female **Race:** 103 White 70 Chinese 22 Other 22 Other Asian **Age range:** 12–82 years	Macitentan 10 mg	Multi-center, open-label extension, single-arm, Phase 3 study

OL = open-label.

Study population /Sample size

The study enrolled 14 pediatric subjects aged 12–17 years who had completed the MAESTRO study. 1 additional pediatric subject in the MAESTRO study had his 18th birthday during the MAESTRO study, enrolled in the MAESTRO OL study as an adult, and therefore is not included in the MAESTRO OL pediatric analysis presented here. 1 pediatric patient had DS. All 14 pediatric subjects completed the MAESTRO OL study [Table 2].

Table 2 Disposition of subjects – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Disposition of subjects - subgroup of subjects aged 12-17 years
Analysis Set: All-enrolled set

	DB-Macitentan[c] n	DB-Placebo[c] n	Total n
Subjects enrolled			14
Subjects treated	12	2	14
Subjects completed treatment[a]	0	0	0
Subjects who prematurely discontinued study treatment	12	2	14
Subjects completed study[b]	12	2	14
Subjects who prematurely discontinued study	0	0	0

(a) Subjects considered to have completed the study treatment as per protocol (derived from the "Exposure" eCRF).
(b) Subjects considered to have completed the study as per protocol (derived from the "End of study" eCRF).
(c) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_DISP_AGE_ENR, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/t_disp_age.sas

Treatments

Subjects were enrolled into the OL study without knowledge of their previous study treatment (macitentan or placebo).

Outcomes / endpoints

EFFICACY:

Efficacy was assessed on an exploratory basis in this study. The endpoints were defined as:

• Change from DB baseline* to Week 16 in the DB study, Month 6, and Month 12 in the OL study, in:

– Exercise capacity, as measured by the 6MWD;

– WHO FC;

– Dyspnea (assessed by the Borg dyspnea index);

– Oxygen saturation, assessed by pulse oximetry: peripheral oxygen saturation

(SpO2) at rest before the 6-minute walk test (6MWT).

*DB baseline is defined as the last value assessed prior to the DB treatment start date.

SAFETY:

For the evaluation of treatment-emergent safety endpoints, the observation period for each individual subject started at the time of the first administration of macitentan and ended with the permanent discontinuation of macitentan + 30 days, regardless of study (i.e., DB or OL).

The safety variables assessed were:

• Treatment-emergent adverse events (AEs) up to 30 days after study treatment discontinuation;

• AEs leading to premature discontinuation of study treatment;

• Deaths up to 30 days after study treatment discontinuation;

• Treatment-emergent serious AEs (SAEs) up to 30 days after study treatment discontinuation;

• Treatment-emergent AEs of special interest (AESIs: anemia, hypotension, edema/fluid overload) up to 30 days after study treatment discontinuation;

• Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation;

• Change from baseline** up to 30 days after study treatment discontinuation in laboratory variables;

• Treatment-emergent alkaline aminotransferase (ALT) and/or aspartate aminotransferase (AST) abnormality (> 3 × upper limit of normal [ULN]; > 5 × ULN; > 8 × ULN) associated or not with total bilirubin > 2 × ULN up to 30 days after study treatment discontinuation;

• Change from baseline** up to 30 days after study treatment discontinuation in vital signs (arterial blood pressure [BP], pulse rate) and body weight.

** Baseline is defined as the last value assessed prior to the macitentan treatment start date.

Statistical Methods

No statistical hypothesis was considered for this OL extension study. Two analysis sets were defined:

The All-enrolled analysis set (ENR) included all subjects enrolled in AC-055-308 / MAESTRO-OL, whether or not they took at least one dose of macitentan during the OL study.

The All-treated DB + OL set (TTS) comprised:

• All subjects who received at least one dose of macitentan in AC-055-308 / MAESTRO-OL

AND

• All subjects who received macitentan during the AC-055-305 / MAESTRO-DB and were not enrolled in the OL study.

No primary efficacy variables were described in this study. All efficacy analyses were considered exploratory and were performed on the ENR, and were evaluated over the Combined DB + OL period, using the DB baseline.

The safety data were analyzed descriptively for the Combined DB + OL period, using the TTS.

Results

Recruitment / Number analysed

The study enrolled 14 pediatric subjects aged 12–17 years who had completed the MAESTRO study. 1 additional pediatric subject in the MAESTRO study had his 18th birthday during the MAESTRO study, enrolled in the MAESTRO OL study as an adult, and therefore is not included in the MAESTRO OL pediatric analysis presented here. 1 pediatric patient had DS. All 14 pediatric subjects completed the MAESTRO OL study [Table 2].

Table 2 Disposition of subjects – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Disposition of subjects - subgroup of subjects aged 12-17 years
Analysis Set: All-enrolled set

	DB-Macitentan[c] n	DB-Placebo[c] n	Total n
Subjects enrolled			14
Subjects treated	12	2	14
Subjects completed treatment[a]	0	0	0
Subjects who prematurely discontinued study treatment	12	2	14
Subjects completed study[b]	12	2	14
Subjects who prematurely discontinued study	0	0	0

(a) Subjects considered to have completed the study treatment as per protocol (derived from the "Exposure" eCRF).
(b) Subjects considered to have completed the study as per protocol (derived from the "End of study" eCRF).
(c) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_DISP_AGE_ENR, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/t_disp_age.sas

Efficacy results

All efficacy endpoints in MAESTRO OL were exploratory. The main exploratory efficacy endpoint was change from baseline in exercise capacity as measured by 6MWD, where baseline was defined as the last value assessed prior to randomization into the MAESTRO study.

The change from MAESTRO baseline in exercise capacity, as measured by 6MWD, was assessed at Week 16 (EOT of the MAESTRO study), and Month 6 and Month 12 of the MAESTRO OL study.

In the overall MAESTRO OL population, for subjects who were randomized to macitentan in the MAESTRO study, and who continued to receive macitentan in the MAESTRO OL study, the mean (standard deviation [SD]) change from baseline was 24.4 (71.0) m at Week 16, 26.2 (77.9) m at Month 6 and 26.5 (79.8) m at Month 12. For subjects who were randomized to placebo in the MAESTRO study and who received macitentan in the MAESTRO OL study, the mean (SD) change from baseline was 18.2 (53.0) m at Week 16, 43.4 (51.5) m at Month 6 and 39.9 (55.1) m at Month 12 [D-18.003, section 11.2.1].

In the pediatric sub-set, for subjects who were randomized to macitentan in the MAESTRO study, and who continued to receive macitentan in the MAESTRO OL study, the mean (SD) change from baseline was 14.8

(28.3) m at Week 16, 20.3 (77.0) m at Month 6, and 15.1 (61.8) m at Month 12. For subjects who were randomized to placebo in the MAESTRO study and who received macitentan in the MAESTRO OL study, the mean (SD) change from baseline was 46.0 (35.4) m at Week 16, 36.0 (42.4) m at Month 6, and 89.0 (2.8) m at Month 12 [Table 7 and Figure 1].

Table 7 Absolute values and changes from DB-baseline for 6MWD – combined DB + OL period (imputed values) – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Absolute values and change from DB baseline for 6MWD - combined DB + OL period (imputed values) - subgroup of subjects aged 12-17 years
Analysis Set: All-enrolled set

Six Minute Walk Distance (6MWD) (m)

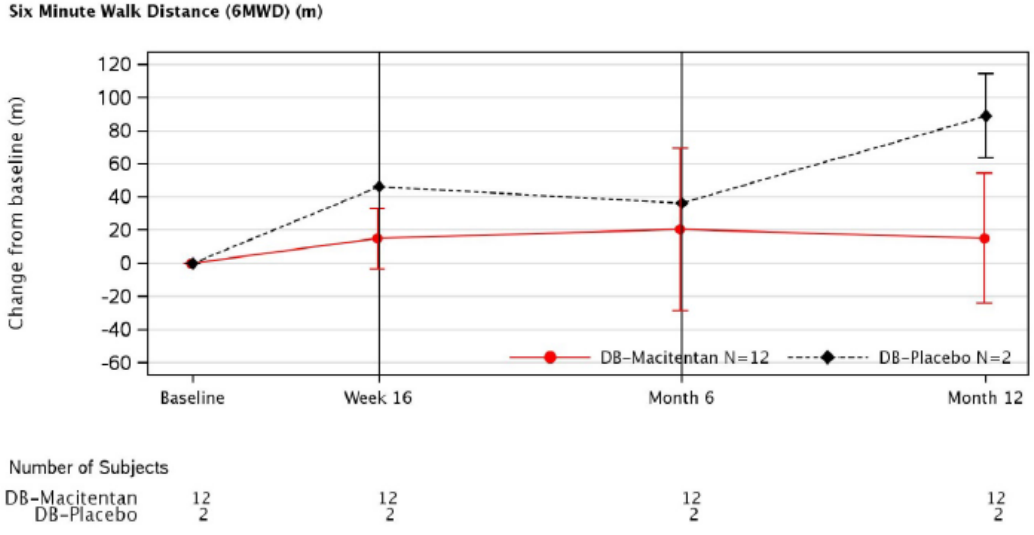
	DB-Macitentan[d] N = 12	DB-Placebo[d] N = 2
Number of subjects included in the analysis		
n	12	2
Baseline		
Mean	382.5	351.0
SD	57.9	38.2
Median	401.0	351.0
Q1 , Q3	350.0, 430.0	324.0, 378.0
Min , Max	265, 440	324, 378
Week 16		
Mean	397.3	397.0
SD	61.6	2.8
Median	394.5	397.0
Q1 , Q3	354.5, 448.0	395.0, 399.0
Min , Max	290, 482	395, 399
Imputation for missing values		
n	0	0
LOCF[a]	0	0
Death[b]	0	0
Ad-hoc rule[c]	0	0
Change from baseline		
Mean	14.8	46.0
SD	28.3	35.4
Median	15.5	46.0
Q1 , Q3	-7.5, 43.0	21.0, 71.0
Min , Max	-39, 50	21, 71
Month 6		
Mean	402.8	387.0
SD	57.0	4.2
Median	407.5	387.0
Q1 , Q3	383.0, 436.5	384.0, 390.0
Min , Max	276, 485	384, 390
Imputation for missing values		
n	0	0
LOCF[a]	0	0
Death[b]	0	0
Ad-hoc rule[c]	0	0
Change from baseline		
Mean	20.3	36.0
SD	77.0	42.4
Median	12.5	36.0
Q1 , Q3	1.5, 43.5	6.0, 66.0
Min , Max	-164, 165	6, 66
Month 12		
Mean	397.6	440.0
SD	63.5	35.4
Median	408.5	440.0

Q1 , Q3	349.5, 447.0	415.0, 465.0
Min , Max	270, 480	415, 465
Imputation for missing values		
n	0	0
LOCF[a]	0	0
Death[b]	0	0
Ad-hoc rule[c]	0	0
Change from baseline		
Mean	15.1	89.0
SD	61.8	2.8
Median	16.0	89.0
Q1 , Q3	-22.5, 37.0	87.0, 91.0
Min , Max	-86, 170	87, 91

SD=Standard Deviation
(a) imputed with last observation carried forward;
(b) imputed with 0 meters;
(c) imputed with ad-hoc rule defined in AC-055-305.
(d) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_6MWDDBOL_AGE_ENR, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/t_6mwddbol_age.sas

Figure 1 **Mean (95% CL) for change from DB baseline in 6MWD – combined DB + OL period (imputed values) subgroup of subjects aged 12–17 years**

ACT-064992
Protocol: AC-055-308
Mean (95% CL) for change from DB baseline in 6MWD - combined DB + OL period (imputed values) - subgroup of subjects aged 12-17 years
Analysis Set: All-enrolled set



CL=Confidence Limit.
Output: F_6MWDIDBOL_AGE_ENR, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/f_6mwddboli_age.sas

Assessor's comments

Results show that efficacy in the pediatric sub-set is similar to the one observed in the overall MAESTRO population.

However, it should be noted that the reduced sample size (12 subjects in the macitentan arm and 2 subjects in the placebo arm) makes it difficult to draw clear conclusions with this regard.

Safety results

Safety was evaluated for the entire duration of macitentan exposure in MAESTRO and MAESTRO OL. The observation period for each individual subject started at the time of the first administration of macitentan, regardless of whether this occurred in the MAESTRO or MAESTRO OL study, and ended with the permanent discontinuation of macitentan + 30 days. Baseline values were defined as the last value assessed before the first exposure to macitentan, regardless of whether the first dose of macitentan was in the MAESTRO or MAESTRO OL study.

Safety analyses for the overall MAESTRO OL population are shown for context. However, caution should be used when comparing percentages of pediatric subjects to those of the MAESTRO OL population overall, due to the low number of pediatric subjects enrolled.

Exposure to study treatments in the pediatric population

The median duration of exposure to study treatment (including interruptions) in the pediatric sub-set (combined DB+OL) was 167.71 weeks [Table 8].

The median duration of exposure to study treatment (including interruptions) in the pediatric sub-set (OL) was 151.21 weeks [Table 9].

For context, the median duration of exposure to study treatment in the overall MAESTRO OL population (including interruptions) was approximately 131.93 weeks [D-18.003, section 12.1.1.1].

Table 8 Study treatment exposure combined DB + OL – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Study treatment exposure combined DB+OL - subgroup of subjects aged 12-17 years
Analysis Set: All-treated DB + OL set

	DB-Macitentan[a] N = 12	DB-Placebo[a] N = 2	Total N = 14
Duration of study treatment (weeks)			
n	12	2	14
Mean	163.55	181.57	166.12
SD	28.73	44.85	29.93
Median	167.71	181.57	167.71
Q1 , Q3	154.93, 183.36	149.86, 213.29	149.86, 183.43
Min , Max	85.1, 188.6	149.9, 213.3	85.1, 213.3
Study treatment exposure, interruptions excluded (weeks)			
n	12	2	14
Mean	163.31	181.57	165.92
SD	29.24	44.85	30.37
Median	167.50	181.57	167.50
Q1 , Q3	154.93, 183.21	149.86, 213.29	149.86, 183.43
Min , Max	83.0, 188.6	149.9, 213.3	83.0, 213.3
Cumulative duration of study treatment [n (%)]			
At least 4 weeks	12 (100)	2 (100)	14 (100)
At least 8 weeks	12 (100)	2 (100)	14 (100)
At least 12 weeks	12 (100)	2 (100)	14 (100)
At least 16 weeks	12 (100)	2 (100)	14 (100)
At least 20 weeks	12 (100)	2 (100)	14 (100)
At least 24 weeks	12 (100)	2 (100)	14 (100)
At least 28 weeks	12 (100)	2 (100)	14 (100)
At least 32 weeks	12 (100)	2 (100)	14 (100)
At least 36 weeks	12 (100)	2 (100)	14 (100)
At least 40 weeks	12 (100)	2 (100)	14 (100)
At least 44 weeks	12 (100)	2 (100)	14 (100)
At least 48 weeks	12 (100)	2 (100)	14 (100)
At least 52 weeks	12 (100)	2 (100)	14 (100)
At least 56 weeks	12 (100)	2 (100)	14 (100)
At least 60 weeks	12 (100)	2 (100)	14 (100)
At least 64 weeks	12 (100)	2 (100)	14 (100)
At least 68 weeks	12 (100)	2 (100)	14 (100)
At least 72 weeks	12 (100)	2 (100)	14 (100)
At least 76 weeks	12 (100)	2 (100)	14 (100)
At least 80 weeks	12 (100)	2 (100)	14 (100)
At least 84 weeks	12 (100)	2 (100)	14 (100)
At least 88 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 92 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 96 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 100 weeks	11 (91.7)	2 (100)	13 (92.9)

SD=Standard Deviation
Exposure to Macitentan in AC-055-305 and AC-055-308 is displayed.
(a)DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_TREXP_AGE_TTS, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_dsur/program_output/t_trexp_age.sas

Table 9 Study treatment exposure OL – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Study treatment exposure OL - subgroup of subjects aged 12-17 years
Analysis Set: All-enrolled set

	DB-Macitentan[a] N = 12	DB-Placebo[a] N = 2	Total N = 14
Duration of study treatment (weeks)			
n	12	2	14
Mean	147.33	181.57	152.22
SD	28.68	44.85	31.71
Median	151.21	181.57	151.21
Q1 , Q3	138.71, 167.14	149.86, 213.29	147.71, 167.43
Min , Max	69.0, 172.4	149.9, 213.3	69.0, 213.3
Study treatment exposure, interruptions excluded (weeks)			
n	12	2	14
Mean	147.10	181.57	152.02
SD	29.20	44.85	32.14
Median	151.00	181.57	151.00
Q1 , Q3	138.71, 167.00	149.86, 213.29	147.71, 167.43
Min , Max	66.9, 172.4	149.9, 213.3	66.9, 213.3
Cumulative duration of study treatment [n (%)]			
At least 4 weeks	12 (100)	2 (100)	14 (100)
At least 8 weeks	12 (100)	2 (100)	14 (100)
At least 12 weeks	12 (100)	2 (100)	14 (100)
At least 16 weeks	12 (100)	2 (100)	14 (100)
At least 20 weeks	12 (100)	2 (100)	14 (100)
At least 24 weeks	12 (100)	2 (100)	14 (100)
At least 28 weeks	12 (100)	2 (100)	14 (100)
At least 32 weeks	12 (100)	2 (100)	14 (100)
At least 36 weeks	12 (100)	2 (100)	14 (100)
At least 40 weeks	12 (100)	2 (100)	14 (100)
At least 44 weeks	12 (100)	2 (100)	14 (100)
At least 48 weeks	12 (100)	2 (100)	14 (100)
At least 52 weeks	12 (100)	2 (100)	14 (100)
At least 56 weeks	12 (100)	2 (100)	14 (100)
At least 60 weeks	12 (100)	2 (100)	14 (100)
At least 64 weeks	12 (100)	2 (100)	14 (100)
At least 68 weeks	12 (100)	2 (100)	14 (100)
At least 72 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 76 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 80 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 84 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 88 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 92 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 96 weeks	11 (91.7)	2 (100)	13 (92.9)
At least 100 weeks	11 (91.7)	2 (100)	13 (92.9)

SD=Standard Deviation
Exposure to Macitentan during AC-055-308 is displayed.
(a) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_TREXP_OL_AGE_ENR, Produced by verbiol1 on 11MAY2018 9:32 (CET), SDTM production date: 29JAN2018
Program: val_dsur/program_output/t_trexpol_age.sas

Adverse events in the pediatric population

The proportion of subjects aged 12–17 years with at least 1 treatment-emergent adverse event (AE) was 92.9% (n = 13) [Table 10]. These rates are comparable to those in the overall MAESTRO OL population (91.0%, n = 202 [D-18.003, table 12-3]). No AEs of severe intensity were reported for pediatric subjects [Table 10]. For context, AEs of severe intensity were reported for 23.9% (n = 53) of subjects in the overall MAESTRO OL

population [D-18.003, section 12.2.2]. AEs that were considered by the investigator to be drug-related were reported for 50% (n = 7) of pediatric subjects [Table 10]. For context, drug-related AEs were reported for 35.1% of the overall MAESTRO OL population [D-18.003, table 12-3].

Table 10 Overview of treatment-emergent adverse events – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Overview of treatment-emergent adverse events (AE) - subgroup of subjects aged 12-17 years
Analysis Set: All-treated DB + OL set

Characteristic	DB-Macitentan[a] N = 12 n (%)	DB-Placebo[a] N = 2 n (%)	Total N = 14 n (%)
Subjects with at least one AE	12 (100)	1 (50.0)	13 (92.9)
Severe AE	0	0	0
Drug-Related AE	7 (58.3)	0	7 (50.0)
AE leading to study drug discontinuation	2 (16.7)	0	2 (14.3)
Serious AE	1 (8.3)	1 (50.0)	2 (14.3)
Drug-Related serious AE	0	0	0
Fatal serious AE	0	0	0
Drug-Related fatal serious AE	0	0	0
AE of special interest related to:	5 (41.7)	0	5 (35.7)
hypotension	1 (8.3)	0	1 (7.1)
oedema and fluid overload	0	0	0
anaemia	4 (33.3)	0	4 (28.6)

The observation period for each individual subject starts at the time of the first administration of Macitentan and ends with the permanent discontinuation of Macitentan + 30 days, regardless of study (i.e., AC-055-305 or AC-055-308).
(a) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_AEOV_AGE_TTS, Produced by verbiol1 on 24MAY2018 9:49 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/t_aeov_age.sas

Hemoglobin decreased and upper respiratory tract infection were the most frequently reported AEs, each with a frequency of 28.6% (n = 4) [Table 11]. Other AE terms reported for > 1 pediatric subject were alanine aminotransferase increased (n = 3), cough (n = 3), viral upper respiratory tract infection (n = 3), respiratory tract infection viral (n = 2), abdominal pain (n = 2), bronchitis (n = 2), headache (n = 2), rhinitis allergic (n = 2), dizziness (n = 2), and sinus arrhythmia (n = 2). All other AE terms reported were reported for only 1 subject. The pattern of AEs observed in the pediatric population was similar to that observed in the overall MAESTRO OL population.

Table 11 Treatment-emergent adverse events by preferred term – subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Treatment-emergent adverse events (AE) by preferred term - subgroup of subjects aged 12-17 years
Analysis Set: All-treated DB + OL set

Preferred Term	DB-Macitentan[a] N = 12 n (%)	DB-Placebo[a] N = 2 n (%)	Total N = 14 n (%)
Subjects with at least one AE	12 (100)	1 (50.0)	13 (92.9)
Haemoglobin decreased	4 (33.3)	0	4 (28.6)
Upper respiratory tract infection	4 (33.3)	0	4 (28.6)
Alanine aminotransferase increased	3 (25.0)	0	3 (21.4)
Cough	3 (25.0)	0	3 (21.4)
Abdominal pain	2 (16.7)	0	2 (14.3)
Bronchitis	2 (16.7)	0	2 (14.3)
Headache	2 (16.7)	0	2 (14.3)
Rhinitis allergic	2 (16.7)	0	2 (14.3)
Sinus arrhythmia	2 (16.7)	0	2 (14.3)
Viral upper respiratory tract infection	2 (16.7)	1 (50.0)	3 (21.4)
Acne	1 (8.3)	0	1 (7.1)
Alopecia	1 (8.3)	0	1 (7.1)
Animal bite	1 (8.3)	0	1 (7.1)
Anxiety	1 (8.3)	0	1 (7.1)
Autoimmune thyroiditis	1 (8.3)	0	1 (7.1)
Chest pain	1 (8.3)	0	1 (7.1)
Conjunctivitis	1 (8.3)	0	1 (7.1)
Constipation	1 (8.3)	0	1 (7.1)
Contusion	1 (8.3)	0	1 (7.1)
Cyanosis	1 (8.3)	0	1 (7.1)
Depression	1 (8.3)	0	1 (7.1)
Dermatitis allergic	1 (8.3)	0	1 (7.1)
Dizziness	1 (8.3)	1 (50.0)	2 (14.3)
Dizziness exertional	1 (8.3)	0	1 (7.1)
Dyspnoea	1 (8.3)	0	1 (7.1)
Ejection fraction decreased	1 (8.3)	0	1 (7.1)
Epistaxis	1 (8.3)	0	1 (7.1)
Exercise tolerance decreased	1 (8.3)	0	1 (7.1)
Fall	1 (8.3)	0	1 (7.1)
Fatigue	1 (8.3)	0	1 (7.1)
Gastrooesophageal reflux disease	1 (8.3)	0	1 (7.1)
Goitre	1 (8.3)	0	1 (7.1)
Haemoptysis	1 (8.3)	0	1 (7.1)
Human chorionic gonadotropin increased	1 (8.3)	0	1 (7.1)
Hyperthyroidism	1 (8.3)	0	1 (7.1)
Hypotension	1 (8.3)	0	1 (7.1)
Loss of consciousness	1 (8.3)	0	1 (7.1)
Lymphadenopathy	1 (8.3)	0	1 (7.1)
Nasal congestion	1 (8.3)	0	1 (7.1)
Nasopharyngitis	1 (8.3)	0	1 (7.1)
Oxygen saturation decreased	1 (8.3)	0	1 (7.1)
Pregnancy	1 (8.3)	0	1 (7.1)
Pruritus	1 (8.3)	0	1 (7.1)
Respiratory tract infection viral	1 (8.3)	1 (50.0)	2 (14.3)
Rhinitis	1 (8.3)	0	1 (7.1)
Serum ferritin decreased	1 (8.3)	0	1 (7.1)
Viral infection	1 (8.3)	0	1 (7.1)
Viral pharyngitis	1 (8.3)	0	1 (7.1)
Vision blurred	1 (8.3)	0	1 (7.1)
Vomiting	1 (8.3)	0	1 (7.1)
Herpangina	0	1 (50.0)	1 (7.1)
Hypoxia	0	1 (50.0)	1 (7.1)
Tonsillitis	0	1 (50.0)	1 (7.1)

Frequencies represent the number of subjects with the event.
Preferred Terms are based on MedDRA version 20.0.

Deaths

There were no deaths in pediatric subjects.

Serious adverse events

2 pediatric subjects (14.3%) experienced a total of 3 serious AEs (SAEs), all of which occurred during the OL study [Table 14]. 1 subject experienced an event of hypoxia that was considered to be of moderate intensity and not related to the study drug.

The other subject experienced events of viral pharyngitis and anxiety. The event of viral pharyngitis was reported to be of moderate intensity and the event of anxiety of mild intensity. Neither event was considered by the investigator to be related to the study drug. Detailed narratives of the events are provided in the MAESTRO OL clinical study report (CSR) [D-18.003, section 15.4.2].

For context, 67 (30.2%) of subjects in the overall MAESTRO OL population experienced at least 1 SAE during the combined MAESTRO / MAESTRO OL studies [D-18.003, section 12.3.2].

Table 14 Treatment-emergent serious adverse events by preferred term – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Treatment-emergent serious adverse events (SAE) by preferred term - subgroup of subjects aged 12-17 years
Analysis Set: All-treated DB + OL set

Preferred Term	DB-Macitentan[a] N = 12 n (%)	DB-Placebo[a] N = 2 n (%)	Total N = 14 n (%)
Subjects with at least one SAE	1 (8.3)	1 (50.0)	2 (14.3)
Anxiety	1 (8.3)	0	1 (7.1)
Viral pharyngitis	1 (8.3)	0	1 (7.1)
Hypoxia	0	1 (50.0)	1 (7.1)

Frequencies represent the number of subjects with the event.
Preferred Terms are based on MedDRA version 20.0.
The observation period for each individual subject starts at the time of the first administration of Macitentan and ends with the permanent discontinuation of Macitentan + 30 days, regardless of study (i.e., AC-055-305 or AC-055-308).
(a) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_SAEPR_AGE_TTS, Produced by verbiol1 on 11MAY2018 16:29 (CET), SDTM production date: 29JAN2018
Program: val csr/program output/t saepr age.sas

Adverse events leading to discontinuation of study treatment

2 pediatric subjects (14.3%) prematurely discontinued study treatment due to an AE [Table 15].

1 subject discontinued due to pregnancy. She underwent induced abortion. The other subject discontinued due to hemoglobin decrease. The event was assessed as non-serious and related to study drug by the investigator [Section 5.3.1] Detailed narratives of the events are provided in the MAESTRO OL CSR [D-18.003, section 15.4.3].

For context, 27 (12.2%) of subjects in the overall MAESTRO OL population prematurely discontinued study treatment due to an AE [D-18.003, section 12.3.3].

Table 15 Adverse events leading to premature discontinuation of study treatment by preferred term – subgroup of subjects aged 12–17 years

ACT-064992
Protocol: AC-055-308
Adverse events (AE) leading to premature discontinuation of study treatment by preferred term - subgroup of subjects aged 12-17 years
Analysis Set: All-treated DB + OL set

Preferred Term	DB-Macitentan[a] N = 12 n (%)	DB-Placebo[a] N = 2 n (%)	Total N = 14 n (%)
Subjects with at least one AE	2 (16.7)	0	2 (14.3)
Haemoglobin decreased	1 (8.3)	0	1 (7.1)
Pregnancy	1 (8.3)	0	1 (7.1)

Frequencies represent the number of subjects with the event.
Preferred Terms are based on MedDRA version 20.0.
The observation period for each individual subject starts at the time of the first administration of Macitentan and ends with the permanent discontinuation of Macitentan + 30 days, regardless of study (i.e., AC-055-305 or AC-055-308).
(a) DB-Macitentan group subjects are subjects who received macitentan in the MAESTRO study. DB-Placebo group subjects are subjects who received placebo in the MAESTRO study
Output: T_AEPDPR_AGE_TTS, Produced by verbiol1 on 11MAY2018 9:33 (CET), SDTM production date: 29JAN2018
Program: val_csr/program_output/t_aepdpr_age.sas

Safety topics of special interest

AEs of special interest were defined as 'Anaemia', 'Hypotension', and 'Oedema and fluid overload' [Standardized MedDRA Query defined in D-18.003, section 9.8.2.2.1].

Anemia

4 subjects (28.6%) in the pediatric sub-set experienced AEs of hemoglobin decrease during the MAESTRO / MAESTRO OL studies [Table 16]. None of the AEs were reported as serious. 1 subject prematurely discontinued MAESTRO OL study drug due to the AE of hemoglobin decrease. 1 subject was discussed in the Clinical Overview addendum written for the MAESTRO study [D-17.321, section 5.3.1].

A second subject experienced a decrease of hemoglobin of mild intensity on MAESTRO OL Day 910, when hemoglobin concentration was 103 g/L (normal range 120–160 g/L) compared to 137 g/L (normal range 135–175 g/L) on OL Day 1. Study treatment was continued at the same dose and the event remained unresolved at the end of the study. On Day 1060 (EOT visit) the subject's hemoglobin was 126 g/L.

A third subject experienced decreased hemoglobin of mild intensity on MAESTRO OL Day 813, when hemoglobin concentration was 135 g/L, compared to 158 g/L on MAESTRO OL Day 1 (normal range 120–160 g/L). Study

treatment continued at the same dose and the event remained unresolved at the end of the study. On Day 1240 (end-ofstudy [EOS] visit), the subject's hemoglobin concentration was 163 g/L.

A fourth subject experienced 3 events of decrease of hemoglobin on MAESTRO OL on Days 92, 358, and 806. The subject's hemoglobin concentration on MAESTRO OL Day 1 was 192 g/L, and decreased to 169 g/L, 153 g/L, and 163 g/L on Days 92, 358, and 806, respectively (normal range 120–160 gL). The subject prematurely discontinued MAESTRO OL study treatment on Day 1184; on this day hemoglobin concentration was 151 g/L. On Day 1198 (EOS visit), the subject's hemoglobin concentration was 158 g/L.

For context, 37 subjects (16.7%) in the overall MAESTRO OL population had at least 1 AE related to anemia in the MAESTRO / MAESTRO OL studies, and 8 subjects discontinued study treatment due to anemia/decreased hemoglobin AEs [D-18.003, section 12.3.5.1].

Marked laboratory abnormalities relevant to anemia

No subjects in the pediatric sub-set had hemoglobin decreases from baseline to ≤ 100 g/L or decreases from baseline of ≥ 50 g/L [Table 19]. For context, 3 subjects in the overall MAESTRO OL population had a marked reduction of hemoglobin values to > 80 and ≤ 100 g/L, and 19 subjects had decreases from baseline of ≥ 50 g/L [D-18.003, section 12.3.5.1].

Hypotension

1 pediatric subject (7.1%) experienced an AE related to hypotension during the MAESTRO / MAESTRO OL studies [Table 17]. The event of hypotension on MAESTRO OL Day 782 was moderate in intensity and considered non-serious and related to the study drug by the investigator. Study treatment was continued at the same dose. The event was unresolved at the end of the study. For context, 8 subjects (3.6%) in the overall MAESTRO OL population had at least 1 AE related to hypotension in the MAESTRO / MAESTRO OL studies [D-18.003, section 12.3.5.2].

Edema and fluid overload

No pediatric subject had an AE related to edema and fluid overload during the MAESTRO / MAESTRO OL studies [Table 18]. For context, 27 subjects (12.2%) in the overall MAESTRO OL population experienced at least 1 AE related to edema and fluid overload [D-18.003, section 12.3.5.3].

Liver tests

1 pediatric subject had treatment-emergent liver test abnormalities > 3 × upper limit of the normal range (ULN) during the MAESTRO / MAESTRO OL studies. This subject was discussed in the addendum to the Clinical Overview for the MAESTRO study [D-17.321]. The event was not serious and did not lead to premature discontinuation of study treatment [D-18.003, section 12.3.5.4]. For context, there were 5 cases of treatment-emergent liver test abnormalities > 3 × ULN in the overall MAESTRO OL population [D-18.003, section 12.3.5.4].

Assessor's comments

Overall, the available data indicate that the safety profile of macitentan in adolescent pediatric subjects, at the same dose as in adults (10 mg o.d.), is similar to that in adults.

Again, the limited data from the MAESTRO study do not allow any meaningful clinical assessment of the safety macitentan in the pediatric ES population.

2.3.3. Discussion on clinical aspects

A total of 14 pediatric subjects were treated with macitentan in the MAESTRO OL study at the same dose used in adults (10 mg once daily [o.d.]). The exploratory efficacy data collected in pediatric subjects do not suggest any potential difference in terms of response compared to the overall patient population. However, the limited data from do not allow any meaningful clinical assessment of the efficacy of macitentan in the pediatric Eisenmenger Syndrome population.

Overall, the safety data were consistent with those seen in the overall MAESTRO OL population both in frequency and distribution/type of AE. No deaths were reported in pediatric subjects. SAEs and AEs leading to premature discontinuation of study treatment were reported for pediatric subjects at rates similar to those reported for the overall MAESTRO OL population. Consequently, the available data indicate that the safety profile of macitentan in adolescent pediatric subjects, at the same dose as in adults (10 mg o.d.), is similar to that in adults and is aligned with the safety section in the approved labeling information of Opsumit.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

In the absence of any significant new data on effectiveness or new safety concerns, there is no need for an update of the product information. In accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance and therefore do not require further regulatory action on the marketing authorisation for the above mentioned product.

4. Additional clarification requested

Not applicable