17 August 2017
EMA/792503/2017
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/P46/006

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

On 31st May, the MAH submitted the final clinical study report for AC-055-305 study (MAESTRO), 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 MAESTRO (AC-055-305) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

No paediatric formulation was used and all subjects in this study received the commercially available adult formulation 10 mg film-coated tablets.

2.3. Clinical aspects

2.3.1. Introduction

Macitentan is an orally active endothelin receptor antagonist (ERA), active on both endothelin (ET) ET_A and ET_B receptors.

It was approved under the brand name Opsumit® in December 2013, based on data generated in a long-term Phase 3 study (AC-055-302, SERAPHIN) with a morbidity/mortality primary endpoint 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 Group 1 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.

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.

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, was conducted in subjects with ES. 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's Syndrome (DS) represent an important subset in 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.

Given 15 adolescents were randomized into the MAESTRO 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 MAESTRO study was not part of the macitentan Paediatric Investigation Plan agreed upon for the PAH indication.

The MAH submitted a final report for:

- AC-055-305, MAESTRO (**MA**citentan in **E**isenmenger **S**yndrome **T**o **R**est**O**re exercise capacity).

2.3.2. Clinical study

AC-055-305, MAESTRO (MAcitentan in Eisenmenger Syndrome To RestOre exercise capacity)

Description

A multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to evaluate the effects of macitentan on exercise capacity in subjects with Eisenmenger Syndrome.

Methods

Objective(s)

The primary objective was to demonstrate that macitentan improves exercise capacity in comparison to placebo in subjects with ES.

The secondary objectives were to evaluate the effects of macitentan in comparison to placebo on:

· WHO FC,

· Dyspnea (assessed by the Borg dyspnea index),

· Quality of Life (QoL; assessed by the Short-Form 36 [SF-36] questionnaire).

The exploratory objectives were:

· To evaluate the effects of macitentan in comparison to placebo on:

– Systemic oxygen saturation,

– N-terminal pro-B type natriuretic peptide (NT-pro-BNP) and potential additional biomarkers,

– Hemodynamic parameters (in a subset of subjects).

· To evaluate the safety and tolerability of macitentan in this subject population.

Study design

This was a prospective, multi-center, double-blind (DB), randomized, placebo-controlled, parallel-group Phase 3 study that evaluated the efficacy, safety and tolerability of macitentan 10 mg versus placebo

administered for 16 weeks in subjects with ES. At selected specialized sites, eligible subjects could opt to participate in a hemodynamic sub-study that assessed hemodynamic exploratory endpoints by cardiac catheterization.

Subjects were randomized in a 1:1 ratio to receive either macitentan 10 mg or placebo. Subjects were initially stratified by location of cardiac defect (isolated atrial septal defect [ASD] or combined ASD/VSD [ventricular septal defect], with VSD ≤ 1 cm in diameter and ASD > 2 cm in diameter, versus isolated VSD or combined ASD/VSD, with VSD > 1 cm in diameter regardless of the size of the ASD defect) and participation in the hemodynamic sub-study (yes/no). Following Protocol Amendment 2, subject allocation to treatment groups was stratified by WHO functional class (FC; I versus III/IV), presence of Down Syndrome (DS) (yes/no), and participation in the hemodynamic sub-study (yes/no).

The study included the following periods:

Screening period: The Screening period lasted a maximum of 30 days from Visit 1 up to Randomization (Visit 2).

Treatment period: At Visit 2 (Day 1), eligible subjects were randomized to receive the first dose of study treatment. The treatment period lasted up to Week 16 (End-of-Treatment [EOT], Visit 6), or finished earlier in case of premature discontinuation of study treatment (premature EOT). Regular scheduled assessments were performed every 4 weeks during the 16-week treatment period.

After premature study treatment discontinuation period: Subjects who prematurely discontinued study treatment (i.e., prior to Week 16) were required to perform a premature EOT visit (Visit 6) as soon as possible and, whenever possible, no later than 7 days after the last dose of study treatment, and thereafter a Week 16 visit (Visit 6a). Subjects who completed the 16-week DB treatment were eligible to enter an open-label (OL), non-comparative extension study (AC-055-308) comprised of a single 10 mg macitentan arm. Subjects who prematurely discontinued DB treatment and had performed the Week 16 visit (Visit 6a) were also eligible to enter the OL extension study, unless they had discontinued study treatment due to elevated liver tests (LTs) or an adverse event (AE) that was considered related to study treatment.

Safety follow-up period: A 30-day Safety follow-up was performed for all subjects who did not enter the OL extension study (irrespective of whether or not study treatment was prematurely discontinued), as well as for subjects who entered the OL extension study after prematurely discontinuing study treatment, if the 30-day follow-up period concluded prior to initiation of OL study treatment. Safety data collected included AEs, serious adverse events (SAEs), serum pregnancy test, LT evaluation and changes in concomitant medications.

For subjects who entered the OL extension study, new AEs/SAEs after initiation of OL study treatment were reported and followed up in the OL extension study.

End-of-Study (EOS): The EOS for an individual subject corresponded to the last visit performed in the DB study.

A Study Steering Committee was involved in the design of the study, provided guidance on the study conduct as needed, and reviewed relevant screening data in order to corroborate the anatomic diagnosis of ES and confirm subject eligibility (both for the main study and sub-study) before a subject was randomized.

An independent Data Monitoring Committee reviewed blinded and/or unblinded data on a regular basis during the study to ensure subject safety.

Study population /Sample size

It was planned to randomize a total of 220 subjects in the overall study. A total of 226 subjects were actually randomized in a 1:1 ratio to macitentan 10 mg (n=114) and placebo (n=112), of which 39 subjects (20 macitentan and 19 placebo) participated in the hemodynamic sub-study.

Key inclusion and exclusion criteria included:

- Males and females ≥ 12 years of age with ES, including subjects with DS were enrolled. Enrollment into the exploratory hemodynamic sub-study was restricted to males and females ≥ 18 years of age, and subjects with DS were excluded from that sub-study.
- All subjects were required to have a confirmed diagnosis of ES (according to the European Society of Cardiology and European Respiratory Society Guidelines):

  (a) Established by echocardiography as:

  – Large congenital shunting defect at atrial, ventricular or arterial level (ASD, VSD, partial or complete atrioventricular septal defect [AVSD], patent ductus arteriosus [PDA], aortopulmonary [AP] window, total anomalous pulmonary venous return [TAPVR], and partial anomalous pulmonary venous return [PAPVR]; in isolation or combination); and

  – Right-to-left shunt or bi-directional shunt with prevalent right-to-left direction.

  The defects could be either unoperated or previously palliated surgically (provided significant residual defect remained).

  (b) Additionally, resting peripheral oxygen saturation (SpO2) was to be ≤ 90% and >70% during Screening.
- Subjects were required to have met the following catheterization criteria, with the cardiac catheterization performed within 5 years prior to Randomization or during the Screening period in the main study, and within 30 days prior to Randomization in the hemodynamic sub-study:

  – Mean resting pulmonary arterial pressure (mPAP) > 25 mmHg

  – Pulmonary capillary wedge pressure (PCWP), or mean left atrial pressure (mLAP), or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg

  – Pulmonary vascular resistance (PVR) ≥ 800 dyn·s/cm5 or ≥ 10 Wood units
- Specific dispositions for confirming ES during Screening by alternative procedures (limited central venous catheterization and advanced cardiac imaging), if needed, were made for subjects with DS (except those with arterial defects as the sole shunt lesions [PDA, AP window] and/or TAPVR, PAPVR).
- Subjects with WHO FC ≥ II were included.
- Subjects were required to reliably perform the 6-minute walk test (6MWT: minimum 50 m and maximum 450 m).
- Subjects were excluded if they had:

  – Known moderate-to-severe restrictive (i.e., total lung capacity [TLC] < 60% of predicted value) or obstructive (i.e., forced expiratory volume in one second [FEV1] < 80% of predicted value, and FEV1 / forced vital capacity [FVC] < 70%) lung disease

  – Significant left ventricular dysfunction (ejection fraction < 45%)

– Iron deficiency, defined as serum ferritin < 10 µg/L

– Treatment with endothelin receptor antagonists (ERAs) or prostanoids within 1 month prior to Randomization

– Initiated a phosphodiesterase-5 (PDE-5) inhibitor within 1 month prior to Randomization, or if the PDE-5 inhibitor dose had not been stable within 1 month prior to Randomization

– Initiated diuretics within 1 week prior to Randomization or if their diuretic treatment had not been stable within 1 week prior to Randomization

– Planned to have treatment, or had treatment with another investigational drug within 1 month prior to Randomization

Treatments

The investigational treatment was macitentan 10 mg film-coated tablets, administered orally once daily in the morning .

Placebo was provided as film-coated tablets that were indistinguishable in appearance to the macitentan tablets.

Outcomes/endpoints

Efficacy

Primary efficacy endpoint

Change from baseline to Week 16 in exercise capacity, as measured by the 6-minute walk distance (6MWD)

Secondary efficacy endpoints

Change from baseline to Week 16 in:

– WHO FC

– Dyspnea (assessed by the Borg dyspnea index)

– QoL (assessed by the SF-36 questionnaire)

Exploratory efficacy endpoints

Main study

• Percent of baseline NT-pro-BNP at EOT

• Change from baseline to Week 8 and Week 16 in systemic oxygen saturation, assessed by pulse oximetry: SpO2 at rest before the 6MWT and 0, 1 and 2 min after the end of the 6MWT

• Change from baseline to Week 8 and Week 16 in heart rate (HR) recovery (HRR) at 1 and 2 min post 6MWT (HRR 1= HR0 min post6MWT – HR 1 min post 6MWT; HRR 2= HR0 min post 6MWT – HR 2 min post 6MWT)

Sub-study

• Percent of baseline indexed pulmonary vascular resistance (PVRi) at Week 16

• Change from baseline to Week 16 in other cardiac hemodynamic parameters:

– mPAP

– mean right atrial pressure (mRAP)

– Indexed pulmonary blood flow / indexed systemic blood flow (Qpi/Qsi)

– Systemic vascular resistance index (SVRi)

– PVRi/SVRi

Safety

• Decrease in SpO_2>10% at rest at any time from baseline up to 30 days after study treatment discontinuation

• Treatment-emergent 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 SAEs up to 30 days after study treatment discontinuation

• Treatment-emergent AEs of special interest up to 30 days after study treatment discontinuation

• Treatment-emergent marked laboratory abnormalities (MLA) up to 30 days after study treatment discontinuation

• Change from baseline up to 30 days after study treatment discontinuation in laboratory parameters

• Treatment-emergent ALT and/or AST abnormality (> 3 and ≤ 5 × ULN; > 5 and ≤ 8 × ULN; > 8 × ULN) associated or not with total bilirubin > 2 × ULN, up to 30 days after study treatment discontinuation

• Additional treatment-emergent hemoglobin laboratory abnormalities 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, HR) and body weight

• Change from baseline up to 30 days after study treatment discontinuation in ECG variables

• Treatment-emergent ECG abnormalities up to 30 days after study treatment discontinuation

This study was conducted in accordance with Good Clinical Practice guidelines. The main features are summarized in

Table 1.

Table 1 MAESTRO study main characteristics

	Study objectives	Patients screened/ Evaluable	Demographic characteristics	Treatment/ dose	Design/type of control/ blinding
AC-055-305 (MAESTRO)	**Primary objective:** To demonstrate that macitentan improves exercise capacity (6MWD) in comparison to placebo in subjects with ES. **Secondary objectives:** to evaluate the effects of macitentan in comparison to placebo on: • WHO FC,	**Screened:** 319 subjects **Randomized:** 226 subjects **Treated:** 226 subjects **Evaluable efficacy:** 226 subjects	Sex: 76 male, 150 female Race: 109 White, 0 Black, 94 Asian 23 Other. Age range: 12-82 years	Macitentan 10 mg or . Placebo / o.d.	Double-blind

Study objectives	Patients screened/ Evaluable	Demographic characteristics	Treatment/ dose	Design/type of control/ blinding
• Dyspnoea (assessed by Borg dyspnoea index) • Quality of Life (assessed by the SF 36 questionnaire)	**Evaluable PK:** n/a **Evaluable safety:** 226 subjects			

6MWD = 6-minute walk distance; SF 36 = Short Form (36) Health Survey; WHO FC = World Health Organization functional class.

Statistical Methods

Primary efficacy endpoint

The null hypothesis was that there was no difference between macitentan and placebo for the mean change from baseline to Week 16 in 6MWD.

The main analysis was performed on the Full analysis set (FAS), i.e., all randomized subjects in the treatment group to which they were randomized and by imputing missing values at Week 16 according to pre-defined rules. The null hypothesis was tested by means of an analysis of covariance (ANCOVA) and rejected upon achieving a statistically significant difference at a predefined nominal significance level of α = 0.05 2-sided. The model for the change from baseline to Week 16 in 6MWD included treatment, presence of DS (yes/no), WHO FC (II vs III/IV) as categorical factors, and baseline 6MWD value as covariate.

The initial sample size estimation was based on the following assumptions:

• Normal distribution of the primary endpoint, with a pooled standard deviation (SD) = 75 m

• Minimum clinically relevant mean treatment difference to be detected = 35 m (macitentan vs placebo)

• Two-sided type-I error of 5% and type-II error of 10% (i.e., power of 90%).

A sample size of 98 subjects per treatment group has 90% power to detect a true treatment difference between macitentan and placebo of 35 m with a true SD for the primary endpoint of 75 m, based on a 2-sided significance level of 5% using the Student t-test.

It was planned to randomize ca. 220 subjects (110 per treatment arm), allowing for approximately 10% early drop-out.

Given the uncertainty of the variability for the primary endpoint in this subject population, a blinded sample size review was planned and performed to check the validity of the initial assumptions. Based on the results, it was recommended not to increase the sample size.

Secondary efficacy endpoints

To control for multiplicity across the primary and secondary efficacy endpoints, it was planned to analyze secondary endpoints hierarchically according to the sequence pre-specified in the protocol, each at the same significance level that was used for the primary endpoint, i.e., 0.05 two-sided level, if the following conditions were met:

• The predefined nominal significance level ($p<\alpha$ two-sided) was reached for the primary efficacy endpoint

• The predefined nominal significance level ($p<\alpha$ two-sided) was reached for all the previous endpoints in the sequence.

The improvement from baseline to Week 16 in WHO FC was analyzed by means of a logistic regression model including treatment and location of cardiac defect as categorical factors.

The change from baseline to Week 16 in Borg dyspnea index and SF-36 scores were analyzed by means of an ANCOVA model including treatment and location of cardiac defect as categorical factors, and baseline index/score as covariate.

Results

Recruitment / Number analysed

In the MAESTRO study, a total of 319 subjects were screened, of whom 226 were randomized to macitentan 10 mg (n = 114) and placebo (n = 112).

The study randomized 15 pediatric subjects aged 12 to 17 years, 13 of whom were treated with macitentan 10 mg and 2 of whom were treated with placebo. Additionally, all pediatric subjects completed the MAESTRO study and enrolled in the MAESTRO OL study. The baseline disease characteristics for pediatric subjects are summarized in Table 5. There was only 1 pediatric patient with DS (included in the macitentan arm).

Baseline data

Demographics characteristics for subjects aged 12-17 years are summarized below:

Table 4 **Demographics characteristics for subjects aged 12–17 years, Full analysis set**

ACT-064992
Protocol: AC-055-305
Demographics characteristics for subjects aged 12 - 17 years
Analysis Set: Full analysis set

	Macitentan 10 mg N = 13	Placebo N = 2	Total N = 15
Sex [n (%)]			
n	13	2	15
Male	1 (7.7)	1 (50.0)	2 (13.3)
Female	12 (92.3)	1 (50.0)	13 (86.7)
Age (years)			
n	13	2	15
Mean	14.7	13.5	14.5
SD	1.5	0.7	1.5
Median	14.0	13.5	14.0
Q1 , Q3	14.0, 16.0	13.0, 14.0	14.0, 16.0
Min , Max	12, 17	13, 14	12, 17
Weight (kg)			
n	13	2	15
Mean	43.2	38.0	42.5
SD	10.9	4.2	10.3
Median	42.2	38.0	41.0
Q1 , Q3	37.0, 52.0	35.0, 41.0	37.0, 52.0
Min , Max	26, 65	35, 41	26, 65
Height (cm)			
n	13	2	15
Mean	153.2	159.0	153.9
SD	9.8	12.7	9.9
Median	156.0	159.0	156.0
Q1 , Q3	147.0, 160.0	150.0, 168.0	147.0, 162.0
Min , Max	130, 165	150, 168	130, 168
BMI (kg/m^2)			
n	13	2	15
Mean	18.33	15.05	17.89
SD	4.15	0.78	4.02
Median	17.30	15.05	17.30
Q1 , Q3	16.40, 21.10	14.50, 15.60	15.60, 21.10
Min , Max	11.9, 26.0	14.5, 15.6	11.9, 26.0
Race [n (%)]			
n	13	2	15
Chinese	5 (38.5)	0	5 (33.3)
Other Asian	5 (38.5)	1 (50.0)	6 (40.0)
White	3 (23.1)	1 (50.0)	4 (26.7)
Ethnicity [n (%)]			
n	13	2	15
Not Hispanic or Latino	13 (100)	2 (100)	15 (100)
Geographical region [n (%)]			
n	13	2	15
Asia-Pacific	10 (76.9)	1 (50.0)	11 (73.3)
Western Europe-Israel	2 (15.4)	0	2 (13.3)
Eastern Europe	1 (7.7)	1 (50.0)	2 (13.3)

BMI=Body Mass Index, SD=Standard Deviation

Baseline disease characteristics are presented in the following table:

Table 5 Baseline disease characteristics for subjects aged 12–17 years, Full analysis set

ACT-064992
Protocol: AC-055-305
Baseline disease characteristics for subjects aged 12 - 17 years
Analysis Set: Full analysis set

	Macitentan 10 mg N = 13	Placebo N = 2	Total N = 15
Down syndrome status [n (%)]			
n	13	2	15
Yes	1 (7.7)	0	1 (6.7)
No	12 (92.3)	2 (100)	14 (93.3)
Time from ES diagnosis (years)			
n	13	2	15
Mean	2.18	6.97	2.82
SD	2.28	9.53	3.71
Median	0.98	6.97	0.98
Q1 , Q3	0.34, 4.46	0.23, 13.70	0.33, 5.29
Min , Max	0.0, 6.2	0.2, 13.7	0.0, 13.7
6MWD at baseline (m)			
n	13	2	15
Mean	386.9	351.0	382.1
SD	57.6	38.2	55.8
Median	403.0	351.0	399.0
Q1 , Q3	362.0, 438.0	324.0, 378.0	338.0, 438.0
Min , Max	265, 440	324, 378	265, 440
WHO functional class at baseline [n (%)]			
n	13	2	15
II	12 (92.3)	1 (50.0)	13 (86.7)
III	1 (7.7)	1 (50.0)	2 (13.3)
Borg dyspnea score at baseline			
n	13	2	15
Mean	2.46	3.50	2.60
SD	1.49	0.71	1.44
Median	2.00	3.50	3.00
Q1 , Q3	1.00, 4.00	3.00, 4.00	1.00, 4.00
Min , Max	0.5, 5.0	3.0, 4.0	0.5, 5.0
SpO2 at rest at baseline (%)			
n	13	2	15
Mean	85.5	79.5	84.7
SD	3.2	13.4	5.1
Median	86.0	79.5	86.0
Q1 , Q3	84.0, 87.0	70.0, 89.0	82.0, 89.0
Min , Max	80, 90	70, 89	70, 90
PDE-5 inhibitors at baseline [n (%)]			
n	13	2	15
No	12 (92.3)	2 (100)	14 (93.3)
Yes	1 (7.7)	0	1 (6.7)
SILDENAFIL CITRATE	1 (7.7)	0	1 (6.7)
Smoking behaviour [n (%)]			
n	13	2	15
Never	13 (100)	2 (100)	15 (100)

6MWD=6-minute walk distance, ES=Eisenmenger syndrome, PDE-5=Phosphodiesterase-5, SD=Standard Deviation

Efficacy results

The primary endpoint of MAESTRO was change from baseline to Week 16 in exercise capacity, as measured by 6-minute walk distance (6MWD).

The main analysis was based on an analysis of covariance model adjusted for randomized treatment group, DS status, WHO FC at baseline, and baseline 6MWD as covariates.

The mean (standard deviation [SD]) change from baseline to Week 16 in 6MWD in the overall population was an increase of 18.3 (84.4) m and 19.7 (53.0) m in the macitentan and placebo group, respectively. The least-square (LS) mean difference (95% confidence limits [CL]) in the overall population between macitentan and placebo for the change from baseline to Week 16 was –4.7 m (-22.8, 13.5); p = 0.612. The primary endpoint was therefore not met.

To assess the robustness of the results when classifying subjects according to important demographic characteristics, the following post-hoc analyses of 6MWD by age categories were performed:

- Change from baseline to Week 16 by age categories
- Between-Treatment analysis of change from baseline to Week 16 by treatment within subgroups – Exploratory analysis: summary of treatment-by-subgroup interaction tests by age categories
- Forest plot of change from baseline to Week 16 – Exploratory subgroup analysis by age categories

The mean (SD) change from baseline to Week 16 in 6MWD in pediatric subjects was an increase of 20.9 (34.9) m and 46.0 (35.4) m in the macitentan and placebo group, respectively [Table 2]. The LS

mean difference (95% CL) between macitentan and placebo for the change from baseline to Week 16 was –15.7 m (–110.3, 78.9); p = 0.744 [Table 3].

Table 2 **6MWD: Change from baseline to Week 16 in subjects 12–17 years, Full analysis set**

	Macitentan 10 mg N = 13	Placebo N = 2
Number of subjects included in the analysis		
n	13	2
Baseline		
Mean	386.9	351.0
SD	57.6	38.2
Median	403.0	351.0
Q1 , Q3	362.0, 438.0	324.0, 378.0
Min , Max	265, 440	324, 378
Week 16		
Mean	407.8	397.0
SD	70.1	2.8
Median	399.0	397.0
Q1 , Q3	369.0, 472.0	395.0, 399.0
Min , Max	290, 534	395, 399
Imputation for missing values at week 16		
n	0	0
Without an event[a]	0	0
With an event[b]		
Death	0	0
Within-Treatment change from baseline		
Mean	20.9	46.0
SD	34.9	35.4
Median	21.0	46.0
Q1 , Q3	-6.0, 44.0	21.0, 71.0
Min , Max	-39, 94	21, 71
Between-Treatment difference vs. Placebo		
Mean	-25.1	
SD	34.9	
SE	26.5	
95% CL of mean	-82.4, 32.2	
Median	-27.0	
95% CL of median	-110.0, 73.0	
P-value Wilcoxon rank sum test	0.3953	

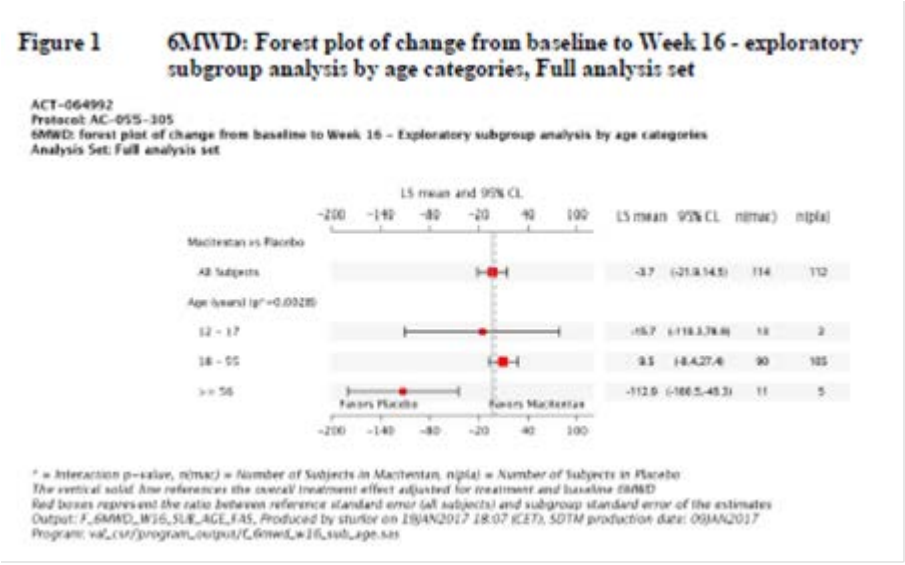
The 6MWD value presented at Week 16 is either the value at Visit 6 or Visit 6a in case of premature study treatment discontinuation. If missing: (a) imputed with ad-hoc rule; (b) imputed with 0 meters.
CL=Confidence Limit, SD=Standard Deviation, SE=Standard Error
Source: [Table 6]

Table 3 **6MWD: Between-Treatment analysis of change from baseline to Week 16 by treatment within subgroups - exploratory analysis: summary of treatment-by-subgroup interaction tests by age categories, Full analysis set**

	Macitentan 10 mg	Placebo	Macitentan - Placebo
Age: 12 - 17 years			
Number of subjects included in the analysis	13	2	
LS mean	24.2	39.9	-15.7
SE	17.5	44.7	48.0
95% CL	-10.4, 58.7	-48.2, 127.9	-110.3, 78.9
P-value			0.7438
Age: 18 - 55 years			
Number of subjects included in the analysis	90	105	
LS mean	31.1	21.7	9.5
SE	6.7	6.2	9.1
95% CL	18.0, 44.3	9.5, 33.8	-8.4, 27.4
P-value			0.2976
Age: >= 56 years			
Number of subjects included in the analysis	11	5	
LS mean	-109.1	3.8	-112.9
SE	19.3	28.3	34.3
95% CL	-147.1, -71.0	-51.8, 59.5	-180.5, -45.3
P-value			0.0012
Treatment-by-subgroup interaction p-value:	0.0028		

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and subgroup variable (as factors), Baseline 6MWD (as covariate), and the interaction treatment-by-subgroup variable. If the interaction is not statistically significant at 0.01, estimates are derived from the same model without the interaction term.
ANCOVA=Analysis of covariance, CL=Confidence Limit, LS Mean=Least Square Mean, SE=Standard Error
Source: [Table 7]

Figure 1 **6MWD: Forest plot of change from baseline to Week 16 - exploratory subgroup analysis by age categories, Full analysis set**



No further efficacy analyses for the pediatric sub-set were performed.

Safety results

The mean duration of exposure to study treatment in the overall population (including/excluding interruptions) was approximately 16 weeks in the macitentan and placebo groups.

The mean duration of exposure (including interruptions) to study treatment for pediatric subjects was approximately 16 weeks (similar to the overall population) and was similar in the macitentan and placebo groups [Table 8].

All 15 pediatric subjects completed 16 weeks of double-blind therapy and were subsequently enrolled in the open-label extension study (MAESTRO/AC-055-308), which is still ongoing.

Table 8 **Study treatment exposure for subjects aged 12–17 years, Safety analysis set**

ACT-064992
Protocol: AC-055-305
Study treatment exposure for subjects aged 12 - 17 years
Analysis Set: Safety analysis set

	Macitentan 10 mg N = 13	Placebo N = 2
Duration of study treatment (weeks)		
n	13	2
Mean	16.20	15.86
SD	0.29	0.20
Median	16.14	15.86
Q1 , Q3	16.00, 16.29	15.71, 16.00
Min , Max	16.0, 17.0	15.7, 16.0
Study treatment exposure, interruptions excluded (weeks)		
n	13	2
Mean	16.20	15.86
SD	0.29	0.20
Median	16.14	15.86
Q1 , Q3	16.00, 16.29	15.71, 16.00
Min , Max	16.0, 17.0	15.7, 16.0
Cumulative duration of study treatment [n (%)]		
At least 4 weeks	13 (100)	2 (100)
At least 8 weeks	13 (100)	2 (100)
At least 12 weeks	13 (100)	2 (100)
At least 16 weeks[a]	13 (100)	2 (100)
At least 20 weeks	0	0

(a) minus a time window of 6 days.
SD=Standard Deviation

The proportion of subjects aged 12-17 years with at least 1 treatment-emergent AE was 76.9% (n = 10) in the macitentan group and 50% (n = 1) in the placebo group [Table 9].

These rates are comparable to those in the overall MAESTRO population (66.7% in the macitentan group and 62.5% in the placebo group [D-16.551, table 12-2]).

All AEs in pediatric subjects were of mild or moderate intensity, whereas AEs of severe intensity were reported for 3.5% (n = 4) in the macitentan group and 2.7% (n = 3) in the placebo group in the overall MAESTRO population . AEs that were considered by the investigator to be drug-related were reported for 38.5% (n = 5) pediatric subjects in the macitentan group and none in the placebo group.

Table 9 Overview of treatment-emergent adverse events for subjects aged 12–17 years, Safety analysis set

ACT-064992
Protocol: AC-055-305
Overview of treatment-emergent adverse events (AE) for subjects aged 12 - 17 years
Analysis Set: Safety analysis set

Characteristic	Macitentan 10 mg N = 13 n (%)	Placebo N = 2 n (%)
Subjects with at least one AE	10 (76.9)	1 (50.0)
Severe AE	0	0
Drug-related AE	5 (38.5)	0
AE leading to study drug discontinuation	0	0
Serious AE	0	0
Drug-related serious AE	0	0
Fatal serious AE	0	0

Allergic rhinitis and sinus arrhythmia were the most frequently reported AEs, with a frequency of 15.4% (n = 2) in the macitentan group [Table 10]. Dyspnea/exertional dyspnea was reported in 1 pediatric subject in each of the macitentan and placebo groups. All other AEs were reported in individual subjects in the macitentan group

Table 10 Treatment-Emergent adverse events by preferred term for subjects aged 12–17 years, Safety analysis set

ACT-064992
Protocol: AC-055-305
Treatment-Emergent adverse events (AE) by preferred term for subjects aged 12 - 17 years
Analysis Set: Safety analysis set

Preferred Term	Macitentan 10 mg N = 13 n (%)	Placebo N = 2 n (%)
Subjects with at least one AE	10 (76.9)	1 (50.0)
Rhinitis allergic	2 (15.4)	0
Sinus arrhythmia	2 (15.4)	0
Acne	1 (7.7)	0
Alanine aminotransferase increased	1 (7.7)	0
Autoimmune thyroiditis	1 (7.7)	0
Bronchitis	1 (7.7)	0
Conjunctivitis	1 (7.7)	0
Cyanosis	1 (7.7)	0
Dizziness	1 (7.7)	0
Dyspnoea	1 (7.7)	0
Epistaxis	1 (7.7)	0
Fatigue	1 (7.7)	0
Haemoglobin decreased	1 (7.7)	0
Headache	1 (7.7)	0
Nasopharyngitis	1 (7.7)	0
Pruritus	1 (7.7)	0
Upper respiratory tract infection	1 (7.7)	0
Dyspnoea exertional	0	1 (50.0)

Deaths

There were no deaths in pediatric subjects, whereas 1 treatment-emergent serious adverse event (SAE) with fatal outcome was reported in an adult subject who received macitentan.

Serious adverse events

There were no SAEs in pediatric subjects during the 16 weeks of DB treatment in MAESTRO, whereas a total of 9 adult subjects, 7 (6.1%) in the macitentan group and 2 (1.8%) in the placebo group, experienced at least 1 treatment-emergent SAE in the overall MAESTRO population .

Adverse events leading to discontinuation of study treatment

There were no AEs leading to premature study treatment discontinuation in pediatric subjects, whereas a total of 4 adult subjects (2 macitentan, 2 placebo) had at least 1 AE that led to discontinuation of study treatment in the overall MAESTRO population .

Safety topics of special interest

Anemia

In the pediatric population, 1 subject on macitentan 10 mg had an AESI related to anemia), whereas 7 subjects in the overall population (6 macitentan, 1 placebo) had 1 treatment-emergent AESI related to anemia, reported as decreased hemoglobin (3 macitentan, 0 placebo), anemia (2 macitentan, 1 placebo), and iron deficiency anemia (1 macitentan, 0 placebo). None of these AEs were reported as serious or led to the discontinuation of study treatment. The AESI in the pediatric population involved a 14-year-old Chinese female subject and was reported as decreased hemoglobin, which was of mild intensity On Day 56, her hemoglobin concentration was 140 g/L compared to 171 g/L (normal range 114-151 g/L) at screening (Day −6). Study treatment was continued at the same dose and the event resolved without sequelae on Day 60 when a hemoglobin concentration of 166 g/L was reported. The subject completed the study on Day 115 and was enrolled into the extension study AC-055-308 on that day. A detailed subject narrative is provided in the MAESTRO CSR.

There were no further AESIs related to anemia reported in pediatric subjects.

- *Marked laboratory abnormalities relevant to anemia*

In the overall population, hemoglobin decreases from baseline of between ≥ 20 g/L and < 50 g/L were reported for 50 (22.1%) subjects, 40 (35.1%) in the macitentan group and 10 (8.9%) in the placebo group. Similarly, 3 pediatric subjects (23.1%) in the macitentan group had hemoglobin decreases from baseline of between ≥ 20 g/L and < 50 g/L vs none in the placebo group [Table 11].

Hypotension

6 adult subjects (3 macitentan, 3 placebo) each had a treatment-emergent AE of hypotension. None of the AEs were reported as serious or led to the discontinuation of study treatment. No pediatric subject had an AE related to hypotension.

Edema and fluid overload

A total of 14 adult subjects (8 macitentan, 6 placebo) had at least 1 treatment-emergent AE of special interest related to edema and fluid overload, with peripheral edema the most frequently reported (5 macitentan, 4 placebo). None of the AEs was reported as serious or led to the discontinuation of study treatment. No pediatric subject had an AE related to edema and fluid retention.

Liver tests

In the overall population a marked increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to (> 3 × upper limit of normal range [ULN]) was observed in 1 subject in each treatment group. A marked increase in ALT and AST to > 3 × ULN was observed for 1 adult subject in the placebo group, which led to the discontinuation of study treatment. In the pediatric population, a marked increase in ALT to > 3 × ULN was reported for 1 subject. This 16-year-old, white, female subject on macitentan 10 mg had an ALT increase of 4.2 × ULN (83 IU/L, normal range = 5–20 IU/L) at the End of Treatment on Day 114. All previous ALT and AST values reported by the central laboratory during the study for that subject, except for a mild elevation of ALT on Day 29 (24 IU/L), were within the normal range. The subject had no medical history related to liver test abnormalities, nor associated symptoms such as jaundice, hepatic enlargement or any other clinical signs of liver abnormality. Alkaline phosphatase and bilirubin remained within normal range throughout the study. The study treatment was continued at the same dose throughout the study. On Day 114, she was enrolled into the OL extension study (AC-055-308) as per protocol, based on local laboratory results, which were within normal range for liver parameters.

Additional information from the ongoing AC-055 308 OL extension study

Increased ALT was reported as a non-serious AE of mild intensity in the AC-055-308 OL extension study, starting on MAESTRO Day 114 (OL Day 1). The study drug was interrupted on OL Day 5 awaiting ALT re-test. The central laboratory re-tests performed on OL Day 7 were within normal range for liver parameters as well as local laboratory re-tests]. Therefore, based on multiple repeat central and local laboratory tests, it was concluded that the isolated central laboratory ALT elevation on Day 114 was a false positive signal; concomitant local laboratory analyses were within normal range, as well as the central laboratory retest performed within 7 days of first sample analysis. Macitentan was therefore reintroduced on OL Day 14 as per protocol. The subject continued and is still ongoing in the extension study, having recently completed Month 12 visit with no further out-of-range liver elevations.

2.3.3. Discussion on clinical aspects

The primary endpoint for MAESTRO was the change from baseline to Week 16 in 6MWD. The short term improvement in the 6MWT has been the most frequently used primary endpoint in the pivotal studies for the registration of PAH drugs, making it an important reference tool. Nevertheless, this approach has its limitations considering the lack of clear correlation between improvement in exercise capacity and overall survival (EMEA/CHMP/EWP/356954/2008).

The mean (SD) change from baseline to Week 16 in 6MWD in the FAS was an increase of 18.3 (84.4) m and 19.7 (53.0) m in the macitentan and placebo group, respectively, with a LS mean difference (95% CL) between macitentan and placebo of –4.7 m (−22.8, 13.5) (p = 0.612). The primary endpoint was therefore not met.

In pediatric subjects, there was a mean increase of 20.9 m and 46.0 m from baseline to Week 16 in the macitentan and placebo group, respectively. The LS mean difference (95% CL) between macitentan and placebo was –15.7 m (–110.3, 78.9) favouring placebo; p = 0.744. Although that the treatment effect appears to be similar to the one observed in the overall population, due to the small number of pediatric subjects and the imbalance between the treatment groups (n=13 on macitentan, n=2 on placebo), these results should be interpreted with caution.

Overall, the safety data were similar to those seen in the overall population both in frequency and distribution/type of AE. No deaths, SAEs or AEs leading to premature discontinuation of study treatment were reported in pediatric subjects. Although only 15 pediatric subjects were randomized in this study, the safety profile of macitentan in pediatric subjects, at the same dose as in adults (10 mg o.d.), appears to be similar to that in adults and aligned with the approved labeling information of Opsumit.

3. Rapporteur's overall conclusion and recommendation

The limited data from the MAESTRO study do not allow any meaningful clinical assessment of the efficacy of macitentan in the pediatric Eisenmenger Syndrome population. Overall, the safety data were similar to those seen in the overall population.

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.

☒ **Fulfilled:**

No regulatory action required.