EMA/620481/2019
Committee for Medicinal Products for Human Use (CHMP)

# Withdrawal assessment report

## Opsumit

International non-proprietary name: macitentan

Procedure No. EMEA/H/C/002697/II/0029

## Note

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

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## Assessment Timetable

| Timetable | Planned date | Actual date |
|---|---|---|
| Start of procedure: | 15 Sep 2018 | 15 Sep 2018 |
| CHMP Rapporteur Assessment Report | 09 Nov 2018 | 08 Nov 2018 |
| CHMP Co-Rapporteur Assessment Report | 09 Nov 2018 | 09 Nov 2018 |
| PRAC Rapporteur Assessment Report | 16 Nov 2018 | 23 Nov 2018 |
| PRAC members comments | 21 Nov 2018 | 21 Nov 2018 |
| Updated PRAC Rapporteur Assessment Report | 22 Nov 2018 | 28 Nov 2018 |
| PRAC endorsed relevant sections of the assessment report [3] | 29 Nov 2018 | 29 Nov 2018 |
| CHMP members comments | 03 Dec 2018 | 03 Dec 2018 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 06 Dec 2018 | 07 Dec 2018 |
| Request for Supplementary Information | 13 Dec 2018 | 13 Dec 2018 |
| Re-start of procedure: | 28 Jan 2019 | |
| CHMP Rapporteur Assessment Report | 26 Feb 2019 | 26 Feb 2019 |
| PRAC Rapporteur Assessment Report | 01 Mar 2019 | 04 Mar 2019 |
| PRAC members comments | 06 Mar 2019 | n/a |
| Updated PRAC Rapporteur Assessment Report | 07 Mar 2019 | n/a |
| PRAC endorsed relevant sections of the assessment report [3] | 14 Mar 2019 | 14 Mar 2019 |
| CHMP members comments | 18 Mar 2019 | 18 Mar 2019 |
| Updated CHMP Rapporteur(s) Assessment Report | 21 Mar 2019 | 22 Mar 2019 |
| 2nd Request for Supplementary Information | 28 Mar 2019 | 28 Mar 2019 |
| Re-start of procedure: | 14 Oct 2019 | |
| CHMP Rapporteur Assessment Report | 12 Nov 2019 | |
| PRAC Rapporteur Assessment Report | 15 Nov 2019 | |
| PRAC members comments | 20 Nov 2019 | |
| Updated PRAC Rapporteur Assessment Report | 21 Nov 2019 | |
| PRAC endorsed relevant sections of the assessment report [3] | 28 Nov 2019 | |
| CHMP members comments | 02 Dec 2019 | |
| Updated CHMP Rapporteur(s) Assessment Report | 05 Dec 2019 | |
| Opinion | 12 Dec 2019 | |

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# List of abbreviations

| | |
|---|---|
| 6MWD: | 6-minute walk distance |
| 6MWT: | 6-minute walk test |
| AE: | Adverse event |
| ANCOVA: | Analysis of covariance |
| CHMP: | Committee for Medicinal Products for Human Use |
| CI: | Confidence interval |
| CL: | Confidence limit |
| CO: | Cardiac output |
| CSAC: | Country-specific adjudication committee |
| CSR: | Clinical study report |
| CTEPH: | Chronic thromboembolic pulmonary hypertension |
| DB: | Double-blind |
| EOS: | End-of-study |
| EOT: | End-of- treatment |
| EQ-5D: | Euro Quality of Life-5D |
| ERA: | Endothelin receptor antagonist |
| ET: | Endothelin |
| $ET_A$: | Endothelin A |
| $ET_B$: | Endothelin B |
| EU: | European Union |
| FAS: | Full Analysis Set |
| FC: | Functional class |
| HSSI: | Health state summary index |
| LOCF: | Last observation carried forward |
| LS: | Least squares |
| MERIT-1: | DB study AC-055E201 |
| MERIT-2: | OL study AC-055E202 |
| MPAP: | Mean pulmonary arterial pressure |
| MRAP: | Mean right atrial pressure |
| NT-proBNP: | N-terminal pro B-type natriuretic peptide |
| o.d.: | Once daily |
| OL: | Open-label |
| OPUS: | OPsumit USers Registry |
| PAH: | Pulmonary arterial hypertension |
| PAH-SYMPACT™: | Pulmonary Arterial Hypertension–Symptom and Impact™ |
| PDE-5: | Phosphodiesterase type 5 |
| PEA: | Pulmonary endarterectomy |
| PH: | Pulmonary hypertension |
| PI: | Product Information |

| | |
|---|---|
| PPS: | Per-protocol Set |
| PTOP: | Post-treatment observation period |
| PVR: | Pulmonary vascular resistance |
| RHC: | Right heart catheterization |
| RMP: | Risk Management Plan |
| SAE: | Serious adverse event |
| SAP: | Statistical Analysis Plan |
| SCE: | Summary of Clinical Efficacy |
| SD: | Standard deviation |
| SGC: | Soluble guanylate cyclase |
| $SvO_2$: | Mixed venous oxygen saturation |
| VAS: | Visual analog scale |
| WHO: | World Health Organization |

# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Actelion Registration Limited submitted to the European Medicines Agency on 28 August 2018 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA and IIIB |

Extension of Indication to include treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), based on the pivotal study MERIT-1 (AC-055E201), together with 6 months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202), as well as a drug-drug interaction (DDI) study (AC-055-122) of macitentan and rosuvastatin, a DDI study (AC-055-123) of macitentan and riociguat, and observational data from the OPUS Registry (OPsumit USers Registry; cut-off date of 17 April 2018).

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 are being updated and the Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to implement editorial changes and to align the annexes with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet.

An updated Risk Management Plan (RMP) version 9.2 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the RMP.

## *Information relating to orphan designation*

Macitentan (Opsumit), was designated as an orphan medicinal product EU/3/11/909 on 27 September 2011, for the treatment of pulmonary arterial hypertension (PAH). Macitentan has been authorised in the EU as Opsumit since 20 December 2013.

The new indication (i.e.: treatment of CTEPH), which is the subject of this application, does not fall within the above mentioned orphan designation (i.e.: treatment of PAH). In the classification of Pulmonary Hypertension, PAH corresponds to Group 1 while CTEPH corresponds to Group 4. They are therefore considered as separate conditions.

The applicant did not request an orphan designation for macitentan for the treatment of CTEPH within the EU. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non-orphan indication in the same marketing authorisation. Consequently, the MAH is committed to request the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products within 2 days after the receipt of the CHMP opinion (if positive to the grant of the new indication). Should the MAH not request the withdrawal of the orphan designation within the said deadline, nor request re-examination in accordance with Article 16(4) of Commission Regulation (EC) No. 1234/2008, the validation of this variation application becomes automatically null and void with retroactive effect.

### *Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/PDCO/217421/2017 on the granting of a product-specific waiver (EMEA-001032-PIP02-17) for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH). The waiver covers all subsets of the paediatric population with CTEPH, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

### *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

To date, one medicinal product has been approved in the EU for the treatment of CTEPH: riociguat (Adempas®), a soluble guanylate cyclase (sGC) stimulator. It was granted orphan market exclusivity in the treatment of CTEPH until 26 March 2024.

The applicant concludes that macitentan (Opsumit) and riociguat (Adempas®) do not have the same mechanism of action or structural molecular features, and therefore are not considered similar. The applicant's conclusion is endorsed (see attached similarity assessment report)

### Derogation(s) of market exclusivity

Not applicable

### *Protocol assistance*

The MAH did not seek Protocol assistance at the CHMP.

# 2. Scientific discussion

## *2.1. Introduction*

Macitentan (ACT-064992) (N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl) oxy] ethoxy]-4-pyrimidinyl]-N'-propylsulfamide) is an orally active, dual endothelin (ET) receptor antagonist (ERA). *In vitro*, macitentan selectively inhibits the binding of endothelin-1 (ET-1) to $ET_A$ and $ET_B$ receptors as well as the effects mediated by these receptors in functional assays [see Marketing Authorisation Application (MAA) Module 2.6.2, EMEA/H/C/002697/00].

Macitentan 10 mg once daily (o.d.) was approved on 20 December 2013 in the EU for the treatment of pulmonary arterial hypertension (PAH) and is marketed under the trade name Opsumit®. Macitentan is approved for PAH in more than 50 countries, including the US and Japan.

It was approved in Brazil for the treatment of CTEPH on 9 July 2018. It has been accepted for review by the US FDA for the treatment of adults with inoperable CTEPH (World Health Organization [WHO] Group 4).

This dossier is submitted to provide the efficacy and safety results of the MERIT-1 and MERIT-2 study to support the use of macitentan 10 mg once daily for the treatment of inoperable CTEPH.

The intended indication is:

Chronic thromboembolic pulmonary hypertension (CTEPH)

Opsumit is indicated for the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) in adult patients of WHO FC II to III, to improve exercise capacity (see section 5.1).

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which is considered acceptable.

As the purpose of this type II variation is to add a new therapeutic indication to the Opsumit Marketing Authorisation (MA) in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH), this application would increase environmental exposure to macitentan and the environmental risk assessment (ERA) has been updated.

### 2.2.1. Ecotoxicity/environmental risk assessment

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006).

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

$$PEC_{SW} = \frac{DOSEai \cdot F_{pen}}{WASTEWinhab \cdot DILUTION}$$

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

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

*DILUTION* = 10 (–)

$F_{pen}$ represents the fraction of a population receiving the drug substance during a given time. The applicant has revised the $F_{pen}$ refinement and updated the environmental risk assessment based on prevalence data of PAH and CTEPH in Sweeden and Great Britain (Rådegran 2016, NHS 2018 and ONS 2017) respectevely, wich according to the applicant are the countries with the highest PAH and CTEPH prevalences:

The prevalence of PAH I Sweeden is 4.9/100,000 inhabitants. Thus, in Europe with a population of 518,330,149 inhabitants a maximum number of 25,399 can be treated with macitentan per year.

The prevalence of CTEPH in Great Britain is 35/1,000,000. In Europe, with a population of 518,330,149 inhabitants a maximum number of 18,142 patients can be treated with macitentan per year.

The maximum daily dose is 10 mg/day. The treatment time is throughout the year (365 days). Thus, a total amount of macitentan of 158.9 kg/year is used in Europe. This predicted amount used per year is evenly distributed over the year and throughout the geographic area. Consequently, a market penetration factor $F_{pen}$ of 0.000084 can be calculated as follows:

$F_{pen}$ = consumption / (DDD x inhabitants x 365)

Consumption= (Daily dose x treatment time x prevalence)

DDD or Daily dose = 10 mg x inhab x day $^{-1}$

Treatment time = 365 days

Prevalence PH = 25,399 patients

Prevalence CTEPH =18,142 patients

Inhabitants =518,330,149.

This $F_{pen}$ value (0.000084) value is used in the PEC calculation instead of the EMEA default value of 0.01.

The resulting $PEC_{sw}$ as calculated by the applicant is 0.00042 ng/L, which is below the EMA action limit of 0.01 µg/L.

### 2.2.2. Discussion on non-clinical aspects

The $F_{pen}$ refinement as presented by the applicant would require further clarifications to be accepted. The Applicant stated that $F_{pen}$ value is based on PAH and CTEPH prevalence data in Sweeden and Great Britain, respectevely, which are the countries with the highest PAH and CTEPH prevalences. Submitted references show the PAH prevalences vary largely among different member states (i.e. from 4.6 per million in Spain to 25 per million in Sweden) and thus the prevalence data of PAH from Sweden are acceptable for the refinement of $F_{pen}$. However, the Applicant should clarify how prevalence of CTEPH in Great Britain was calculated or use prevalence data from a reliable source as Orphanet . In both cases , PAH and CTEPH, prevalence data should be also updated with the most recent published data of European population (1st January of 2018) and $PEC_{surfacewater}$ value should be recalculated with the the new $F_{pen}$ values (OC).

According to the EMA guideline on the environmental risk assessment of medicinal products for human use, the submission of data on log Kow is part of a Phase I ERA to allow for a PBT screening. Information on the log Kow of Macitentan was provided as a IB variation (EMEA/H/C/002697/IB/0002). The Applicant determined the log Kow value for macitentan according to the slow stirring method (OECD 123) as it was recommended by the CHMP during the marketing authorization procedure. The log Kow values was 3.91, which is lower than the EMA trigger value for log Kow of 4.5. Therefore, macitentan has not to be screened for persistence, bioaccumulation and toxicity.

### 2.2.3. Conclusion on the non-clinical aspects

Considering the above data, macintentan is not expected to suppose a risk for the environment. However, the ERA for macitentan should be updated with prevalence data from orphanet.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

This application concerns the use of macitentan 10 mg o.d. for the treatment of CTEPH in adult patients of WHO functional class (FC) II to III deemed inoperable [i.e., not candidates for pulmonary endarterectomy (PEA)], to improve exercise capacity. Patients with recurrent or persistent CTEPH after PEA are excluded from the proposed indication, because they were excluded in the phase II MERIT-1 single pivotal study.

The new indication is supported by the pivotal phase II study MERIT-1 (AC-055E201), together with 6

months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202), and observational data from the OPUS Registry (OPsumit USers Registry; cut-off date of 17 April 2018). A drug-drug interaction (DDI) study (AC-055-122) of macitentan and rosuvastatin and a DDI study (AC-055-123) of macitentan and riociguat, are also submitted to include a statement about the lack of interaction with these drugs in section 4.5.

## GCP

The MAH has provided an ambiguous statement for a list of 25 studies that is inconsistent with the list of studies provided within the application (Module 1.9). The statement reads "The applicant confirms that the above study conducted within the European Union meets the ethical requirements of Directive 2001/20/EC". It is unknown if this is a typo erratum (it should read "above studies") or if it refers to only one of these 25 studies.

In addition, most of these 25 studies included in the list are not included in the submission, while study AD-055E202 (MERIT-2, which is an open label extension of the "pivotal" phase II study MERIT-1), is included in the submission as supportive, but not included in the list of studies in the GCP statement (see RSI). According to European regulation, applications based on a single pivotal trial should be particularly compelling. In this case, the applicant statement is ambiguous on whether all studies, or only a part of them, are GCP compliant. This issue should be clarified. In addition, the results of any audits or inspections available for this clinical trial should be submitted (see RSI).

- **Tabular overview of clinical studies**

The clinical development program for macitentan in the treatment of CTEPH includes a single, Phase 2 study in adult subjects with inoperable CTEPH (AC-055E201/MERIT-1) [Ghofrani HA, et al. Lancet Respir Med. 2017;5:785-94] [Torbicki A. Lancet Respir Med. 2017;5:762-763], and the ongoing open-label (OL) extension for that study (AC-055E202/MERIT-2) [Module 5.3.5.1].

**Table 1**].

Additional "outcome" data (WHO functional class [FC], 6MWD, hospitalization) on macitentan (including in combination with riociguat) are available from the OPUS Registry [Table 1].

**Table 1. Summary of clinical studies contributing efficacy and post-marketing registry with outcome data**

| Study [Doc No.] | Study population | Study objectives | Number of subjects<br><br>Treatment/dose/route<br><br>Median treatment duration | Type of control/blinding/ design | Efficacy endpoints |
|---|---|---|---|---|---|
| **MERIT-1** (AC-055E201) Completed [Ghofrani et al, 2017]<br><br>FSFV:<br>20 August 2014<br>LSLV:<br>28 September 2016 | Adult subjects with inoperable CTEPH (symptomatic PH in WHO FC II, III or IV due to CTEPH)[a] | **Primary:** To evaluate the effect of macitentan 10 mg on PVR at rest in comparison with placebo.<br><br>**Secondary:**<br>To evaluate the effects of macitentan 10 mg on exercise capacity, dyspnea, and WHO FC in comparison with placebo.<br><br>**Safety:** To evaluate the safety and tolerability of macitentan 10 mg. | **Screened:** 186;<br>**Randomized:** 80 (macitentan = 40; placebo = 40);<br>**Treated and evaluable:** All 80 subjects.<br><br>**Treatment**<br>Macitentan 10 mg o.d.<br>Placebo o.d.<br>Oral<br><br>**Median treatment duration**<br>Macitentan: 24.2 weeks<br>Placebo: 24.1 weeks | Randomized, double-blind, placebo-controlled, parallel-group | **Primary endpoint:** PVR at rest at Week 16.<br><br>**Secondary endpoints:**<br>- Exercise capacity (6MWD),<br>- Borg dyspnea index (collected at end of 6MWT),<br>- Proportion of subjects with worsening in WHO FC.<br><br>**Exploratory endpoints[c]:**<br>- Time to first PH-related disease progression,<br>- NT-proBNP,<br>- Change from baseline in PAH-SYMPACT™ symptom and impact part scores, |

| Study [Doc No.] | Study population | Study objectives | Number of subjects<br><br>Treatment/dose/route<br><br>Median treatment duration | Type of control/blinding/ design | Efficacy endpoints |
|---|---|---|---|---|---|
| | | | | | - Change from baseline in quality of life assessed by the EQ-5D. |
| **MERIT-2** (AC-055E202; Extension of MERIT-1)<br>Ongoing<br><br>FSFV:<br>9 February 2015<br>Cut-off:<br>17 October 2017 | Adult subjects with inoperable CTEPH who completed MERIT-1 as scheduled | **Efficacy:** To evaluate the long-term effects of macitentan 10 mg on exercise capacity and WHO FC<br><br>**Safety:** To evaluate the long-term safety and tolerability of macitentan 10 mg. | **Enrolled:** 76 subjects (DB macitentan = 40; DB placebo = 36);<br>**Treated and evaluable:** All 76 subjects<br><br>**Treatment**<br>Macitentan 10 mg o.d.<br>Oral<br><br>**Median treatment duration**<br>18.4 months[b] | Long-term, single-arm, open-label extension study of MERIT-1 | **Exploratory endpoints:**<br>- Exercise capacity (6MWD),<br>- Borg dyspnea index (collected at end of 6MWT),<br>- Proportion of subjects with worsening in WHO FC. |
| **OPUS** Opsumit USers Registry AC-055-503 (post-marketing registry)<br>Ongoing<br><br>Cut-off:<br>17 April 2018 | Any patient newly initiated on macitentan (Opsumit) | To characterize the safety profile and to describe the clinical characteristics and outcomes of patients newly treated with Opsumit in the post-marketing setting | **CTEPH: 45**<br>(including 27 on soluble guanylate cyclase stimulator background therapy)<br>**Treatment**<br>Macitentan 10 mg o.d.<br>Oral<br>**Median treatment duration**<br>9.9 months[d] | Uncontrolled, prospective observational macitentan drug registry | **Outcome assessments:**<br>- 6MWD<br>- WHO FC<br>-Hospitalization |

[a] For subjects in WHO FC III or IV at baseline, PH advanced therapies were allowed (i.e., PDE-5 inhibitors, oral or inhaled prostanoids) at a stable dose for at least 1 month before baseline RHC and up to end-of-treatment.
[b] study treatment duration up to 17 October 2017 [Source: Module 5.3.5.3, Appendix 1 table 2 (T_EXP_SS)].
[c] Additional exploratory measures are presented in the CSR [Source: Module 5.3.5.1, section 11.2.2].
[d] Up to 17 April 2018 [Source: Module 5.3.5.4, table 11].

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CSR = clinical study report; CTEPH = chronic thromboembolic pulmonary hypertension; DB = double-blind; EQ-5D = Euro Quality of Life-5D; FC = functional class; FSFV = first subject first visit; LSLV = last subject last visit; o.d. = once daily; NT-proBNP = N-terminal pro B-type natriuretic peptide; PDE-5 = phosphodiesterase type 5; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; WHO = World Health Organization.

## 2.3.2. **Pharmacokinetics**

To support this application the company has submitted two new pharmacokinetic drug drug interaction (DDI) studies (AC-055-122 and AC-055-123) and pharmacokinetic data of the MERIT-1 study (AC-055-E201). Further the applicant submitted a clinical overview in which the pharmacokinetic properties of macitentan are shortly described. This overview refers to previously submitted data and compares the pharmacokinetic results of CTEPH patients (from MERIT study) to previously collected data of PAH patients.

The results of the DDI studies and the PK results of the MERIT study and the comparison of pharmacokinetic results of CTEPH patients and PAH patients are presented below.

### *Absorption*
N/A.

### *Distribution*
N/A.

### *Elimination*
N/A.

## *Dose proportionality and time dependencies*
N/A.

## *Special populations*
N/A.

## *Pharmacokinetic interaction studies*

Two new drug-drug interaction clinical pharmacology studies of macitentan with rosuvastatin (AC-055-122) and riociguat (AC-055-123) to investigate the effect on intestinal BCRP transporters have been submitted (please see the table below). In vitro, macitentan inhibits breast cancer resistance protein (BCRP) transporters with a 50% inhibitory concentration of 1.0 µM. BCRP is an efflux pump located in the gut, liver canalicular membrane, and kidney, and is exposed to intracellular drug concentrations in the liver and the kidney. Considering the high degree of plasma protein binding, free plasma concentration of macitentan is not expected to inhibit BCRP-mediated transport in the liver or the kidney. However, the extent of the effect of macitentan, if any, on intestinal BCRP is unknown.

This information is of clinical relevance in the context of the new indication pursued in patients with CTEPH, as the only drug approved in this indication (riociguat) is a BCRP substrate.
Both studies were conducted in full conformance with the principles of the 'Declaration of Helsinki' and with the laws and regulations of Germany. A written commitment to comply with International Council for Harmonisation (ICH)-GCP and the study protocol was obtained from the investigator. Prior to the start of the studies/implementation of the amendments, the German Agency and Ethics Committee reviewed and approved the protocol and their amendments.

**Table 1 Completed clinical pharmacology studies**

| Study [Doc No.] | Study objectives | Subjects enrolled/ evaluable for pharmacology & safety | Demographic characteristics | Treatment/dose/route of administration | Design/type of control/blinding |
|---|---|---|---|---|---|
| AC-055-122 [D-18.042] | *Primary objective*<br>• To evaluate the effect of macitentan at steady state on the PK of single-dose rosuvastatin in healthy male subjects.<br>*Secondary objectives*<br>• To evaluate the tolerability and safety of concomitant administration of macitentan and rosuvastatin in healthy male subjects.<br>• To evaluate the PK of macitentan and ACT-132577 at trough. | **Enrolled & evaluable safety:** 20 subjects<br><br>**Evaluable PK:** 18 subjects | Sex: Male<br><br>Ethnicity: 19 White, 1 American Indian or Alaska Native<br><br>Age range: 19–55 years<br><br>BMI range: 19.6–28.7 kg/m$^2$ | Oral macitentan<br>Oral rosuvastatin<br><br>**Treatment A:**<br>Day 1: a single dose of rosuvastatin 10 mg followed by a PK and safety evaluation period of 96 h.<br><br>**Treatment B:**<br>**B1:** a single oral dose of 30 mg (3 × 10 mg tablets) macitentan on Day 5 + o.d. oral dose of 10 mg macitentan from Days 6–9.<br><br>**B2:** a single oral dose of rosuvastatin 10 mg on Day 10 + o.d. oral dose of macitentan 10 mg from Days 10–16. | Single-center, open-label, one-sequence, two treatment |
| AC-055-123 [D-18.171] | *Primary objective*<br>• To evaluate the effect of macitentan at steady state on the PK of riociguat after a single dose of riociguat in healthy male subjects.<br>*Secondary objectives*<br>• To evaluate the effect of macitentan at steady state on the PK of the metabolite of riociguat, M1, after a single dose of riociguat in healthy male subjects.<br>• To evaluate the PK of macitentan and its active metabolite, ACT-132577, at trough.<br>• To evaluate the tolerability and safety of concomitant administration of macitentan and riociguat in healthy male subjects. | **Enrolled & evaluable PK & safety:** 20 subjects | Sex: Male<br><br>Ethnicity: 19 White, 1 Asian<br><br>Age range: 22–45 years<br><br>BMI range: 19.2–29.8 kg/m$^2$ | Oral macitentan<br>Oral riociguat<br><br>**Treatment A:**<br>Day 1: a single dose of riociguat 1 mg followed by a PK and safety evaluation period of 96 h.<br><br>**Treatment B:**<br>**B1:** a single oral dose of 30 mg (3 × 10 mg tablets) macitentan on Day 5 + o.d. oral dose of 10 mg macitentan from Days 6–9.<br><br>**B2:** a single oral dose of 1 mg riociguat on Day 10 + o.d. oral dose of macitentan 10 mg from Days 10–15. | Single-center, open-label, one-sequence, two treatment |

BMI = body mass index; o.d. = once daily; PK = pharmacokinetics.

## Analytical Method

Pre-study validation

The bioanalytical method was assessed previously in the MAA and it was considered adequate.

In study validation

A total of 1130 plasma samples were received. Out of these, 890 samples for rosuvastatin and 240 samples for macitentan, and ACT-132577 were analysed.

**Clinical Study Report AC-055-122**

Bioanalytical study No.: BA-17.040

ACT-064992 (Macitentan) and its metabolite ACT-132577
The concentrations of ACT-064992 and its metabolite ACT-132577 samples from clinical study AC-055-122 were quantified using a LC-MS/MS in human $K_3$EDTA plasma method following protein precipitation, in a concentration range from 1.00-2000.00 ng/mL as validated in studies BA-13.225 and BA-14.033.
The 240 study samples were analyzed in three batches from November 29th, 2017 to December 18th, 2017.

Each batch contained nine calibration samples, at least three sets of three QCs, a blank sample. To minimize carry-over during measurement, double-blank samples (no reference item and no internal standard) were included in each batch.

An interference test showed that rosuvastatin at a concentration of 50.0 nglmL had no influence on the quantification of ACT-064992 or ACT-132577 in human plasma (the interference of rosuvastatin as part of batch 1 failed due to a sample preparation error).

The between-run precision (%CV) and accuracy (%RD) of the calibration standards for ACT-064992 ranged from 1.8% to 5.8% and from -4.4 % to 4.7%, respectively.

The between-run precision (%CV) and accuracy (%RD) of the calibration standards for ACT-132577 ranged from 1.1% to 6.6 % and from -2.0 %to 3.3%, respectively.

The between-run precision and precision QCs of ACT-064992 ranged from 2.3% to 4.9% and from -3.9 % to 5.9%, respectively.

the between-run precision and precision QCs of ACT-132577 ranged from 2.7% to 5.1 %, and from -4.1%to 3.6%, respectively.

Neither the calibration standards nor the QCs were rejected.

No sample reanalysis was performed.

The incurred sample re-analysis was performed in a total of 25 samples for both analytes. The results show that 100 % for both ACT-064992 and ACT-132577 of the ISR measurements were within ±20 %.

Rosuvastatin

ACC Project-No.: 314B17
The quantification of rosuvastatin in the study samples was performed by using an LC-MS/MS detection method following liquid-liquid extraction, as validated in ACC Project-No. 307B17-Val.
Plasma samples were stabilised with sodium acetate buffer immediately upon sampling in the clinic to prevent the chemical instability of 5S-lactone of rosuvastatin and its possible inter-conversion to rosuvastatin at natural pH.

In Supplement 1 to the Validation Report the calibration range of the standard curve is specified as 0.0400 ng/ml to 50.0 ng/ml for rosuvastatin. In the present study, the upper limit of quantification was reduced but remained within the validated calibration range. The calibration range used was 0.0400 ng/ml to 25.0 ng/ml for rosuvastatin.

The 890 study samples were analysed in 11 runs from November 28th, 2017 to December 05th, 2017.
Each batch contained ten calibration samples in singlet, at two sets of five QCs, a blank sample.
The between-run precision (%CV) and accuracy (%RD) of the calibration standards ranged from 1.5% to 3.7% and from -5.1% to 5.6%, respectively.

The between-run precision and precision QCs ranged from 1.9% to 6.1% and from -9.3 % to 4.0, respectively.

Three calibration standards and three QCs were rejected. Not more than one was rejected at the same run for both calibration standard and QC. For run 03 the LLOQ was rejected.

A total of fifty-four (54) individual samples were re-analysed (6.07% of the total samples analysed) due to the following reason:

- The LLOQ of Run-03 was rejected due to analytical reason. All samples with concentrations below the next lowest calibration standard was repeated (20 samples),
- Sample preparation error (7 samples),
- Confirmation measurement (27 samples). The value of the first measurement was reported for these samples.
-

The original values, repeat values and accepted values have been submitted for each repeated sample.

The incurred sample re-analysis was performed in a total of 96 samples. The results show that 100 % of the ISR measurements were within ±20 %.

**Clinical Study Report AC-055-122**

A total of 1000 plasma samples were received. Out of these, 760 samples for riociguat and its metabolite desmethyl-riociguat and 240 samples for macitentan, and ACT-132577 were analysed.

ACT-064992 (Macitentan) and its metabolite ACT-132577

Bioanalytical study no. BA-17.047
The concentrations of ACT-064992 and its metabolite ACT-132577 samples from clinical study AC-055-122 were quantified using a LC-MS/MS in human $K_3$EDTA plasma method following protein precipitation, in a concentration range from 1.00-2000.00 ng/mL as validated in studies BA-13.225 and BA-14.033.
The 240 study samples were analyzed in three batches from January 26$^{th}$, 2018 to February 02$^{nd}$, 2018.
Each batch contained nine calibration samples, at least three sets of three QCs, a blank sample. To minimize carry-over during measurement, double-blank samples (no reference item and no internal standard) were included in each batch.

An interference test showed that riociguat at a concentration of 500.0 nglmL had no influence on the quantification of ACT-064992 or ACT-132577 in human plasma (the interference of riociguat as part of batch 1 failed due to a sample preparation error).

The between-run precision (%CV) and accuracy (%RD) of the calibration standards for ACT-064992 ranged from 1.1% to 3.5% and from -1.9% to 1.3%, respectively.

The between-run precision (%CV) and accuracy (%RD) of the calibration standards for ACT-132577 ranged from 0.2% to 4.2% and from -3.2 %to 2.8%, respectively.

The between-run precision and precision QCs of ACT-064992 ranged from 3.1% to 7.7% and from -3.4% to 1.6%, respectively.

The between-run precision and precision QCs of ACT-132577 ranged from 2.6% to 6.2%, and from -3.5% to 1.7%, respectively.

No calibration standard was rejected and only one QC was out of the acceptance range for both analytes.
No sample reanalysis was performed.

The incurred sample re-analysis was performed in a total of 26 samples for both analytes. The results show that 96.2% and 100 % for ACT-064992 and ACT-132577, respectively, of the ISR measurements were within ±20 %.

Riociguat and its metabolite desmethyl-riociguat

ACC Project-No.: 316B17

The quantification of riociguat and its metabolite desmethyl-riociguat in the study samples was performed by using LC-MS/MS detection method following liquid/liquid extraction in a concentration range from 0.200-100.00 ng/mL for both analytes, as validated in ACC Project-No. 315B17-Val.

The 760 study samples were analyzed in eleven batches from January 29th, 2018 to February 09th, 2018.
The between-run precision (%CV) and accuracy (%RD) of the calibration standards for riociguat ranged from 1.8% to 4.2% and from -3.6% to 7.3%, respectively.

The between-run precision (%CV) and accuracy (%RD) of the calibration standards for desmethyl-riociguat ranged from 0.2% to 4.2% and from -3.2 %to 2.8%, respectively.

The between-run precision and precision QCs of riociguat ranged from 2.7% to 5.7% and from -6.5% to 1.1%, respectively.

The between-run precision and precision QCs desmethyl-riociguat ranged from 3.2% to 5.0%, and from -3.0% to 2.8%, respectively.

Neither the calibration standards nor the QCs were rejected.

A total of two (2) and one individual samples were re-analysed for riociguat and desmethyl-riociguat, respectively (0.26% and 0.13% of the total samples analysed) due to the following reason:

- Sample preparation error (1 sample for each analytes),
- Sample above the ULOQ (1 samples for riociguat). The sample was diluted (1:10) and measured again to be within the linearity range
-

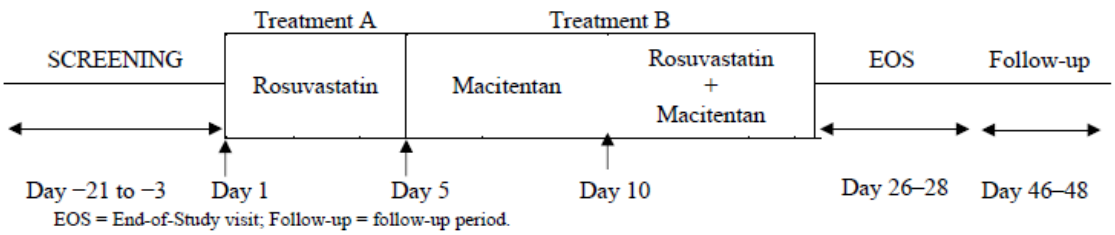
The original values, repeat values and accepted values have been submitted for each repeated sample.

The incurred sample re-analysis was performed in a total of 80 samples for both analytes. The results show that 90.0% and 88.8% for riociguat and desmethyl-riociguat, respectively, of the ISR measurements were within ±20 %.

**Clinical Study Report AC-055-122 (EudraCT Number: 2017-003095-31)**

This was a single-center, open-label, one-sequence, two-treatment, Phase 1 studies to evaluate the effect of macitentan at steady-state on the PK of single-dose rosuvastatin in healthy male subjects.
The study design is presented in Figure below.

**Figure 1 Study design**



EOS = End-of-Study visit; Follow-up = follow-up period.

The clinical part was performed at CRS Clinical Research. Services Mannheim, Grenadierstr. 1, 68167 Mannheim, Germany between November 03rd, 2017 and November December 04th, 2017 and the principal investigator was Dr. Armin Schultz, MD.

The protocol version 1 (dated August 10th, 2017) was amended to change inclusion criteria 5 and exclusion criteria 6 and 7. The resulting amended protocol is Version 2 dated October 11th, 2017.
Prior to the start of the study/implementation of the amendment, the national health authority of Germany and Ethics Committee reviewed and approved the protocol on October 25th, 2017.

Treatments administered
The subjects remained fasted from at least 10 h prior to and up to 4 h after rosuvastatin administration. Water intake (except for the 240 mL used for dosing) was restricted from 1 h prior to until 1 h after rosuvastatin or rosuvastatin + macitentan administration.

Treatment A (rosuvastatin alone)

A single oral dose of rosuvastatin 10 mg administered in the fasted state on Day 1 followed by a PK and safety evaluation period of 96 h.

Treatment B (macitentan + rosuvastatin):
A single oral loading dose of macitentan 30 mg (3 × 10 mg tablets) administered in the fasted state on Day 5; thereafter, macitentan 10 mg was administered once daily (o.d.) from Day 6 to Day 16 (i.e., 11 doses).

A single oral dose of rosuvastatin 10 mg was administered concomitantly with macitentan in the morning of Day 10, in the fasted state, followed by a PK and safety evaluation period of 168 hours (Day 10 to Day 17).

***Assessor´s comment:***
*The study design was in line with current regulatory guidelines on the conduct of DDI studies.*
*Due to the long t½ of ACT-132577 (48 h), a single sequence design (rosuvastatin alone followed by rosuvastatin + macitentan) was selected to avoid a lengthy washout period and unnecessary prolongation of subjects' participation in the study.*
*The dose range of rosuvastatin is 5–40 mg orally o.d. and the usual therapeutic dose is 10–20 mg. The PK of rosuvastatin is dose-proportional and rosuvastatin 10 mg was used in published DDI studies with rosuvastatin as a substrate [Crestor SmPC, Polli 2013]. Therefore, the dose of rosuvastatin 10 mg was considered acceptable. Since rosuvastatin has linear pharmacokinetics, it is sufficient to investigate the pharmacokinetics of the victim drug after a single-dose with and without treatment with the perpetrator drug. Any dose in the linear range can be used. This is in accordance with the DDI Guideline.*
*A loading dose of 30 mg of macitentan was administered on Day 5 in order to reach steady-state of macitentan and ACT-132577 earlier thereby shortening study treatment duration. On Days 6 through Day 16, each subject received the approved dose of 10 mg o.d. macitentan. This is also in accordance with DDI Guideline that states "in some cases, alternative perpetrator drug regimens, such as a high single-dose, may be used to reach concentrations higher than the maximum steady state concentrations during the plasma concentration time-course of the probe drug".*

Blood sampling

For rosuvastatin, during the treatment days, 5.5 ml of blood samples were drawn in labeled tubes containing Li-heparin as anticoagulant, at the following times: pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0 and 96 hours post-doses. All samples were stored in an upright position at ≤ -70 ºC until shipment.
At each time point for macitentan and ACT-132577 blood sampling, 2.7 mL of blood were collected from the subject in Monovette Sartedt® tubes $K_3$EDTA at the following times pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 120.0, 144.0 and 168.0 hours post-dose.. All samples were stored in an upright position at ≤ -20 ºC until shipment
For Macitentan trough (pre-dose) PK sampling were collected at 24.0, 48.0, 72.0, 96.0, 120.0, 144.0 and 168 hours post-dose.

***Assessor´s comment:***
*The blood sampling period for rosuvastatin, macitentan and ACT-132577 is considered acceptable.*
*The duration of the treatment with the perpetrator drug is long enough to certify that it covers at least 90% of the plasma concentration-time curve (sampling period) of the victim drug.*

Pharmacokinetic endpoints

The plasma PK parameters of rosuvastatin were derived by non-compartmental analysis of the plasma concentration-time profiles using WinNonlin version 6.4 (Pharsight Inc., Mountain View, USA). The PK endpoints were compared between Treatment A (rosuvastatin) and Treatment B2 (rosuvastatin + macitentan).

- $AUC_{0-t}$ of rosuvastatin following administration of rosuvastatin alone (Treatment A) and under conditions of macitentan steady-state plasma kinetics (Treatment B2) calculated according to the linear trapezoidal rule.
- $AUC_{0-\infty}$ of rosuvastatin following administration of rosuvastatin alone (Treatment A) and under conditions of macitentan steady-state plasma kinetics (Treatment B2).

- $C_{max}$ of rosuvastatin following administration of rosuvastatin alone (Treatment A) and under conditions of macitentan steady-state plasma kinetics (Treatment B2).
- $t_{max}$ of rosuvastatin following administration of rosuvastatin alone (Treatment A) and under conditions of macitentan steady-state plasma kinetics (Treatment B2).
- t½ of rosuvastatin following administration of rosuvastatin alone (Treatment A) and under conditions of macitentan steady-state plasma kinetics (Treatment B2).
-

Secondary PK endpoints

$C_{trough}$ of macitentan and ACT-132577 during macitentan administration (Treatments B1 and B2). The measured individual trough plasma concentrations of macitentan and ACT-132577 were used to directly obtain $C_{trough}$, which was used to investigate attainment of steady-state conditions,

***Assessor´s comment:***
*Pharmacokinetic software and method for $AUC_{0-t}$ and $C_{max}$ estimation are considered acceptable.*
*The non-compartmental linear-trapezoidal calculation is adequate.*
*The PK endpoints selected for the study were in line with current regulatory guidelines on the conduct of DDI studies [EMA 2012].*
*The PK parameters were calculated on the basis of the actual blood sampling time points.*
*The measured individual trough plasma concentrations of macitentan and ACT-132577 were used to directly obtain $C_{trough}$, which was used to investigate attainment of steady-state conditions.*

Statistical methods

Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analysis and the reporting of clinical and pharmacokinetic data.

The effect of macitentan on $AUC_{0-\infty}$, $AUC_{0-t}$, $C_{max}$, and t½ of rosuvastatin was explored using the ratio of the geometric means and the 90% CI, with Treatment B2 (rosuvastatin + macitentan) as the test treatment versus Treatment A (rosuvastatin alone) as the reference treatment. The log-transformed values were analyzed by mixed-effect model including treatment as a fixed factor and subject as a random factor. The model was used to estimate the least squares means and intra-subject variance. Using these estimated least squares means and intra-subject variance, the point estimate and 90% CIs for the difference in means on a log scale between Treatment B2 and Treatment A were constructed. The ratios of geometric means and their 90% CI were calculated from the corresponding back log-transformed contrasts of the mixed-effect models for $AUC_{0-\infty}$, $AUC_{0-t}$, $C_{max}$, and t1/2 of rosuvastatin alone or in the presence of macitentan (Treatment B2 / Treatment A).

Differences for rosuvastatin tmax between treatments were explored using the Wilcoxon signed rank test providing the median difference and its 90% CI

***Assessor´s comment:***
*The statistical analysis all seems appropriate.*

Determination of sample size and Disposition of subjects

A formal sample size calculation was not performed; however, a precision estimate approach was applied for the $C_{max}$ and $AUC_{0-\infty}$ comparison.

Assuming a $CV_w$ of 34% and 21% for $C_{max}$ and $AUC_{0-\infty}$ of rosuvastatin, respectively [Martin 2016], it was estimated that, with a sample size of 16 evaluable subjects, the lower and upper bounds of the 90% CI for the geometric mean ratio Treatment B/Treatment A would be approximately (0.81, 1.23) for $C_{max}$ and (0.88, 1.14) for $AUC_{0-\infty}$ if the estimated ratio was 1.

A total of 20 subjects were enrolled in the study in order to ensure 16 subjects with evaluable PK parameters. All subjects received at least 1 dose of study treatment. Two subjects prematurely discontinued study treatment as well as the study.

- One subject discontinued due to AEs on Day 5, 4 days after receiving Treatment A (rosuvastatin only).

- One subject discontinued by withdrawing consent on Day 9 after receiving Treatment A (rosuvastatin only) on Day 1 followed by Treatment B1 (macitentan only) for 5 days (Days 5–9).

A total of 18 subjects were included in the Per-protocol set (PPS).

All 20 subjects enrolled in the study were male, with 19 white with a mean age of 41.2 years (range: 19–55 years), mean height of 181 com (range: 169-191 cm), mean weight of 81.76 kg (range: 62.9-99.7 kg) and a mean BMI was 24.77 kg/m$^2$(range: 19.6-28.7 kg/m$^2$).

Protocol deviations

Protocol deviations that did not exclude subjects from the analysis sets were reported for 4 subjects (20.0%). These were the EOS visit not performed 10 to 12 days after last study treatment administration (2 subjects), study treatment not administered in the morning (2 subjects), and any circumstances or conditions, which, in the opinion of the investigator, affected full participation in the study or compliance with the protocol (1 subject).

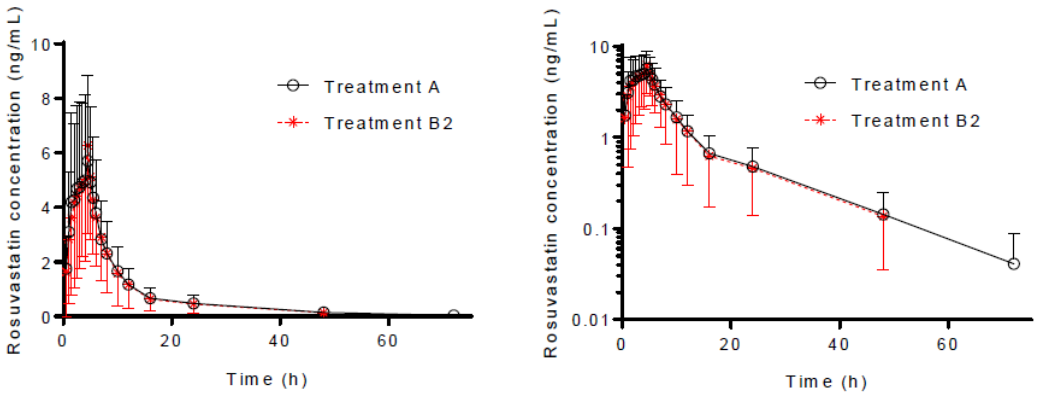
Concomitant treatments during the study

A total of 6 subjects received at least 1 concomitant medication during the study for the treatment of AEs. Of these, 5 subjects received ibuprofen/paracetamol during Treatment B (B1 and/or B2) for headache or back pain. One subject received amoxicillin for the treatment of toothache / tooth abscess in Treatment A.

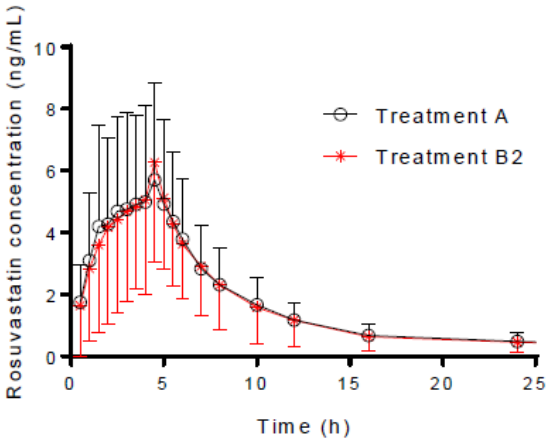
***Assessor´s comment:***
*The number of subjects is adequate to show equivalence based on the intra-subject variability from the previous bioequivalence study.*
*A formal sample size calculation was not performed; however, a intra-subject precision estimate approach was applied for the $C_{max}$ and $AUC_{0-\infty}$ comparison. This is considered acceptable.*
*The study population is considered acceptable with regards to demographic characteristics and the inclusion and exclusion criteria are considered to be acceptable.*
*The subject withdrawals due to adverse events and dropout (freely of consent) are considered to be acceptable.*
*There were some sampling time deviations from scheduled blood sampling times. The pharmacokinetic analysis was based on the actual sampling time points*
*Some subjects took paracetamol/ibuprofen and one subject took amoxicillin, given the nature of medications and the time of administration, these drugs do not present interactions with the medication of the study.*

Results

Arithmetic mean plasma concentration vs time profiles for rosuvastatin by treatment (n = 18; linear and semilogarithmic scales), Per-protocol set




Arithmetic mean plasma concentration vs time profile for rosuvastatin by treatment (n = 18) during the first 24 h after administration, linear scale, Per-protocol set




Summary of pharmacokinetic parameters of rosuvastatin by treatment (PPS) is presented below.

| | | Rosuvastatin | |
|---|---|---|---|
| **Parameter [unit]** | **Statistics** | **Treatment A** | **Treatment B2** |
| **$AUC_{(0-t)}$ [h*ng/mL]** | **N/miss** | 18/0 | 18/0 |
| | **Geometric mean** | 47.20 | 45.71 |
| | **95% CI of geometric mean** | 35.34, 63.04 | 33.49, 62.38 |
| **$AUC_{(0-\infty)}$ [h*ng/mL]** | **N/miss** | 16/2 | 15/3 |
| | **Geometric mean** | 54.27 | 50.81 |
| | **95% CI of geometric mean** | 41.87, 70.35 | 37.66, 68.54 |
| **$C_{max}$ [ng/mL]** | **N/miss** | 18/0 | 18/0 |
| | **Geometric mean** | 5.14 | 5.58 |
| | **95% CI of geometric mean** | 3.81, 6.93 | 4.25, 7.31 |
| **$t_{1/2}$ [h]** | **N/miss** | 16/2 | 16/2 |
| | **Geometric mean** | 14.833 | 16.170 |
| | **95% CI of geometric mean** | 12.733, 17.279 | 13.163, 19.865 |
| **$t_{max}$ [h]** | **N/miss** | 18/0 | 18/0 |
| | **Median** | 4.50 | 4.50 |
| | **Min, Max** | 1.5, 5.5 | 3.5, 5.5 |

Treatments: A = rosuvastatin, B2 = rosuvastatin + macitentan.

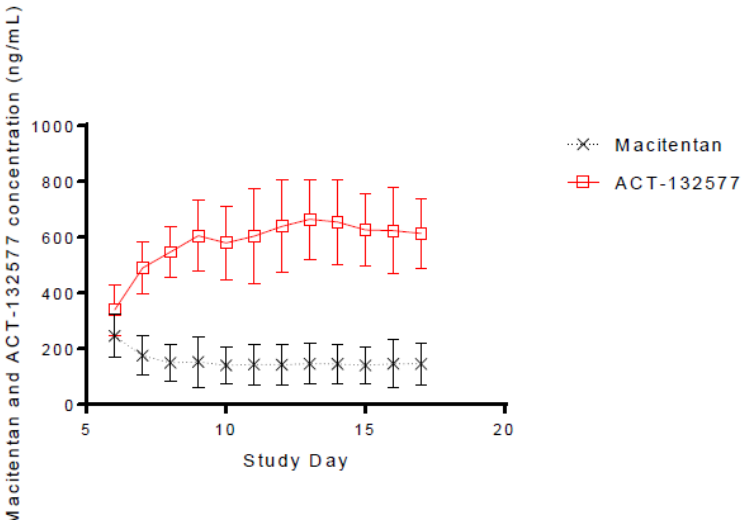
Comparison of main pharmacokinetic parameters of rosuvastatin (PPS) is presented below.

| **Parameter** | **Statistics** | **Rosuvastatin** |
|---|---|---|
| **$AUC_{(0-t)}$** | **N/miss** | 18/0 |
| | **Ratio of geometric means (B2/A)** | 0.9683 |
| | **90% CI of the ratio** | 0.8812, 1.0640 |
| **$AUC_{(0-\infty)}$** | **N/miss** | 14/4 |
| | **Ratio of geometric means (B2/A)** | 0.9581 |
| | **90% CI of the ratio** | 0.8530, 1.0761 |
| **$C_{max}$** | **N/miss** | 18/0 |
| | **Ratio of geometric means (B2/A)** | 1.0851 |
| | **90% CI of the ratio** | 0.9771, 1.2051 |
| **$t_{1/2}$** | **N/miss** | 15/3 |
| | **Ratio of geometric means (B2/A)** | 1.1414 |
| | **90% CI of the ratio** | 0.9847, 1.3232 |
| **$t_{max}$ [h]** | **N/miss** | 18/0 |
| | **Median difference B2-A** | 0.0000 |
| | **90% CI of the median difference** | 0.0000, 0.7500 |

Treatments: A = rosuvastatin, B2 = rosuvastatin + macitentan.

Trough plasma concentrations of macitentan and ACT-132577

Mean trough plasma concentrations of macitentan and ACT-132577 during macitentan administration (Treatments B1 and B2) are graphically presented in the figure below;




It is observed that steady-state conditions for macitentan and ACT-132577 were reached prior to rosuvastatin administration on Day 10. Rosuvastatin did not appear to have an effect on the steady-state concentrations of macitentan and ACT-132577.

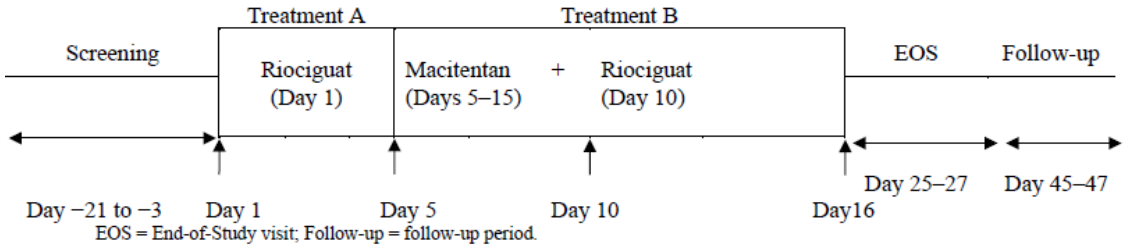
***Assessor´s comment:***
*The mean plasma concentration-time profiles of rosuvastatin were superimposable when administered alone or concomitantly with macitentan. The geometric mean ratios (Treatment B2 [rosuvastatin + macitentan] / Treatment A [rosuvastatin only]) and their 90% CIs for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were 1.09 (0.98, 1.21), 0.97 (0.88, 1.06), and 0.96 (0.85, 1.08), respectively, and were within the established bioequivalence criteria of 0.80 to 1.25. The median difference (Treatment B2 – Treatment A) and its 90% CI for $t_{max}$ of rosuvastatin was 0.0 h (0.00, 0.75). Elimination half-life was also similar between the two treatments.*

*Steady-state conditions for macitentan and ACT-132577 were reached prior to rosuvastatin administration on Day 10. Rosuvastatin did not appear to have an effect on the steady-state concentrations of macitentan and ACT-132577.*
*Based on the pharmacokinetic results of the study, there is no interaction at steady-state between macitentan and rosuvastatin.*

**Clinical Study Report AC-055-123 (EudraCT Number: 2017-003502-41)**

This was a single-center, open-label, one-sequence, two-treatment, Phase 1 study to investigate the effect of macitentan at steady state on the pharmacokinetics of riociguat in healthy male subjects

The study design is presented in Figure below.




The clinical part was performed at CRS Clinical Research. Services Mannheim, Grenadierstr. 1, 68167 Mannheim, Germany between December 20th, 2017 and November February 06th, 2018 and the principal investigator was Dr. Armin Schultz, MD.

The protocol version 1 (dated September 13th, 2017) was amended to change inclusion criteria 5 and exclusion criteria 4, 5 and 6. The resulting amended protocol is Version 2 dated November 15th, 2017. Prior to the start of the study/implementation of the amendment, the national health authority of Germany and Ethics Committee reviewed and approved the protocol on October 25th, 2017.

Treatments administered
The subjects remained fasted from at least 10 h prior to and up to 4 h after rosuvastatin administration. Water intake (except for the 240 mL used for dosing) was restricted from 1 h prior to until 1 h after rosuvastatin or rosuvastatin + macitentan administration.

Treatment A (riociguat alone)
A single oral dose of riociguat 1 mg administered in the fasted state on Day 1 followed by a PK and safety evaluation period of 96 h.

Treatment B (macitentan + riociguat)
B1: a single oral loading dose of macitentan 30 mg (3 × 10 mg tablets) administered in the fasted state on Day 5; thereafter, macitentan 10 mg was administered once daily (o.d.) from Day 6 to Day 15 (i.e., 10 doses).
B2: a single oral dose of riociguat 1 mg was administered concomitantly with macitentan in the morning of Day 10, in the fasted state, followed by a PK and safety evaluation period of 144 h (Day 10 to Day 16).

***Assessor´s comment:***
*The study design was in line with current regulatory guidelines on the conduct of DDI studies.*
*Due to the long t½ of ACT-132577 (48 h), a single sequence design (riociguat alone followed by riociguat + macitentan) was selected to avoid a lengthy washout period and unnecessary prolongation of subjects' participation in the study.*

*The dose range of riociguat is 0.5–2.5 mg orally three times daily (t.i.d.), and the usual therapeutic dose is 1–2.5 mg t.i.d. The PK of riociguat and M1 are dose proportional. In a DDI study with riociguat as a substrate, riociguat 1 mg was successfully used and quantified [Adempas® SmPC, Becker 2016b]. Since riociguat and M1 has linear pharmacokinetics, it is sufficient to investigate the pharmacokinetics of the victim drug after a single-dose with and without treatment with the perpetrator drug. Any dose in the linear range can be used. This is in accordance with the DDI Guideline. In addition, the higher dose of 2.5 mg was not chosen in order to avoid any potential safety issues in case of increase in riociguat concentrations in the presence of macitentan. Therefore, the dose of riociguat 1 mg was considered acceptable.*

*A loading dose of 30 mg of macitentan was administered on Day 5 in order to reach steady-state of macitentan and ACT-132577 earlier thereby shortening study treatment duration. On Days 6 through Day 16, each subject received the approved dose of 10 mg o.d. macitentan. This is also in accordance with DDI Guideline that states "in some cases, alternative perpetrator drug regimens, such as a high single-dose, may be used to reach concentrations higher than the maximum steady state concentrations during the plasma concentration time-course of the probe drug".*

Blood sampling
During the treatment days, 4.9 ml of blood samples were drawn in labeled tubes containing Li-heparin as anticoagulant for riociguat and M1, at the following times: pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0 and 96 hours post-doses. All samples were stored in an upright position at ≤−20 ºC until shipment.

At each time point for macitentan and ACT-132577 blood sampling, 2.7 mL of blood were collected from the subject in Monovette Sartedt® tubes $K_3$EDTA at the following times pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours post-dose. All samples were stored in an upright position at ≤ -20 ºC until shipment.

For Macitentan trough (pre-dose) PK sampling were collected at 24.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours post-dose.

***Assessor´s comment:***
*The blood sampling period for rosuvastatin, macitentan and ACT-132577 is considered acceptable.*

*The duration of the treatment with the perpetrator drug is long enough to certify that it covers at least 90% of the plasma concentration-time curve (sampling period) of the victim drug.*

Pharmacokinetic endpoints
The plasma PK parameters of riociguat and its metabolite M1 were derived by non-compartmental analysis of the plasma concentration-time profiles using WinNonlin version 6.4 (Pharsight Inc., Mountain View, USA). The PK endpoints were compared between Treatment A (riociguat) and Treatment B2 (riociguat + macitentan).

Primary PK endpoints
- $AUC_{0-\infty}$ of riociguat following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- $C_{max}$ of riociguat following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
-

Secondary PK endpoints
- $AUC_{0-\infty}$ of M1 following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- $C_{max}$ of M1 following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- $AUC_{0-t}$ of riociguat and M1 following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- $t_{max}$ of riociguat and M1 following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- t½ of riociguat and M1 following administration of riociguat alone (Treatment A) and concomitantly with macitentan (Treatment B).
- $C_{trough}$ of macitentan and ACT-132577 during Treatment B. The measured individual trough plasma concentrations of macitentan and ACT-132577 were used to directly obtain $C_{trough}$, which was used to investigate attainment of steady-state conditions

***Assessor´s comment:***
*Pharmacokinetic software and method for $AUC_{0-t}$ and $C_{max}$ estimation are considered acceptable.*
*The non-compartmental linear-trapezoidal calculation is adequate.*

*The PK endpoints selected for the study were in line with current regulatory guidelines on the conduct of DDI studies [EMA 2012].*

*The PK parameters were calculated on the basis of the actual blood sampling time points.*
*The measured individual trough plasma concentrations of macitentan and ACT-132577 were used to directly obtain $C_{trough}$, which was used to investigate attainment of steady-state conditions.*

Statistical methods
Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analysis and the reporting of clinical and pharmacokinetic data.

The effect of macitentan on $AUC_{0-\infty}$, $AUC_{0-t}$, $C_{max}$, and t½ of riociguat and M1 was explored using the ratio of the geometric means and the 90% CI, with Treatment B2 (riociguat + macitentan) as the test treatment versus Treatment A (riociguat alone) as the reference treatment. The log-transformed values were analyzed by mixed-effect model including treatment as a fixed factor and subject as a random factor. The model was used to estimate the least squares means and intra-subject variance. Using these estimated least squares means and intra-subject variance, the point estimate and 90% CIs for the difference in means on a log scale between Treatment B2 and Treatment A were constructed. The ratios of geometric means and their 90% CIs were calculated from the corresponding back log-transformed contrasts of the mixed-effect models for $AUC_{0-\infty}$, $AUC_{0-t}$, $C_{max}$, and t½ of riociguat and M1 following administration of riociguat alone (Treatment A) or concomitantly with macitentan (Treatment B2).

Differences between treatments for $t_{max}$ of riociguat and M1 were explored using the Wilcoxon signed rank test providing the median differences and their 90% CIs.

***Assessor´s comment:***
*The statistical analysis all seems appropriate.*

Determination of sample size and Disposition of subjects
A formal sample size calculation was not performed; however, a precision estimate approach was applied for the $C_{max}$ and $AUC_{0-\infty}$ comparison.

Assuming a $CV_w$ of 34% and 21% for $C_{max}$ and $AUC_{0-\infty}$ of rosuvastatin, respectively [Martin 2016], it was estimated that, with a sample size of 16 evaluable subjects, the lower and upper bounds of the 90% CI for the geometric mean ratio Treatment B/Treatment A would be approximately (0.81, 1.23) for $C_{max}$ and (0.88, 1.14) for $AUC_{0-\infty}$ if the estimated ratio was 1.

A total of 20 subjects were enrolled in the study. All subjects received the study treatments and completed the study as planned and were included in the Per-protocol set (PPS).

All 20 subjects enrolled in the study were male, with a mean age of 35.8 years (range: 22–45 years), mean height of 180 cm (range: 169.3-195.6 cm), mean weight of 82.37 kg (range: 65.5-101.0 kg) and a mean BMI was 25.41 kg/$m^2$ (range: 19.2-29.8kg/$m^2$).

Protocol deviations
Protocol deviations that did not exclude subjects from the analysis sets were reported for 5 subjects. These were post-dose safety assessments not performed as per protocol (3 subjects), the EOS visit performed outside the visit window (1 subject), and subject eligibility (exclusion criterion 6 not met) not confirmed prior to enrollment (1 subject). For the protocol deviation related to subject eligibility, re-analysis of the screening sample subsequent to enrollment confirmed the subject´s eligibility. All these protocol deviations were considered not to affect the study results.

Concomitant treatments during the study
A total of 3 subjects received concomitant medications during the study for the treatment of AEs. Two subjects received paracetamol/ibuprofen for the treatment of headache: 1 subject during Treatment A and 1 subject during Treatment B2. One subject received topical acyclovir for the treatment of oral herpes in Treatment B2.

***Assessor´s comment:***
*A formal sample size calculation was not performed; however, an intra-subject precision estimate approach was applied for the $C_{max}$ and $AUC_{0-\infty}$ comparison. This is considered acceptable.*

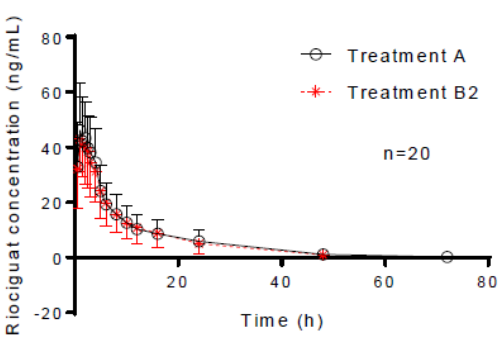
*The study population is considered acceptable with regards to demographic characteristics and the inclusion and exclusion criteria are considered to be acceptable.*
*No subject was withdrawn from the study.*

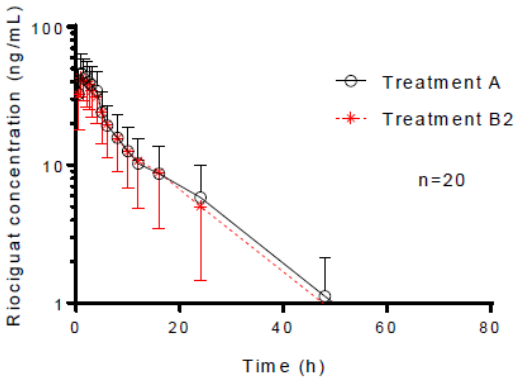
*There were some sampling time deviations from scheduled blood sampling times. The pharmacokinetic analysis was based on the actual sampling time points.*

*Some subjects took paracetamol/ibuprofen and one subject received topical acyclovir, given the nature of medications and the time of administration, these drugs do not present interactions with the medication of the study.*

Results

Arithmetic mean plasma concentration vs time profiles for riociguat by treatment (n = 20; linear and semilogarithmic scales), Per-protocol set.




Summary of pharmacokinetic parameters of riociguat by treatment (PPS) is presented below.

| | | Riociguat | | | |
|---|---|---|---|---|---|
| | | Main analysis N = 20 | | Sensitivity analysis N = 19# | |
| Parameter [unit] | Statistics | Treatment A | Treatment B2 | Treatment A | Treatment B2 |
| $AUC_{(0-t)}$ [h*ng/mL] | Geometric mean | 406.26 | 386.32 | 398.12 | 389.90 |
| | 95% CI of geometric mean | 296.39, 556.86 | 286.34, 521.22 | 286.04, 554.11 | 284.20, 534.93 |
| $AUC_{(0-\infty)}$ [h*ng/mL] | Geometric mean | 411.16 | 393.25 | 402.93 | 396.53 |
| | 95% CI of geometric mean | 300.48, 562.60 | 292.23, 529.18 | 290.03, 559.78 | 289.79, 542.59 |
| $C_{max}$ [ng/mL] | Geometric mean | 47.97 | 45.96 | 48.38 | 46.23 |
| | 95% CI of geometric mean | 41.61, 55.29 | 40.02, 52.78 | 41.67, 56.16 | 39.96, 53.48 |
| $t_{½}$ [h] | Geometric mean | 8.216 | 7.944 | 8.094 | 7.863 |
| | 95% CI of geometric mean | 6.669, 10.122 | 6.365, 9.915 | 6.507, 10.067 | 6.226, 9.930 |
| $t_{max}$ [h] | Median | 1.00 | 1.00 | 1.00 | 1.00 |
| | Min, Max | 0.5, 2.1 | 0.5, 3.0 | 0.5, 2.1 | 0.5, 3.0 |

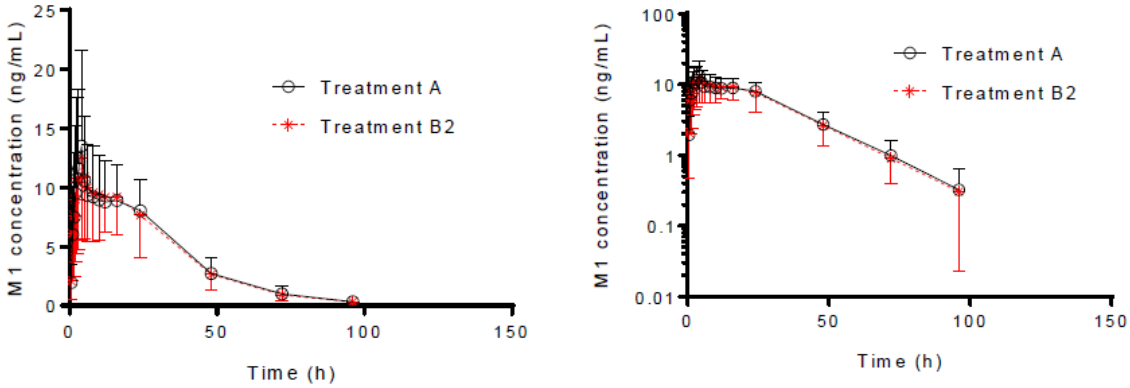
Treatments: A = Riociguat, B2 = Riociguat + Macitentan.

Comparison of main pharmacokinetic parameters of riociguat (PPS) is presented below.

| Parameter | Statistics | Riociguat | |
|---|---|---|---|
| | | Main analysis N = 20 | Sensitivity analysis N = 19# |
| $AUC_{(0-t)}$ | Ratio of geometric means (B2/A) | 0.9509 | 0.9794 |
| | 90% CI of the ratio | 0.8329, 1.0857 | 0.8606, 1.1146 |
| $AUC_{(0-\infty)}$ | Ratio of geometric means (B2/A) | 0.9564 | 0.9841 |
| | 90% CI of the ratio | 0.8388, 1.0906 | 0.8654, 1.1191 |
| $C_{max}$ | Ratio of geometric means (B2/A) | 0.9581 | 0.9556 |
| | 90% CI of the ratio | 0.8976, 1.0227 | 0.8921, 1.0236 |
| $t_{½}$ | Ratio of geometric means (B2/A) | 0.9668 | 0.9715 |
| | 90% CI of the ratio | 0.8829, 1.0587 | 0.8829, 1.0689 |
| $t_{max}$ [h] | Median difference B2-A | 0.0000 | 0.2000 |
| | 90% CI of the median difference | 0.0000, 0.2500 | -0.2500, 0.2500 |

Treatments: A = Riociguat, B2 = Riociguat + Macitentan.

Arithmetic mean (±SD) plasma concentration vs time profiles for riociguat´s metabolite M1, by treatment (linear and semilogarithmic scales), main analysis (n = 20), Per-protocol set




Summary of pharmacokinetic parameters of riociguat´s metabolite M1, by treatment, Per-protocol set

| | | M1 | | | |
|---|---|---|---|---|---|
| | | Main analysis N = 20 | | Sensitivity analysis N = 19# | |
| **Parameter [unit]** | **Statistics** | **Treatment A** | **Treatment B2** | **Treatment A** | **Treatment B2** |
| **$AUC_{(0-t)}$ [h*ng/mL]** | **Geometric mean** | 379.90 | 373.79 | 393.96 | 386.70 |
| | **95% CI of geometric mean** | 325.04, 444.01 | 317.46, 440.11 | 341.11, 455.00 | 330.99, 451.80 |
| **$AUC_{(0-\infty)}$ [h*ng/mL]** | **Geometric mean** | 392.10 | 381.95 | 406.58 | 394.43 |
| | **95% CI of geometric mean** | 336.30, 457.16 | 325.67, 447.96 | 353.04, 468.24 | 338.51, 459.59 |
| **$C_{max}$ [ng/mL]** | **Geometric mean** | 12.10 | 11.91 | 12.77 | 12.21 |
| | **95% CI of geometric mean** | 9.28, 15.77 | 9.45, 15.00 | 9.91, 16.46 | 9.62, 15.49 |
| **$t_{½}$ [h]** | **Geometric mean** | 15.632 | 14.940 | 15.540 | 14.848 |
| | **95% CI of geometric mean** | 14.124, 17.301 | 13.284, 16.803 | 13.969, 17.286 | 13.122, 16.800 |
| **$t_{max}$ [h]** | **Median** | 4.00 | 5.00 | 4.00 | 5.00 |
| | **Min, Max** | 3.0, 24.0 | 2.5, 23.9 | 3.0, 24.0 | 2.5, 23.9 |

Treatments: A = Riociguat, B2 = Riociguat + Macitentan.
# A sensitivity analysis was performed excluding Subject 109 who had extremely low concentrations of macitentan/ACT-132577.

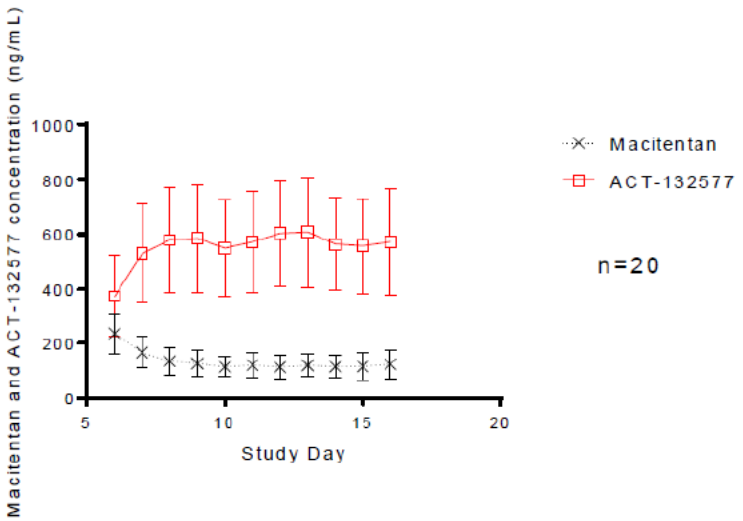
Comparison of main pharmacokinetic parameters of riociguat´s metabolite M1, Per-protocol set are presented below. Results of the sensitivity analysis, excluding 1 subject who had extremely low concentrations of macitentan and ACT-132577, were similar to those of the main analysis.

| Parameter | Statistics | M1 | |
|---|---|---|---|
| | | Main analysis N = 20 | Sensitivity analysis N = 19# |
| $AUC_{(0-t)}$ | Ratio of geometric means (B2/A) | 0.9839 | 0.9816 |
| | 90% CI of the ratio | 0.9147, 1.0583 | 0.9089, 1.0601 |
| $AUC_{(0-\infty)}$ | Ratio of geometric means (B2/A) | 0.9741 | 0.9701 |
| | 90% CI of the ratio | 0.9057, 1.0477 | 0.8985, 1.0474 |
| $C_{max}$ | Ratio of geometric means (B2/A) | 0.9844 | 0.9559 |
| | 90% CI of the ratio | 0.8555, 1.1328 | 0.8324, 1.0977 |
| $t_{½}$ | Ratio of geometric means (B2/A) | 0.9557 | 0.9555 |
| | 90% CI of the ratio | 0.8661, 1.0547 | 0.8610, 1.0604 |
| $t_{max}$ [h] | Median difference B2-A | 0.5000 | 0.5000 |
| | 90% CI of the median difference | -0.2500, 1.0000 | -0.7500, 1.0000 |

Treatments: A = Riociguat, B2 = Riociguat + Macitentan.
# A sensitivity analysis was performed excluding [redacted] who had extremely low concentrations of macitentan/ACT-132577.

Trough plasma concentrations of macitentan and ACT-132577

Mean trough plasma concentrations of macitentan and ACT-132577 during macitentan administration (Treatments B1 and B2; n = 20 & n = 19) are graphically presented in the figure below;




As expected, steady-state conditions for macitentan and ACT-132577 were reached prior to riociguat administration on Day 10. Riociguat did not appear to have an effect on the steady-state concentrations of macitentan and ACT-132577. Results of the sensitivity analysis were similar to those of the main analysis.

***Assessor´s comment:***
*The mean plasma concentration-time profiles of riociguat and its metabolite, M1, were similar when riociguat was administered alone or concomitantly with macitentan. The geometric mean ratios (Treatment B2 [riociguat + macitentan] / Treatment A [riociguat only]) and their 90% CIs for $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and $t_{½}$ of riociguat were 0.96 (0.90, 1.02), 0.95 (0.83, 1.09), 0.96 (0.84, 1.09), and 0.97 (0.88, 1.06), respectively, and were within the established bioequivalence criteria of 0.80 to 1.25. The median difference (Treatment B2 – Treatment A) and its 90% CI for $t_{max}$ of riociguat was 0.0 h (0.00, 0.25).*

*For M1, the geometric mean ratios (Treatment B2 / Treatment A) and their 90% CIs for $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and t½ were 0.98 (0.86, 1.13), 0.98 (0.91, 1.06), 0.97 (0.91, 1.05), and 0.96 (0.87, 1.05), respectively, and were within the established bioequivalence criteria of 0.80 to 1.25. The median difference (Treatment B2 − Treatment A) and its 90% CI for $t_{max}$ of M1 was 0.5 h (-0.25, 1.00).*

*A sensitivity analysis for the PK parameters was performed excluding one subject who had extremely low concentrations of macitentan/ACT-132577. A review of the clinical, bioanalytical conduct, and demographic variables did not provide any explanation for low concentrations of macitentan and ACT-132577 in this subject. In any case, their 90% CIs for $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and t½ of riociguat and M1 were within the established bioequivalence criteria of 0.80 to 1.25.*

*Consistent trough levels of macitentan and ACT-132577, suggestive of the achievement of steady-state conditions, were reached prior to riociguat administration on Day 10.*

*Riociguat did not appear to have an effect on the steady-state concentrations of macitentan and ACT-132577.*

*Results of the sensitivity analysis, excluding 1 subject who had extremely low concentrations of macitentan and ACT-132577, were similar to those of the main analysis. Based on the PK results of the study, there is no interaction between steady-state macitentan and riociguat*

## *Pharmacokinetic results of patients with CTEPH*

In study MERIT-1 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) were treated with macitentan 10mg film-coated tablets or placebo tablets (for a description of the demographics see table 9, page 41. In this study the trough concentrations of macitentan and its metabolite ACT-132577 in plasma have been determined at Week 16 and Week 24, or at EOT in case of premature study treatment. The PK analysis set included a total of 71 subjects (35 macitentan, 36 placebo). The mean trough concentrations of macitentan and its metabolite (ACT-132577) were similar at Week 16 (236.97 ± 95.95 ng/mL and 1064.14 ± 306.87 ng/mL, respectively) and at Week 24/EOT (231.25 ± 127.37 ng/mL and 1065.09 ± 465.39 ng/mL).

***Assessor's comment***

*Sparse samples have been collected in the MERIT- study to characterise the pharmacokinetics in subjects with CTEPH and to allow comparison of pharmacokinetic data between CTEPH and other patient groups. This approach is considered acceptable.*

## *Comparison to previously submitted studies with Macitentan*

In the clinical overview the applicant provided references and listed the previously conducted interaction studies with hormonal contraceptives, Sildenafil, Iloprost, the anticoagulant warfarin. For none of these potentially concomitantly used drugs an interaction has been observed.

Further the applicant refers to previously collected data which show that age does not impact the PK of Macitentan.

The macitentan PK profiles in patients with PAH and CTEPH were found to be comparable based on trough concentrations measured in SERAPHIN and MERIT-1, respectively. According to the applicant this is justifying the use of macitentan 10 mg dose in CTEPH.

**Table 2 Trough concentrations of macitentan and ACT-132577 (active metabolite of macitentan) in SERAPHIN-DB, SERAPHIN-OL and MERIT-1 MERIT-1/ AC-055E201, CTEPH**

| | **MERIT-1/** AC-055E201, CTEPH Week 16 | **SERAPHIN-OL/** AC-055-303, PAH >Week 4 | **SERAPHIN-DB/** AC-055-302, PAH Month 6 | **$C_{trough\ PAH}$* / $C_{trough\ CTEPH}$*** SERAPHIN-OL / * MERIT-1 | **$C_{trough\ PAH}$ */ $C_{trough\ CTEPH}$*** SERAPHIN-DB / MERIT-1 |
|---|---|---|---|---|---|
| N | 35 | 20 | 41 | | |
| Macitentan $C_{trough}$ mean (SD) (ng/mL) | 236.97 (95.95) | 231.9 (140.3) | 291.45 (155.23) | **0.98** | **1.23** |
| ACT-132577 $C_{trough}$ mean (SD) (ng/mL) | 1064.14 (306.87) | 878.4 (266.9) | 837.37 (328.18) | **0.83** | **0.79** |

* at steady state, dose: 10 mg once daily

CTEPH = chronic thromboembolic pulmonary hypertension; $C_{trough}$ = plasma concentration at trough; OL = open-label; PAH = pulmonary arterial hypertension; SD = standard deviation.

**Sources:** SERAPHIN-DB [D-12.473 table 5, table 6]; SERAPHIN-OL [D-13.230 table 6]; MERIT-1 [Module 5.3.5.1 D-17.097 table 15-81].

***Assessor's comment***

*The trough concentrations measured in CTEPH patients (MERIT -1) and PAH patients (SERAPHIN) is comparable, and therefore it is agreed that the exposure is also expected to be comparable between the different patient groups. The adequacy of the proposed dose is discussed in the clinical parts of this report.*

### *Pharmacokinetics using human biomaterials*

N/A.

## 2.3.3. Pharmacodynamics

N/A.

## 2.3.4. PK/PD modelling

N/A.

## 2.3.5. Discussion on clinical pharmacology

To support this application, the results of 2 drug-drug interaction clinical pharmacology studies to investigate the effect on intestinal BCRP transporters and a pharmacokinetic comparison between CTEPH patients and the previously investigated PAH population have been submitted.

According to the applicant the similarities in the trough concentrations of macitentan 10 mg between PAH and CTEPH patients, together with a lack of DDIs with medications relevant for the CTEPH indication, including the most frequently prescribed PH advanced therapy, sildenafil, as well as the only approved therapy, riociguat, provide reassurance regarding the safe use of macitentan in the CTEPH indication. It is agreed that pharmacokinetics of macitentan is comparable between CTEPH patients and the previously investigated PAH population. Taking into account the lack of an interaction with the most relevant drugs and the comparable exposure to macitentan and it's major metabolite, the

previously collected pharmacokinetic data are considered sufficient to support this addition of a new therapeutic indication.

The previously conducted In vitro studies showed that macitentan inhibits breast cancer resistance protein (BCRP) transporters with a 50% inhibitory concentration of 1.0 µM, which is a potentially clinically relevant intestinal concentration. Therefore, previously the potential interactions with substrates of BCRP could not be excluded.

Both interaction studies have the same design, a single-center, open-label, one-sequence, two-treatment, Phase 1 studies to evaluate the effect of macitentan at steady-state on the PK of single-dose of the BCRP substrates rosuvastatin or riociguat and its metabolite in healthy male subjects.

Consistent trough levels of macitentan and ACT-132577, suggestive of the achievement of steady-state conditions, were reached prior to rosuvastatin or riociguat administration on Day 10.
Based on the pharmacokinetic results of the study AC-055-122 and study AC-055-123, there is no interaction at steady-state between macitentan and the BCRP substrates rosuvastatin or riociguat and its metabolite (M1). Based on this it can be concluded that macitentan is not an inhibitor of intestinal BCRP.

### 2.3.6. Conclusions on clinical pharmacology

Based on the pharmacokinetic results of the study AC-055-122 and study AC-055-123, there is no interaction at steady-state between macitentan and rosuvastatin and macitentan and riociguat and its metabolite (M1). Section 4.5 of the SmPC has been updated accordingly.

The pharmacokinetics of Macitentan in CETP patients is comparable to pharmacokinetics in previously investigated patient groups. There is no need for additional pharmacokinetic studies in this new patient group.

## *2.4. Clinical efficacy*

This application is primarily based on the results of the AC-055E201/MERIT-1 study [Ghofrani et al, 2017] and its ongoing OL extension study AC-055E202/MERIT-2, which are discussed in relation to relevant endpoints, as applicable. Additional supportive results from the contemporary real-world OPUS Registry (AC-055-503) are provided.

### 2.4.1. Dose response study(ies)

N/A.

### 2.4.2. Main study(ies)

### Title of Study

**MERIT-1:** Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (No.D-17.097) (AC-055E201) [Ghofrani et al, 2017].

**MERIT-2**, Long term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (AC-055E202).

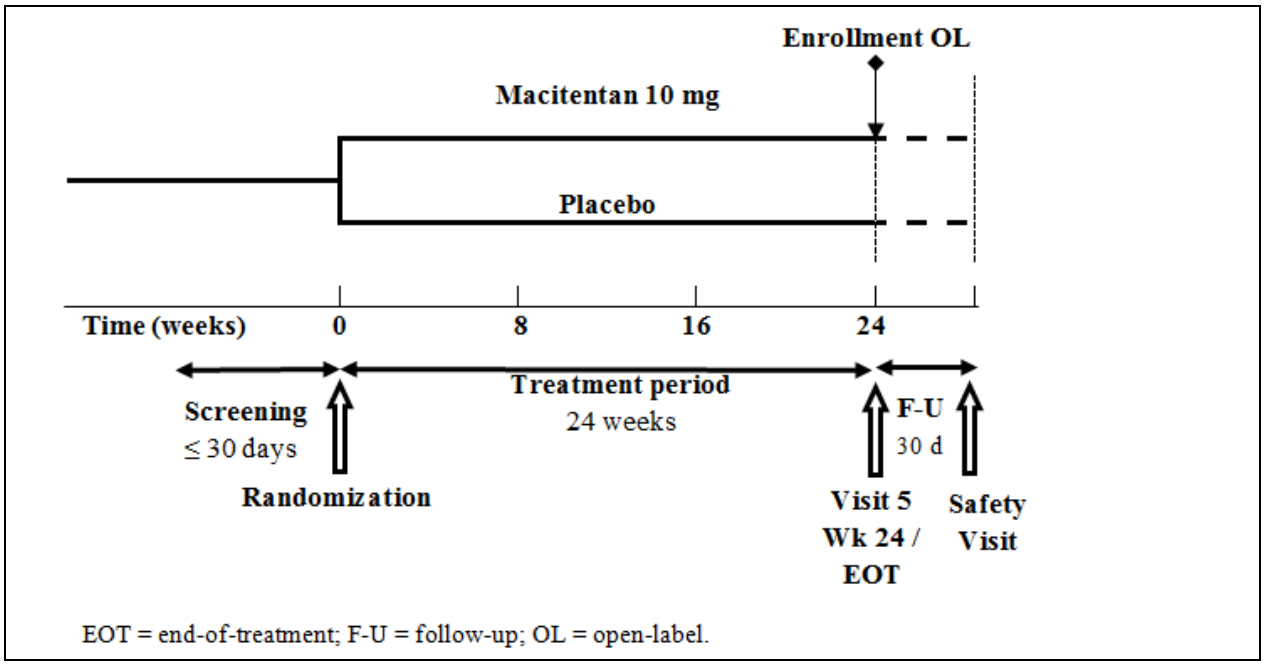
## General study design

MERIT-1 was a prospective, multicenter, DB, randomized, placebo-controlled, parallel-group, Phase 2 study. The study enrolled male and female subjects (≥ 18 and ≤ 80 years old) with inoperable CTEPH as assessed by external adjudication committees. Subjects with previous PEA were not eligible to enter the study. Subjects were required to have symptomatic PH in WHO FC II, III or IV due to CTEPH (Group 4 of the updated Dana Point clinical classification of PH []). 6MWD was to be ≥ 150 m and ≤ 450 m at enrollment. Patients with persistent/recurrent CTEPH were excluded in order to harmonize the eligible population to a degree that would minimize variability of the effect on the primary endpoint and to allow for enrollment of a realistic number of patients in the study (sponsor's explanation). Co-administration of ERAs, guanylate cyclase stimulators, L-arginine, intravenous or subcutaneous prostanoids was not allowed. PH advanced therapies (i.e., PDE-5 inhibitors and oral/inhaled prostacyclin analogs) were permitted for subjects in WHO FC III/IV at baseline. The MERIT-1 study protocol was approved between 5 February 2014 and 9 July 2014, and the first subject, first visit in MERIT-1 was performed on 20 August 2014. Riociguat (an sGC stimulator) was approved in the EU for the treatment of CTEPH on 27 March 2014 (5 months before the first patient who started on macitentan/placebo in the MERIT-1 study). No protocol amendments were introduced to allow for the concomitant administration of riociguat as background therapy in the MERIT-1 study.

The study [Figure 1] included a screening period (up to 30 days) followed by a treatment period where 80 eligible subjects were randomized in a 1:1 ratio to either receive macitentan 10 mg or placebo o.d. during a 24-week treatment period. Regular visits to assess efficacy and safety were scheduled at 8-week intervals during the study.

After the permanent discontinuation of study treatment, all subjects were followed up to collect safety data that included PH-related disease progression, AEs, serious AEs (SAEs), complete laboratory evaluation, for a period of up to 30 days or until start of the OL extension study (described below), whichever occurred first.

**Figure 1. MERIT-1 study design**




**MERIT-2** is an ongoing multicenter, single-arm, OL extension study of the MERIT-1 study to assess the long-term safety, tolerability, and efficacy of macitentan in subjects with inoperable CTEPH. Subjects who remained in the DB study up to Week 24, irrespective of premature discontinuation of study treatment (except if discontinuation was due to a hepatic AE or liver aminotransferase abnormalities) were eligible to enter the MERIT-2 OL extension study. Subjects entered MERIT-2

without knowledge of their study treatment in MERIT-1 (macitentan 10 mg or placebo) at the time of enrollment.

## Study participants

The MERIT-1 study enrolled male and female subjects (≥ 18 and ≤ 80 years old) with inoperable CTEPH. Prior to Randomization, subjects' data were assessed for eligibility for the confirmation of the CTEPH diagnosis and inoperability (due to the localization of obstruction being surgically inaccessible, i.e., distal disease) by 2 types of adjudication committees: Country-Specific Adjudication Committee (CSAC) or a Central Adjudication Committee (for countries without CSAC).

The subjects were required to have:
- Symptomatic pulmonary hypertension (PH) in WHO FC ≥ II,
- Positive ventilation/perfusion scan for segmental / sub-segmental defect(s) in the 12-month period prior to the screening visit or during the screening period,
- Confirmation based on pulmonary angiography and/or computed tomography pulmonary angiography, and/or magnetic resonance angiography in the 12-month period prior to the screening visit or during the screening period.

Subjects had to have been on anti-coagulant treatment for at least 3 months prior to baseline RHC.

Subjects were required to have met the following RHC criteria, with the RHC performed in the 8-week period prior to the screening visit or during the screening period:
- Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg.
- Pulmonary artery wedge pressure ≤ 15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure ≤ 13 mmHg.
- PVR at rest ≥ 400 dyn.sec/cm5.

Furthermore, subjects were required to have two 6-minute walk distance (6MWD) measurements during the screening period of between ≥ 150 m and ≤ 450 m and which did not differ by more than 10%. If the subject was on diuretics and/or calcium channel blockers, the dose had to be stable for at least 1 week prior to baseline RHC. Subjects with a previous pulmonary endarterectomy (PEA) were not allowed to enter the study. Administration of endothelin receptor antagonists, guanylate cyclase stimulators, L-arginine, intravenous or subcutaneous prostanoids, or any investigational drug (other than study drug) was not permitted from 1 month prior to baseline RHC and Randomization (excluding acute administration during a catheterization procedure to test vascular reactivity). However, subjects in WHO FC III/IV were allowed to take phosphodiesterase-5 inhibitors or oral / inhaled prostanoids provided that the dose had been stable for at least 1 month prior to baseline.

## Treatments

The clinical studies in CTEPH (MERIT-1, MERIT-2) used the same dose-strength and formulation (film-coated tablet) of macitentan as in the confirmatory clinical study in PAH, which is identical to the marketed dose and formulation of macitentan.

INVESTIGATIONAL TREATMENT:
BATCH No. / DOSE / ROUTE / REGIMEN / DURATION
Macitentan 10 mg film-coated tablets debossed with '10' on one side.
Batch Number: 330102-00001, UM013

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

## Objectives

**Primary objective**
- To evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) at rest in comparison with placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

**Secondary objectives**

- To evaluate the effects of macitentan 10 mg in comparison with placebo on:
  - Exercise capacity
  - Dyspnea (assessed by the Borg dyspnea index)
  - WHO functional class (FC)

- To evaluate the safety and tolerability of macitentan 10 mg in this subject population.

## Outcomes/endpoints

**MERIT 1:**
The **primary efficacy endpoint** was PVR at rest at Week 16 expressed as percent of baseline PVR at rest.

The **secondary efficacy endpoints** were:

- Change from baseline to Week 24 in exercise capacity, as measured by the 6MWD.
- Change from baseline to Week 24 in Borg dyspnea index collected at the end of the 6-minute walk test (6MWT).
- Proportion of subjects with worsening WHO FC from baseline to Week 24.

**Exploratory efficacy endpoints** were:

- Changes from baseline to Week 8 and 16 in 6MWD, and Borg dyspnea index, and the proportion of subjects with worsening WHO FC from baseline to Weeks 8 and 16.
- Absolute changes over time in RHC variables: mean right atrial pressure, mPAP, cardiac index, total pulmonary resistance, mixed venous oxygen saturation, mean systemic arterial pressure, systemic vascular resistance, pulmonary selectivity index at rest, heart rate recovery (HRR) and N-Terminal ProB-type Natriuretic Peptide (NT-proBNP) and other potential biomarkers.
- Time to first PH-related disease progression up to end-of-study.
- Change from baseline to Week 8 and Week 16 in PAH-SYMPACT™ symptom and impact part scores.
- Quality of life: Change from baseline to Week, 8, Week 16 and Week 24 in quality of life (QoL) assessed by the Euro Quality of life-5D (EQ-5D).

**MERIT-2:**

- Change from baseline to each scheduled time point in exercise capacity, as measured by the 6MWT.
- Change from baseline to each scheduled time point in Borg dyspnea index collected at the end of 6MWT.
- Proportion of subjects with worsening of WHO FC from baseline to each scheduled time point.

## Sample size

Sample size calculations for the comparison of the primary endpoint, percent of baseline PVR at rest at Week 16, between subjects randomized in a 1:1 ratio to placebo or macitentan 10 mg were based on the following assumptions:

- A 2-sided Type I error of 5% and a Type II error of 10% (90% power)
- A ratio of geometric means of percent of baseline PVR at rest at Week 16, GM macitentan 10 mg / GM placebo, equal to 0.75
- A coefficient of variation of the ratio of 0.40
- A normal distribution for the loge transformed percent of baseline PVR.

The geometric mean was chosen as the summary measure of the percent of baseline PVR as it appropriately estimates the mean of the proportion through multiplication (fold changes) rather than addition and consequently is the arithmetic mean of natural log transformed percent of baseline PVR data. Given that percent of baseline PVR values were loge transformed the ratio of geometric means was used to compare the treatment groups thereby representing the mean percent change of the treatment effect. Based on the above assumptions, a total of 78 subjects (39 per arm) were required

to establish superiority of macitentan 10 mg over placebo with 90% power to correctly reject a false null hypothesis in favor of the alternative hypothesis. This test was based on a 2-sided ratio of means t-test for independent samples.

## Randomisation

At Visit 1 (Screening), all screened subjects were assigned a study-specific subject number by the IVRS / IWRS provider. In case of re-screening, the subject number attributed at the time of first screening was also used for the re-screened subject.

At Visit 2 (Randomization), after the eligibility of the subjects was confirmed (by both the investigator and the Adjudication Committee) and prior to the start of study treatment, the investigator/delegate contacted the IVRS / IWRS service provider to randomize the subject. Eligible subjects were randomized (Visit 2) in a 1:1 ratio to either macitentan 10 mg or placebo.

The IXRS assigned a randomization number to the subject and assigned 2 unique medication bottle numbers that matched the treatment arm assigned by the randomization list to the randomization number.

The randomization list was generated by an independent Contract Research Organization (CRO), Almac Clinical Technologies, UK, and kept strictly confidential. A sealed randomization code was kept by Actelion Global Quality Management (GQM) in a safe cabinet.

## Blinding (masking)

This study was performed in a DB fashion. The investigator and study staff, the subjects, the monitors, Actelion and the CRO staff remained blinded to the treatment until study closure.

Until the time of unblinding for final data analysis, the randomization list was kept strictly confidential, and accessible only to authorized persons, (GQM, Clinical Trials Supplies Group and the bioanalytical laboratory [for pharmacokinetic (PK) samples]), who were not involved in the conduct of the study.
The investigational treatment and its matching placebo were indistinguishable and all subject kits were packaged in the same way.

## Statistical methods

### Primary efficacy analysis

The main analysis of the primary endpoint( percent of baseline PVR at rest at Week 16) was performed using the Full Analysis Set ([FAS] i.e., all subjects assigned to a study treatment). The null hypothesis was tested on the primary endpoint by means of an analysis of covariance (ANCOVA) model on the $\log_e$ transformed percent of baseline PVR at rest at Week 16, as the primary endpoint was assumed to be log-normally distributed. Covariates included in the primary model were randomized treatment and the $\log_e$ transformed baseline PVR at rest value.

For the main analysis and sensitivity analyses on PVR, imputation methods pre-specified in the MERIT-1 protocol were applied to subjects with missing PVR values at Week 16 (all 4 in the placebo group; 3 imputed by the median value in the placebo group, i.e., 12% improvement, 1 imputed [due to death] by the largest percent deterioration in the placebo group, i.e., 55%) (MERIT-1 Statistical Analysis Plan; Module 5.3.5.1.).

### Secondary endpoints

For the secondary endpoint, 6MWD, the change from baseline to Week 24 was analyzed by an ANCOVA model, including treatment group and 6MWD baseline value as covariates. Least Squares (LS) estimates for each treatment group and treatment difference were estimated from the model with corresponding means, 95% confidence limits (CLs), and p-value.

For 6MWD analyses, imputation methods pre-specified in the MERIT-1 protocol were applied to subjects with missing values at Week 24 (all 4 in the placebo group; 2 imputed with last observation carried forward [LOCF] and 2 imputed with 0 m due to death [Module 5.3.5.1]).

The Summary of Clinical Efficacy also presents additional sensitivity analyses conducted on 6MWD, encompassing repeated measure analysis, multiple imputation methods (Method 1 and 2), single imputation methods (LOCF, baseline observation carried forward, and Median), analysis of variance, non-parametric analysis (Hodges Lehmann estimator), and the extended model [Module 5.3.5.1, appendix 2]. The objective of these analytical approaches was to provide estimates of the treatment effect using different ways of handling missing data and different statistical models, thereby evaluating the robustness of the conclusions from the main analysis.

The change from baseline to Week 24 in Borg dyspnea index were analyzed by means of an ANCOVA model including treatment group and baseline value as covariates.

The change from baseline to Week 24 in WHO FC (worsening versus unchanged or improved) was analyzed as dichotomous variables by means of an exact logistic regression model adjusted by treatment group and WHO FC at baseline as a covariate.

**Control for multiplicity**

To control for multiplicity across the primary and secondary efficacy endpoints and in order to preserve the overall type 1 error at the pre-defined 2-sided significance level of $\alpha = 0.05$, it was planned to analyze secondary endpoints hierarchically according to the sequence and statistical significance pre-specified in the protocol, based on the following conditions:

- The predefined nominal significance level ($p < \alpha$ two sided) was achieved for the primary efficacy endpoint (percent of baseline PVR at rest at Week 16).
- For the secondary endpoints, the predefined nominal significance level ($p < \alpha$ two sided) was reached for all the previous endpoints in the sequence (i.e., first for the change from baseline to Week 24 in 6MWD, then for the change in Borg dyspnea index and finally for worsening WHO FC).

**Pre-defined supportive/sensitivity analyses in the SAP**
The main analysis was repeated:
• Using scores derived by the alternative imputation rules for the primary endpoint described in the SAP.
• On different analysis sets
− PPS
− FAS by replacing the log transformed percent of baseline PVR as the dependent variable by its overall rank (i.e., ANCOVA on ranks)
− FAS on non-imputed observed data
− FAS using scores derived by alternative imputation rules

**Post-hoc sensitivity analyses**
A *post-hoc* SAP includes the following additional analyses or data presentations [Appendix 16.1.9.1]:

ii) Further Sensitivity Analyses for the Primary Endpoint:
• Baseline carried forward as in imputation method,
• Excluding potential outliers, i.e., subjects with "strange" PVR values ,
• WHO FC at baseline as an additional covariate in the main model for the primary endpoint,
• Change from baseline to Week 16 expressed in absolute values.
• Excluding subjects with PVR > 2000 dyn at baseline or Week 16 and percentage change from baseline PVR at Week 16 of > 100 %.

iii) Further Sensitivity Analyses for the Secondary Endpoint (6MWD):
• Subjects with observed values only (subjects with imputation 6MWD at Week 24 were excluded),
• Adjusted per protocol population (imputation rules were applied),
• Updated figure where 95% confidence intervals (CIs) were replaced by corresponding standard errors of 6MWD estimates at Weeks 8, 16 and 24.

The Applicant has not discussed the optimal estimand for the trial and they are asked to discuss what estimand would be most suitable to describe the treatment effect in the population proposed (see ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials).

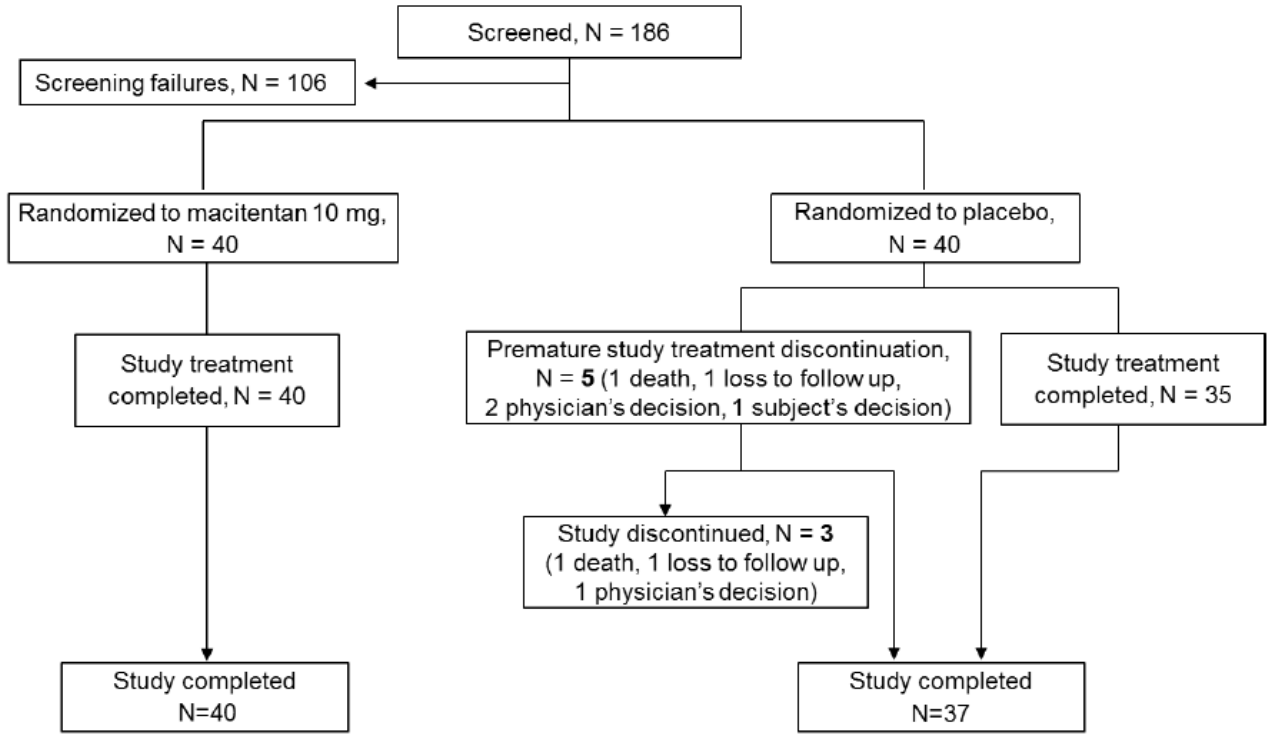
## *Results*

## Participant flow

A total of 186 subjects were screened, of which 80 subjects were randomized (macitentan: 40, placebo: 40). All 80 subjects received study medication [Module 5.3.5.1. MERIT-1 CSR].

A total of 5 subjects (all on placebo) prematurely discontinued study treatment, and 3 of these subjects also prematurely discontinued the study. All 40 subjects in the macitentan group and the remaining 37 subjects in the placebo group completed the study.

**Figure 2. Disposition of subjects in MERIT-1, Screened set**




Source: Table 15-2 (Output: T_SCRFAIL_SCR, Date 01NOV2016), Table 15-4 (Output: T_DISP_SCR, Date 31OCT2016), Table 15-7 (Output: T_PDSTST_SS, Date 31OCT2016), Table 15-8 (Output: T_PDISCST_FAS, Date 31OCT2016) and Appendix 16.2.1.4.

Protocol deviations in MERIT-1

Important protocol deviations were reported in 19 subjects on macitentan (47.5%) and 26 subjects on placebo (65.0%).

Important protocol deviations related to the inclusion/exclusion criteria included 1 subject on placebo (2.5%) who did not personally sign and date the informed consent prior to initiation of a study-mandated procedure, and 1 subject on placebo (2.5%) not compliant with the methods of contraception for females of childbearing potential (not using 2 reliable methods of contraception from Screening and not abstinent as per protocol definition). In addition, unstable diuretic dose for at least 1 week prior to the RHC up to Randomization was reported in 1 subject on macitentan (2.5%) and in 4 subjects on placebo (10.0%); baseline RHC not performed as per study-specific guidelines was reported in 1 subject in each group (2.5% each); and no baseline V/Q scan was reported in 2 subjects on placebo (5.0%). Important protocol deviations during the study treatment period mainly included unstable dose of diuretic treatment from Randomization up to EOT (n=13 [32.5%] macitentan, n=10 [25.0%] placebo), assessment time windows for RHC at Visit 4 or Visit 5a (n=3 [7.5%] macitentan, n=5 [12.5%] placebo), no post-baseline RHC available at Visit 4 or Visit 5a (n=3 [7.5%] placebo) and

lack of laboratory re-test due to decrease in haemoglobin from baseline > 20 g/L (n=5 [12.5%] macitentan, n=2 [5.0%] placebo).

In the assessor's view, the percentage of patients with important protocol deviations was substantial (56%) and not equally distributed between the two treatment groups (47.5% and 65.0% in the macitentan and placebo group, respectively). However, reasons for these protocol deviations and possible implications of these on the efficacy outcome have not been discussed by the MAH and this should be addressed.

## Recruitment

A total of 48 sites in 20 countries screened subjects for recruitment. The study was conducted (i.e., randomized subjects) in a total of 36 sites across 16 countries: Belgium, China, Czech Republic, France, Germany, Hungary, Lithuania, Mexico, Poland, Russia, South Korea, Switzerland, Thailand, Turkey, Ukraine, and the United Kingdom. The distribution of patient recruitment by regions was: Eastern Europe (n=36); Asia (n=29); Western Europe (n=13); Latin-America (n=2); Other (United States, South-Africa) (n=0).

The MERIT-1/MERIT-2 studies were multicenter studies and recruited patients from Europe, Asia, and Latin America.). In the MERIT-1 study, 36.3% of the patients were from Asia, 45.0% from Eastern Europe, 16.3 % from Western Europe and 2.5% from Latin America (please see Table 8 for the distribution). Only a few patients from West-Europe were included and no patients from the USA have been recruited into the MERIT-1 study. The MAH is requested to clarify.

## Conduct of the study

There were 4 placebo subjects with missing values for PVR at Week 16 and for 6MWD at Week 24 [Summary of Clinical Efficacy] in MERIT-1. As of 18 October 2017, a total of 76 subjects entered the ongoing OL extension study MERIT-2.

The median (95% confidence interval [CI]) follow-up for subjects who received macitentan in MERIT-1 and MERIT-2 was 26.2 (23.1, 27.1) months. This included approximately 6 months on MERIT-1 and 20.7 months during MERIT-2 [Module 5.3.5.3. Appendix 1 table 1].

**Table 3. Overview of available data-points in MERIT-1 and MERIT-2**

| | **MERIT-1 N = 80** | | | | **MERIT-2 N = 76** |
|---|---|---|---|---|---|
| | Baseline | Week 8 | Week 16 | Week 24 | Month 6 |
| PVR | 80 subjects | NA** | 76 subjects (4 missing values) | NA | NA |
| 6MWD | 80 subjects | 80 subjects | 79 subjects (1 missing) | 76 subjects (4 missing values) | 68 (8 missing) |
| Exposure | NA | 80 subjects | 79 subjects (1 missing) | 77# subjects (3 missing) | 71 subjects (5 missing) |

*Four subjects from MERIT-1 did not enroll into MERIT-2 due to death (2 subjects), loss-to-follow up (1 subject) and low hemoglobin level (1 subject). Data cut-off 17 October 2017; hence, data for MERIT-2 may be incomplete; **NA=Not applicable

6MWD = 6-minute walk distance; CRF = Case Report Form; PVR = pulmonary vascular resistance.

Source: Module 5.3.5.1 table 11-1, table 11-3, table 11-6, table 12-1; Module 5.3.5.3 appendix 1 table 2; Module 5.3.5.3 table 13.

# (as per CRF, there were 5 placebo subjects who prematurely discontinued, however as per defined treatment window, there were 2 placebo subjects and 1 macitentan subject who received less than 24 weeks of treatment exposure).

**Data error affecting PVR calculation:** Following closure of the MERIT-1 clinical database, the investigator at one Site reported an error in the site's computer application, due to a software upgrade. This error affected hemodynamic parameters values at Week 16 for 1 subject in the macitentan group, as reported in the Clinical Study Report (CSR) [Module 5.3.5.1 section 11.2.1.1]. To ensure there were no systematic issues in the RHC data (i.e., data that might have affected the primary endpoint of the study) a comprehensive assessment of all local RHC values was conducted by the sponsor. This assessment identified 4 incorrect values out of a total of 160 values impacting PVR in the analyses reported in the MERIT-1 CSR.

Additional sensitivity analyses on PVR using corrected values and excluding 4 affected subjects showed a slightly larger treatment effect and the overall conclusion of the study was not affected by these findings [Table 5; Module 5.3.5.1].

## Baseline data

In MERIT-1, a total of 153 subjects considered by the investigators to be inoperable and fulfilling all other eligibility criteria underwent adjudication for operability by either a country-specific adjudication committee (CSAC) or a central adjudication committee (for countries without a CSAC). Of these, 80 subjects were considered inoperable and subsequently randomized. The adjudication process was rigorous, thereby ensuring selection of unequivocally inoperable subjects for the study.

A summary of demographic and baseline characteristics in MERIT-1 is provided in Table 4. As expected for this indication and reflecting a typical inoperable CTEPH population present in clinical practice, subjects were predominantly female (63.8%). The median age at enrollment was 59 years, and the median time since diagnosis was 0.5 years. The population was largely (61.3%) pre-treated with PH advanced therapies and the mean 6MWD at baseline was 352 m, with the majority of subjects in WHO FC III (76.3% and 22.5% in WHO FC III and II, respectively). Subject demographics and disease characteristics at baseline were balanced between the treatment groups. There were slightly more FC III subjects in the placebo group, compared to the macitentan group (82.5% vs 70.0%). Conversely, there were more FC II subjects in the macitentan group, compared to the placebo group (30.0% vs 15.0%). To account for the differences in WHO FC at baseline, a sensitivity analysis adjusting for WHO FC at baseline was performed on PVR and 6MWD; the results confirmed the main analysis on PVR and 6MWD [Section 0 and Section 0].

The proportion of subjects receiving a PH advanced therapy at MERIT-1 baseline was 60.0% and 62.5% in the macitentan and placebo groups, respectively [Table 4]. These included sildenafil/sildenafil citrate (47.5% macitentan, 45.0% placebo) mainly, followed by oral beraprost sodium (12.5% each) and tadalafil (10.0% macitentan, 15.0% placebo) and iloprost (2.5% each) [Module 5.3.5.1 table 15-30]. No subjects took a soluble guanylate cyclase stimulator at baseline. According to the ESC/ERS guideline optimal medical treatment for CTEPH other than PAH medication consists of anticoagulants and diuretics. Considering that not all patients received diuretics at baseline (72.5% and 80.5% of the subjects in the macitentan and placebo group, respectively), the MAH is requested to justify that all patients received optimal standard of care. Approximately 56% of the population had signs of heart failure at baseline.

**Table 4. Summary of demographic and baseline characteristics, MERIT-1 study, FAS**

| | Macitentan 10 mg N=40 | Placebo N=40 | Total N=80 |
|---|---|---|---|
| Sex [n (%)] | | | |
| Male | 14 (35.0) | 15 (37.5) | 29 (36.3) |
| Female | 26 (65.0) | 25 (62.5) | 51 (63.8) |
| Age* - years (range) | 60 (20-80) | 58 (23-78) | 59 (20-80) |
| Race [n (%)] | | | |
| Asian | 15 (37.5) | 15 (37.5) | 30 (37.5) |
| White | 25 (62.5) | 25 (62.5) | 50 (62.5) |
| Geographical region [n (%)] | | | |
| Asia | 15 (37.5) | 14 (35.0) | 29 (36.3) |
| Eastern Europe | 17 (42.5) | 19 (47.5) | 36 (45.0) |
| Latin America | 1 (2.5) | 1 (2.5) | 2 (2.5) |
| Western Europe | 7 (17.5) | 6 (15.0) | 13 (16.3) |
| Time since diagnosis of CTEPH* - years (range) | 0.44 (0.04-10.0) | 0.56 (0.06-10.08) | 0.50 (0.04-10.08) |
| PVR at baseline (dyn.sec/cm5) | | | |
| n | 40 | 40 | 80 |
| Mean | 929.189 | 984.319 | 956.754 |
| SD | 379.651 | 487.059 | 434.783 |
| Median | 910.10 | 927.27 | 916.16 |
| Q1, Q3 | 624.00, 1159.96 | 527.29, 1223.81 | 607.70, 1178.71 |
| Min, Max | 406.56, 2044.44 | 408.16, 2442.11 | 406.56, 2442.11 |
| Six-minute walk distance at baseline (m) | | | |
| n | 40 | 40 | 80 |
| Mean | 353.03 | 351.23 | 352.13 |
| SD | 87.90 | 73.79 | 80.64 |
| Median | 388.0 | 360.0 | 375.0 |
| Q1, Q3 | 285.5, 420.0 | 289.5, 414.5 | 289.5, 417.0 |
| Min, Max | 160.0, 455.0 | 162.0, 467.0 | 160.0, 467.0 |
| WHO functional class at baseline | | | |
| II | 12 (30.0) | 6 (15.0) | 18 (22.5) |
| III | 28 (70.0) | 33 (82.5) | 61 (76.3) |
| IV | 0 | 1 (2.5) | 1 (1.3) |
| PAH-specific background therapy | | | |
| Any | 24 (60.0) | 25 (62.5) | 49 (61.3) |
| PDE5i | 23 (57.5) | 24 (60.0) | 47 (58.8) |
| Inhaled/oral prostanoid | 6 (15.0) | 6 (15.0) | 12 (15.0) |

mRAP= Mean right atrial pressure, PVR= Pulmonary vascular resistance, SD=Standard Deviation, WHO= World Health Organization
* median value (range)

BMI=Body Mass Index, SD=Standard Deviation

Source: Modified from Module 5.3.5.1 table 15-13 (T_DEMOG_FAS), table 15-17 (T_BASDC_FAS), table 15-30 (T_CTSBLSP_FAS).

## Numbers analysed

**MERIT-1 Analysis sets:** All 80 randomized subjects received study treatment. Hence the FAS and the Safety Set are identical. Of the 80 subjects (40 on macitentan and 40 on placebo) included in the FAS, 6 subjects (all on placebo) were excluded from the per protocol set (PPS) for the following reasons [Table 10-2 of the MERIT-1 CSR]: unavailability of post-baseline RHC values (n = 3), RHC not performed at the same location and under the same conditions as baseline (n = 2) and subject with WHO FC II at baseline receiving a PDE-5 inhibitor or oral or inhaled prostanoid treatment prior to Week 16 (n = 1). The PPS included a total of 74 subjects (40 macitentan, 34 placebo).

**Table 10-1 Overview of analysis sets, Full Analysis set**

| Analysis Set | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) | Total N=80 n (%) |
|---|---|---|---|
| Full analysis set | 40 (100) | 40 (100) | 80 (100) |
| Treated with macitentan | 40 (100) | 0 | 40 (50.0) |
| Treated with placebo | 0 | 40 (100) | 40 (50.0) |
| Per-protocol analysis set | 40 (100) | 34 (85.0) | 74 (92.5) |
| Treated with macitentan | 40 (100) | 0 | 40 (50.0) |
| Treated with placebo | 0 | 34 (85.0) | 34 (42.5) |
| Safety set | 40 (100) | 40 (100) | 80 (100) |
| Treated with macitentan | 40 (100) | 0 | 40 (50.0) |
| Treated with placebo | 0 | 40 (100) | 40 (50.0) |
| Pharmacokinetic analysis set | 35 (87.5) | 36 (90.0) | 71 (88.8) |
| Treated with macitentan | 35 (87.5) | 0 | 35 (43.8) |
| Treated with placebo | 0 | 36 (90.0) | 36 (45.0) |

The percentages are based on N.
Source: Modified from Table 15-9 (Output: T_ANSETOV_FAS, Date: 01NOV2016)

**MERIT-2**: a total of 76 subjects (all 40 subjects who received macitentan and 36 out of 40 subjects who received placebo in MERIT-1) were enrolled. All 76 subjects received treatment with macitentan 10 mg in MERIT-2. Four subjects from MERIT-1 did not enrol into MERIT-2: 3 subjects discontinued the MERIT-1 study and 1 subject had low hemoglobin level [Summary of Clinical Efficacy]. Up to the cut-off date of 17 October 2017, a total of 18 subjects prematurely discontinued study treatment, and 11 of these subjects also prematurely discontinued the MERIT-2 study. The reasons for study discontinuation were death (9 subjects), physician's decision (1 subject), and subject's decision (1 subject) [Module 5.3.5.3, appendix 1 table 8, table 9, table 10].

## Outcomes and estimation

### Primary endpoint (mean PVR change from baseline to week 16)

### Main sponsor's analysis (Full Analysis Set)

In the FAS (n = 40 in each group), mean PVR (± SD) decreased from baseline to Week 16 on both macitentan (from 929.2 ± 379.65 dyn.sec/cm5 to 723.1 ± 454.33 dyn.sec/cm5) and placebo (from 984.3 ± 487.06 dyn.sec/cm5 to 898.5 ± 476.34 dyn.sec/cm5) [Table 11-1]. The mean decrease in PVR (± SD) from baseline to Week 16 was 206.1 ± 450.39 dyn.sec/cm5 on macitentan and 85.8 ± 301.47 dyn.sec/cm5 on placebo.

The main analysis for the primary endpoint was the ANCOVA model on log-transformed percent of baseline PVR at Week 16 adjusted by treatment as a factor and log-transformed PVR at baseline as a covariate. From the adjusted model, the treatment effect at Week 16 (ratio of geometric means macitentan/placebo) was 0.84 (95% CL: 0.70, 0.99), p = 0.041, i.e., a 16% reduction in PVR with macitentan compared to placebo [Table 11-2 of the MERIT-1 CSR]. Using median values, the median ratio was 0.82 (95%CI: 0.71 to 0.94) [Table 11-1].

**Table 11-1. Change in PVR from baseline to Week 16, FAS (MERIT-1 CSR)**

With imputation

| | Macitentan 10 mg N=40 | Placebo N=40 |
|---|---|---|
| PVR (dyn.sec/cm5) | | |
| Baseline | | |
| n | 40 | 40 |
| Mean | 929.2 | 984.3 |
| SD | 379.65 | 487.06 |
| Median | 910.1 | 927.3 |
| Q1, Q3 | 624.0, 1160.0 | 527.3, 1223.8 |
| Min, Max | 407, 2044 | 408, 2442 |
| Week 16 | | |
| n | 40 | 40 |
| Mean | 723.1 | 898.5 |
| SD | 454.33 | 476.34 |
| Median | 671.6 | 834.5 |
| Q1, Q3 | 443.4, 828.4 | 474.1, 1234.4 |
| Min, Max | 203, 2868 | 193, 2277 |
| Total number of subjects with imputation of missing values [n (%)] | 0 | 4 (10.0) |
| due to death (by max %BL observed) (a) | 0 | 1 (2.5) |
| by median %BL observed (a) | 0 | 3 (7.5) |
| Change from baseline to Week 16 | | |
| n | 40 | 40 |
| Mean | -206.1 | -85.8 |
| SD | 450.39 | 301.47 |
| Median | -223.7 | -100.5 |
| Q1, Q3 | -417.4, -66.1 | -190.4, 20.2 |
| Min, Max | -848, 1942 | -1230, 642 |
| Percent of baseline | | |
| n | 40 | 40 |
| Geometric mean | 73.0 | 87.2 |
| Geometric CV | 45.3 | 33.5 |
| 95% CL of geometric mean | 63.6, 83.8 | 78.5, 96.7 |
| Median | 71.9 | 88.1 |
| TREATMENT EFFECT | | |
| Geometric mean ratio | 0.84 | |
| 95% CL of geometric mean ratio | 0.71, 0.99 | |
| Median ratio | 0.82 | |
| 95% CL of median ratio | 0.71, 0.94 | |

(a) %BL observed=Percent of baseline PVR observed in the same treatment group times baseline value of the subject
%BL=Percent of baseline value, CL=Confidence limit, CV=Coefficient of variation, PVR=Pulmonary vascular resistance, SD=Standard Deviation
Median ratio according to Hodges-Lehmann with asymptotic Moses CLs.
Source: Modified from Table 15-32 (Output: T_PVR_FAS, date 31OCT2016)

**Supportive per-protocol sponsor's analysis (Per protocol set)**

From the adjusted model in PPS, the treatment effect at Week 16 (Geometric mean ratio macitentan/placebo: 0.87; 95% CI: 0.73, 1.04; p = **0.1302**] [Table 15-34].
The median ratio macitentan/placebo at week 16 is 0.85 (95% CI: 0.74, 0.98) [Table 15-34].

**Table 15-34. Change from baseline to Week 16 in PVR, Per-protocol analysis set (PPS)**

Without imputation

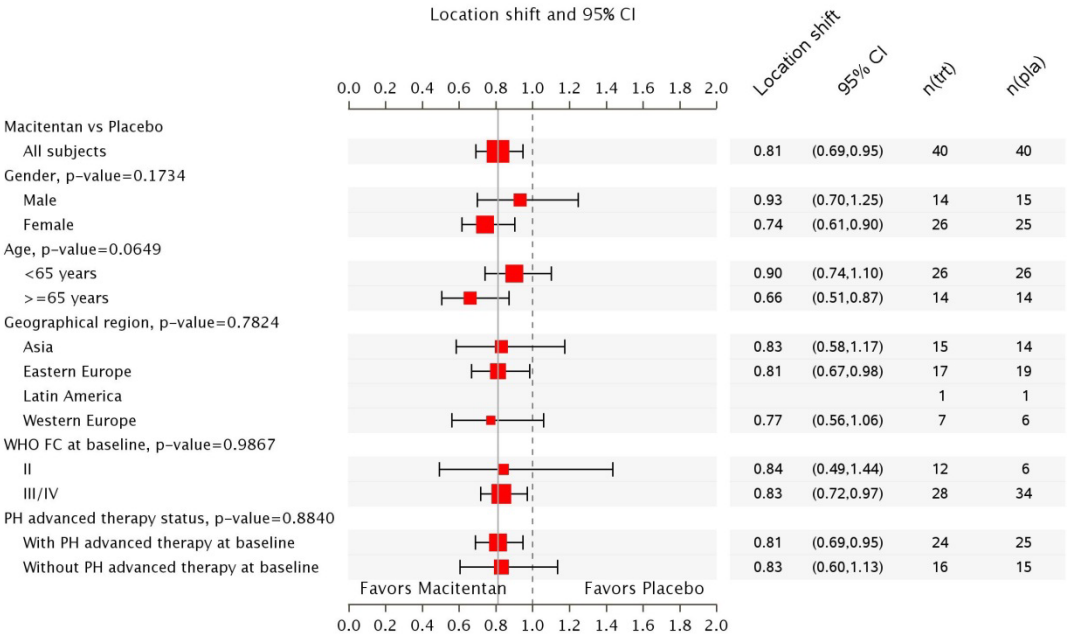
| | Macitentan 10 mg N=40 | Placebo N=34 |
|---|---|---|
| PVR (dyn.sec/cm5) | | |
| Baseline | | |
| n | 40 | 34 |
| Mean | 929.2 | 990.7 |
| SD | 379.65 | 499.19 |
| Median | 910.1 | 935.6 |
| Q1, Q3 | 624.0, 1160.0 | 527.3, 1266.7 |
| Min, Max | 407, 2044 | 408, 2442 |
| Week 16 | | |
| n | 40 | 34 |
| Mean | 723.1 | 877.9 |
| SD | 454.33 | 494.72 |
| Median | 671.6 | 791.7 |
| Q1, Q3 | 443.4, 828.4 | 445.9, 1232.4 |
| Min, Max | 203, 2868 | 193, 2277 |
| Change from baseline to Week 16 | | |
| n | 40 | 34 |
| Mean | -206.1 | -112.9 |
| SD | 450.39 | 305.36 |
| Median | -223.7 | -117.9 |
| Q1, Q3 | -417.4, -66.1 | -191.3, -23.5 |
| Min, Max | -848, 1942 | -1230, 642 |
| Percent of baseline | | |
| n | 40 | 34 |
| Geometric mean | 73.0 | 83.8 |
| Geometric CV | 45.3 | 33.4 |
| 95% CL of geometric mean | 63.6, 83.8 | 74.8, 93.8 |
| Median | 71.9 | 87.3 |
| TREATMENT EFFECT | | |
| Geometric mean ratio | 0.87 | |
| 95% CL of geometric mean ratio | 0.73, 1.04 | |
| Median ratio | 0.85 | |
| 95% CL of median ratio | 0.74, 0.98 | |

Only subjects with baseline and post-baseline are considered
CL=Confidence limit, CV=Coefficient of variation, PVR=Pulmonary vascular resistance, SD=Standard Deviation
Median ratio according to Hodges-Lehmann with asymptotic Moses CLs.
Output: T_PVR_PPS, Produced by biarnall on 01NOV2016 13:43 (CET), SDTM production date: 31OCT2016

**Changes in PVR across sub-groups**

There was no statistically significant indication of heterogeneity of treatment effect across the predefined subgroups based on the interaction tests. Notably, and as observed for 6MWD, the treatment effect was similar in the subgroup of subjects who were receiving PH advanced therapy at baseline. Due to the low number of subjects in some subgroups, e.g., male, Asia, Western Europe and WHO FC II, wider 95% CIs (higher variability around the point estimates of treatment effect) were observed [Figure 3].

**Figure 3 Change from baseline to Week 16 in PVR, expressed as percent of baseline value, MERIT-1, FAS**




n(trt) = No. of Subjects in Macitentan. n(pla) = Number of Subjects in Placebo
The vertical solid line references the overall treatment effect
Levels of confidence are unadjusted. Per subgroup, effects are unadjusted for any other factors. P-values reflect treatment-by-subgroup variable interaction testing on extended main model with subgroup variable effect and its interaction with treatment added. Apparent homogeneity or heterogeneity should not be over-interpreted.
The "Square" displayed on the 95% confidence interval is proportional to the number of subjects with in the subgroup category.

Source: Module 5.3.5.3, figure 13 (F_IPVRACS1_FAS).

**Sensitivity analyses of PVR**

For sensitivity analyses of PVR with corrected values and excluding 4 subjects with incorrect values, the treatment effect at Week 16 was 0.81 (95% CL: 0.69, 0.95) and 0.79 (95% CL: 0.67, 0.93), respectively [Table 5; Module 5.3.5.1].

**Table 5. Comparison of the main analysis on the primary efficacy endpoint of PVR versus analyses with corrected values, and excluding 4 subjects with incorrect values, FAS**

| | Number of subjects, geometric mean ratio (macitentan vs placebo, 95% CLs), p-value[#] | | |
|---|---|---|---|
| **Analyses** | **As reported in the CSR** | **Corrected values** | **Excluding subjects with incorrect values** |
| Main analysis | N = 80<br>0.84 (0.70, 0.99)<br>p = 0.0410 | N = 80<br>0.81 (0.69, 0.95)<br>p = 0.0084 | N = 76<br>0.79 (0.67, 0.93)<br>p = 0.0045 |

Source: Module 5.3.5.1, table 11-2; table 10-1, table 10-2.
[#]ANCOVA including log-transformed PVR at baseline and treatment as covariates in the model.
ANCOVA = analysis of covariance; CL = confidence limit; CSR = clinical study report; FAS = Full Analysis Set; PVR = pulmonary vascular resistance.

Results of the PPS analysis of PVR, as reported in the MERIT-1 CSR, with corrected values, and excluding incorrect values, showed a reduction of 13% (geometric mean ratio: 0.87; 95%CI: 0.73 to

1.04) [Module 5.3.5.1 table 15-35, which are consistent with the non-significance findings in the main PPS analysis (not excluding incorrect values).

**Table 15-35 Between-treatment analysis of PVR at Week 16 expressed as percent of PVR at baseline, Per-protocol Analysis set**

ACT-064992
Protocol: AC-055E201
Between-treatment analysis of PVR at Week 16 expressed as percent of PVR at baseline
Analysis Set: Per-protocol analysis set

| | NDF | DDF | F-value | P-value | Macitentan 10 mg | Placebo | Macitentan - Placebo |
|---|---|---|---|---|---|---|---|
| Number of subjects included in the analysis set | | | | | 40 | 34 | |
| Number of subjects included in the analysis | | | | | 40 | 34 | |
| Type III analysis of effects | | | | | | | |
| Treatment | 1 | 71 | 2.34 | 0.1302 | | | |
| LS mean | | | | | 4.29 | 4.43 | -0.14 |
| SE | | | | | 0.06 | 0.07 | 0.09 |
| 95% CL | | | | | 4.17, 4.41 | 4.30, 4.56 | -0.32, 0.04 |
| Model-adjusted geometric mean ratio | | | | | | | 0.87 |
| 95% CL of model-adjusted geometric mean ratio | | | | | | | 0.73, 1.04 |

CL=Confidence Limit, DDF=Denominator Degrees of Freedom, LS Mean=Least Square Mean, NDF=Numerator Degrees of Freedom, SE=Standard Error
Statistical model is Analysis of Covariance including log(PVR at baseline) as a covariate, with Treatment as factor in the model. Dependent variable is log(percent of baseline PVR at Week 16).
Output: T_PVRAC_PPS, Produced by biarnal1 on 31OCT2016 15:46 (CET), SDTM production date: 31OCT2016
Program: val_csr/program_output/pvr03.sas
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**Secondary outcome: 6MWD**

**Main sponsor's analysis (mean change, FAS)**

In MERIT-1, after 24 weeks of treatment, the mean change in 6MWD from baseline was a highly clinically relevant increase of 35.0 m (± 52.52) on macitentan vs. 1.0 m (± 83.24) on placebo. The LS mean difference of change from baseline to Week 24 (macitentan vs. placebo) of 34.04 m was statistically significant (95% CI: 2.9 to 65.2, p = 0.0326) [Table 6].

**Table 6. Secondary efficacy endpoint: summary of changes in 6MWD (m) from baseline to Week 24, FAS**

| n | Macitentan 10 mg N = 40 Mean ± SD | N | Placebo N = 40 Mean ± SD | Treatment difference analysis |
|---|---|---|---|---|
| **Main analyses:** | | | | **Between treatment analysis[1]** **Difference in Least Square Means (95% CLs) macitentan–placebo** |
| 40 | 35.0 ± 52.52 | 40 | 1.0 ± 83.24 | 34.0 (2.90, 65.19) |

[1] Statistical model: ANCOVA including 6MWD at baseline as a covariate, with treatment as factor in the model.

6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; CL = confidence limit; FAS = Full Analysis Set; SD = standard deviation.

Source: Module 5.3.5.1 table 11-5, table 15-50 (T_6MWDAC_FAS).

There were 4 subjects (all on placebo) with missing 6MWD values at the Week 24 visit. For the main analysis the missing values were imputed according to the following pre-specified criteria:

- Death: 0 m was imputed (2 subjects)
- Lost to follow-up: last available post-baseline value was carried forward (1 subject)
- AE: last available post-baseline value was carried forward (1 subject with arthralgia).

**Supportive per protocol sponsor's analysis (mean change, per-protocol set, PPS)**

In the true PPS without imputation of 6MWD data in those patients without a 6MWD assessment at week 24, a total of 9 subjects on placebo were excluded from the analysis [Table 15-51]: 6 subjects with protocol deviations that led to exclusion from the analysis and 3 ad no 6MWD assessment at Week 24.

The mean change from baseline to Week 24 was 35.0 ± 52.52 m on macitentan and 17.40 m ± 44.79 m on placebo. The LS mean difference for the change from baseline to Week 24 (macitentan vs placebo) was **18.03** (95% CL: –4.90, 40.96; p = **0.1212**) [Table 15-52]. The applicant states that, given the lack of relevance of the PPS to the 6MWT assessment, owing to the application of hemodynamic criteria, this analysis is considered of limited relevance.

**Table 15-52 Between-treatment analysis of change from baseline to Week 24 in 6MWD, Per-protocol analysis set**

Week 24

| | NDF | DDF | F-value | P-value | Macitentan 10 mg | Placebo | Macitentan - Placebo |
|---|---|---|---|---|---|---|---|
| Number of subjects included in the analysis set | | | | | 40 | 34 | |
| Number of subjects included in the analysis | | | | | 40 | 31 | |
| Type III analysis of effects | | | | | | | |
| Treatment | 1 | 68 | 2.46 | 0.1212 | | | |
| LS mean | | | | | 35.18 | 17.14 | 18.03 |
| SE | | | | | 7.59 | 8.62 | 11.49 |
| 95% CL | | | | | 20.03, 50.33 | -0.06, 34.35 | -4.90, 40.96 |

CL=Confidence Limit, DDF=Denominator Degrees of Freedom, LS Mean=Least Square Mean, NDF=Numerator Degrees of Freedom, SE=Standard Error
Statistical model is Analysis of Covariance including 6MWD at baseline as a covariate, with Treatment as factor in the model.
Output: T_6MWDAC_PPS, Produced by biarnall on 01NOV2016 6:56 (CET), SDTM production date: 31OCT2016
Program: val_csr/program_output/smwd03.sas
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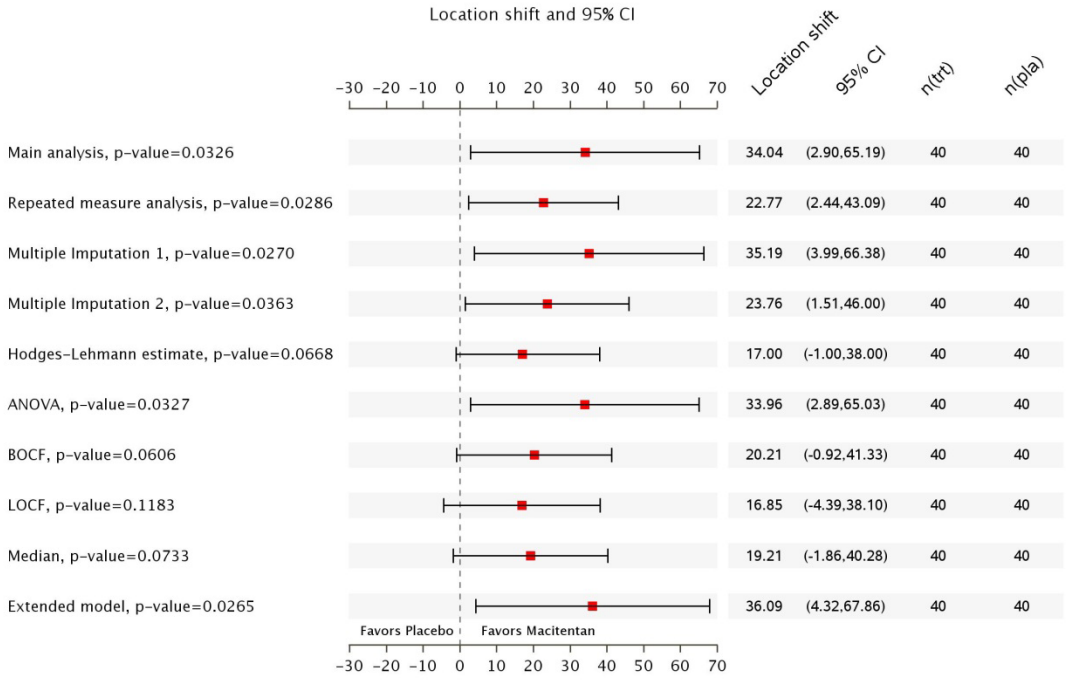
**6MWD – sensitivity analyses**

Several sensitivity analyses on the secondary efficacy endpoint of 6MWD were conducted with the objective of trying to support the robustness of the main analysis [Figure 4].

The sponsor states that, regardless of the sensitivity analysis used, the results in MERIT-1 were consistent and showed a clinically relevant treatment difference in 6MWD between macitentan and placebo [Figure 4]. The purpose of the sensitivity analyses performed was not to show statistical significance but to illustrate the magnitude of treatment effect across different scenarios, as well as the degree of certainty around the true treatment effect. In summary, the sponsor believes that sensitivity analyses suggested that the true effect was not dependent on how the missing data were handled or on the statistical approach used.

The main analysis was repeated:
• Using scores derived by the alternative imputation rules for the primary endpoint described in the SAP.
• On different analysis sets
– PPS
– FAS by replacing the log transformed percent of baseline PVR as the dependent variable by its overall rank (i.e., ANCOVA on ranks)
– FAS on non-imputed observed data
– FAS using scores derived by alternative imputation rules

**Figure 4. Main and sensitivity analyses on 6MWD (changes from baseline to Week 24) in MERIT-1, FAS**




n(trt) = No. of Subjects in Macitentan. n(pla) = Number of Subjects in Placebo
Main analysis: Statistical model is Analysis of Covariance including 6MWD at baseline as a covariate, with Treatment as factor in the model.
Repeated measure analysis: regression model which includes fixed-effect terms for treatment, time, treatment by time interaction and baseline 6MWD (2 subjects who died imputed with 0 meters).
Multiple imputation 1: Multiple imputation method is applied under the assumption of missing at random (except for 2 subjects who died imputed with 0 meters);
Multiple imputation 2: Multiple imputation method is applied under the assumption of missing at random (except for the 2 subjects who died imputed with worst change within the treatment arm they were randomized);
BOCF: Baseline observation carried forward; LOCF: Last Observation Carried Forward; Median: Imputed with the median change within the treatment arm they were randomized;
Extended model: Analysis of Covariance with 6MWD at baseline and WHO functional class at baseline as covariates with Treatment as a factor in the model;

**LS Means= Least Square Means,***ANCOVA model adjusted by 6MWD at baseline as covariate, [1] T_6MWDACO_FAS, [2]T_6MWD_PPS T6MWDAC_PPS,

Source: Module 5.3.5.3 figure 1 (F_6MWD_FP_FAS).

### Subgroups – 6MWD analyses

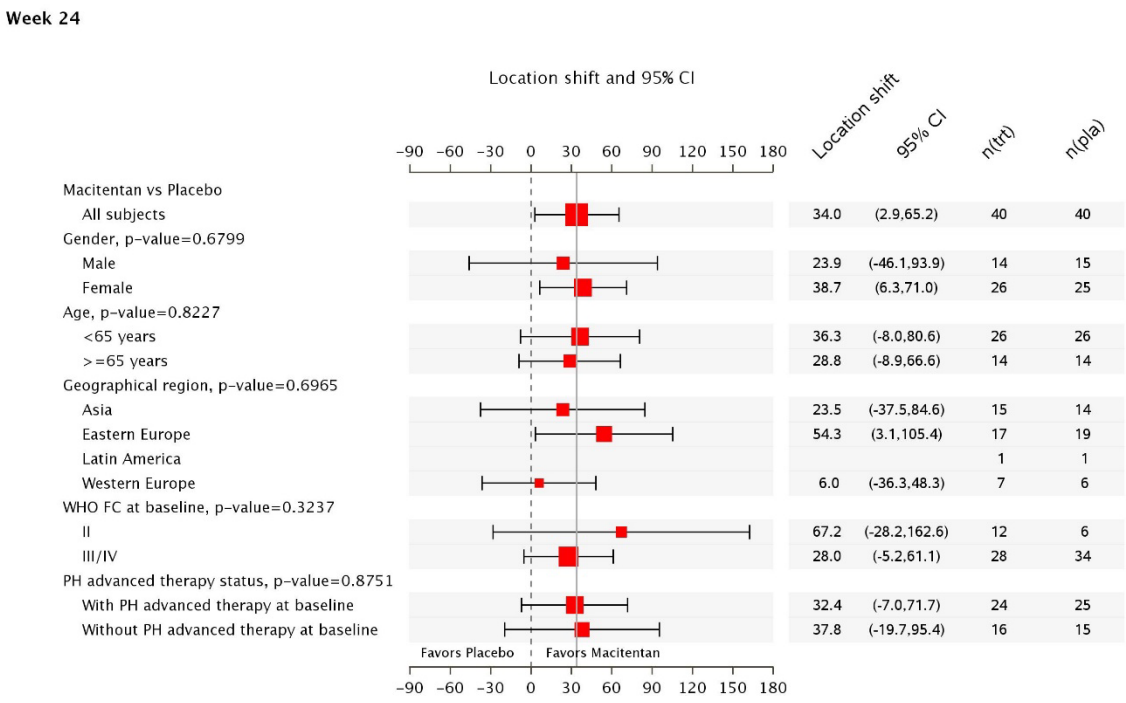
The treatment effect on 6MWD was consistent across all predefined subgroups [Figure 5], including in subjects receiving background PH advanced therapy at baseline (61.3%), including PDE-5 inhibitors (58.8%) [Table 4].

There was no statistically significant indication of heterogeneity of treatment effects for 6MWD across subgroups based on the interaction tests [Figure 5].

The consistency of the effect observed in the subgroups with/without PH advanced therapy at baseline in MERIT-1 [Figure 5] is considered of significant clinical importance, as it provides reassurance regarding the efficacy of macitentan on top of PH advanced therapies commonly used in CTEPH in a real-world setting.

Due to the low number of subjects in the subgroup of Western Europe (13 subjects from Belgium, France, Germany, Switzerland, United Kingdom, and Turkey), 6MWD results should be considered with caution; efficacy in this subgroup should be regarded in terms of the positive PD effect observed [see Section 0].

**Figure 5** **Forest plot of change in 6MWD from baseline to Week 24 per subgroup and overall, FAS**

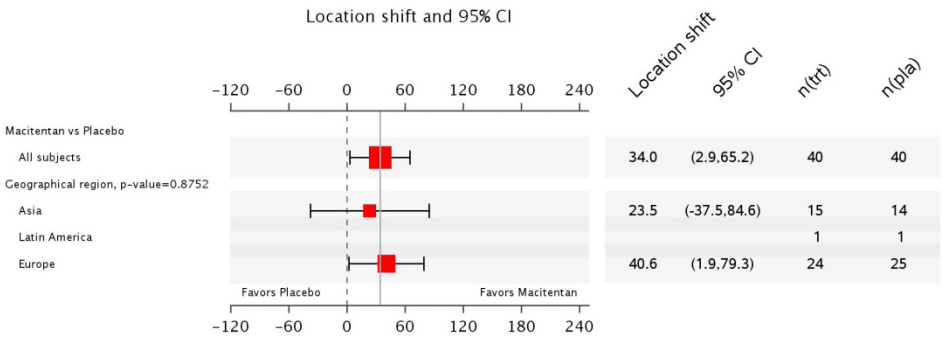



n(trt) = No. of Subjects in Macitentan. n(pla) = Number of Subjects in Placebo
The vertical solid line references the overall treatment effect
Levels of confidence are unadjusted. Per subgroup, effects are unadjusted for any other factors. P-values reflect treatment-by-subgroup variable interaction testing on extended main model with subgroup variable effect and its interaction with treatment added. Apparent homogeneity or heterogeneity should not be over-interpreted.
The "Square" displayed on the 95% confidence interval is proportional to the number of subjects with in the subgroup category.

Source: Module 5.3.5.3 figure 2 (F_6MWDACS1_FAS).

Given the small group of Western European patients compared to the subgroup of Eastern Europe (36 subjects from Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine), these two subgroups were pooled to represent a more reasonably sized but still relevant subgroup of patients (subgroup: Europe, n = 49), for a *post-hoc* analysis [Figure 6]. The LS mean difference of change from baseline to Week 24 (macitentan vs placebo) in 6MWD was 40.6 m (95% CI: 1.9, 79.3). There was no indication of heterogeneity of treatment effects for 6MWD across regions where Europe was defined as above, p = 0.8752 [Figure 6].

**Figure 6** **Forest plot of change from baseline to Week 24 in 6MWD within the subgroup of geographical regions in MERIT-1, FAS**




Source: Module 5.3.5.3, figure 3 (F_6MWDACSP_FAS).

Region Europe includes the following countries: Belgium, France, Germany, Switzerland, United Kingdom, Turkey, Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine.

**Other secondary endpoints**

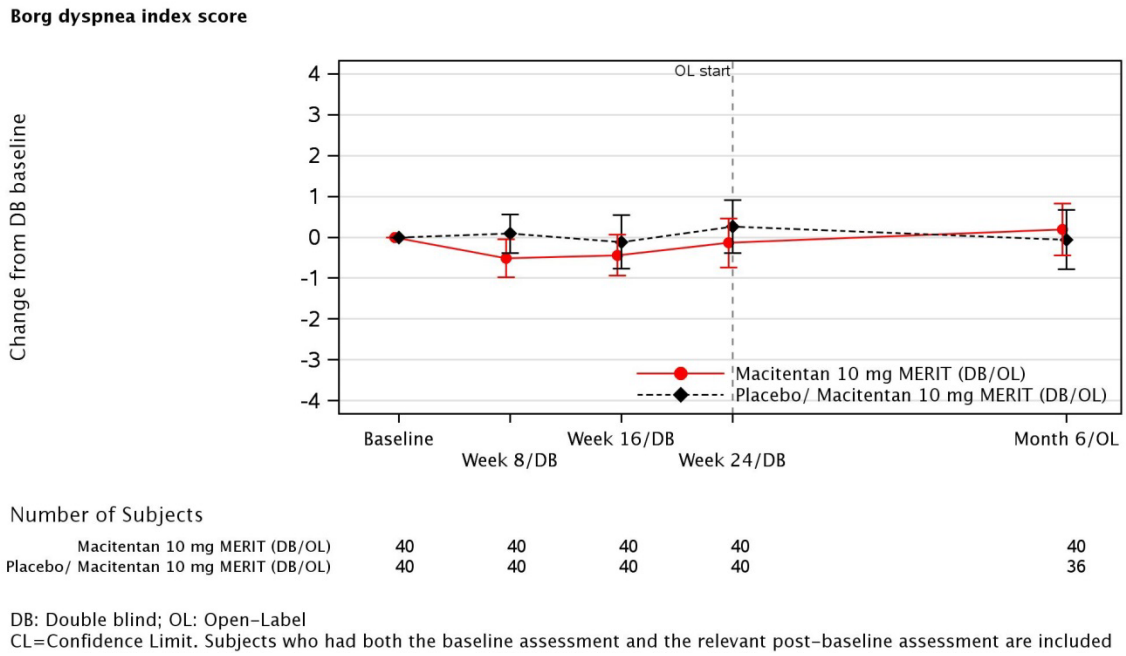
The confirmatory testing for the secondary endpoints ended with the secondary endpoint of Borg dyspnea index, as the first statistically non-significant result in the testing sequence.

**Borg dyspnea index**

The Borg dyspnea index was collected immediately following a 6MWT. In MERIT-1, a small change from baseline to Week 24 in Borg dyspnea index was observed in both groups.

The Borg dyspnea index rated dyspnea severity on a scale from 0 ('Nothing at all') to 10 ('Very, very severe – maximal'). Over time, no change in Borg dyspnea index was observed [Figure 9]. At baseline, the mean score was 4.2 ± 2.52 for macitentan and 4.2 ± 2.14 for placebo. At Week 24, the mean score was 4.1 ± 2.52 for macitentan and 4.4 ± 2.45 for placebo. From adjusted model, the mean change from baseline to Week 24 did not show a statistically significant difference between treatment groups (–0.39, 95% CL: –1.21, 0.43, p = 0.3492) [Table 15-58].

**Figure 7 Mean change in Borg dyspnea index from baseline in MERIT-1 to post-baseline visits in MERIT-2, FAS**




DB: Double blind; OL: Open-Label
CL=Confidence Limit. Subjects who had both the baseline assessment and the relevant post-baseline assessment are included

Source: Module 5.3.5.3 figure 24 (F_IBORG_TIME_FAS).

The results for Borg dyspnea index over the first 24 weeks of DB treatment, while not statistically significantly different, showed a trend for improvement (reduction in score) in the macitentan group and a trend for worsening (increase in score) in the placebo group. Given the timing of this assessment immediately following the 6MWT, the data suggest a different (lower) level of effort invested at post-baseline visits in the macitentan vs. placebo group, resulting in a potential underestimation of the true treatment effect of macitentan.

**Change in WHO FC from baseline**

From baseline to Week 24, the majority of subjects (n = 31, 77.5% macitentan, n = 29, 72.5% placebo) did not show a change in the status of WHO FC [Table 11-8]. Worsening of WHO FC from baseline to Week 24 was reported for 3 subjects on placebo. One of these subjects worsened from FC III to IV but for the remaining two subjects who prematurely discontinued due to death, missing FC values were imputed as FC IV. The odds ratio for the proportion of subjects with worsening WHO FC at Week 24 (macitentan vs placebo: 0.212, 95% CL: < 0.001, 1.464, p = 0.0962) favored macitentan [Table 15-63]. The results imply that the odds of worsening in WHO FC at Week 24 on macitentan were approximately 79% lower than on placebo. However, this result needs to be interpreted with caution due to small number of subjects with worsening of WHO FC. From baseline to Week 24, WHO

FC improved for 9 subjects (22.5%) on macitentan (6 subjects from III to II and 3 subjects from II to I) and for 8 subjects (20.0%) on placebo (1 subject IV to III, 6 subjects III to II and 1 subject II to I) [Table 11-8].

**Table 11-8 Shift table of change in WHO FC from baseline to Week 24, FAS**

| Treatment | Baseline | Week 24 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Class I | | Class II | | Class III | | Class IV | | Missing |
| | | n | (%) | n | (%) | n | (%) | n | (%) | n (%) |
| Macitentan (N=40) 10 mg | Class I | 0 | | 0 | | 0 | | 0 | | 0 |
| | Class II | 3 | (7.5) | 9 | (22.5) | 0 | | 0 | | 0 |
| | Class III | 0 | | 6 | (15.0) | 22 | (55.0) | 0 | | 0 |
| | Class IV | 0 | | 0 | | 0 | | 0 | | 0 |
| | Missing | 0 | | 0 | | 0 | | 0 | | 0 |
| | Total | 3 | (7.5) | 15 | (37.5) | 22 | (55.0) | 0 | | 0 |
| Placebo (N=40) | Class I | 0 | | 0 | | 0 | | 0 | | 0 |
| | Class II | 1 | (2.5) | 4 | (10.0) | 0 | | 1 | (2.5) | 0 |
| | Class III | 0 | | 6 | (15.0) | 25 | (62.5) | 2 | (5.0) | 0 |
| | Class IV | 0 | | 0 | | 1 | (2.5) | 0 | | 0 |
| | Missing | 0 | | 0 | | 0 | | 0 | | 0 |
| | Total | 1 | (2.5) | 10 | (25.0) | 26 | (65.0) | 3 | (7.5) | 0 |

| | Macitentan 10 mg N=40 | Placebo N=40 |
|---|---|---|
| n | 40 | 40 |
| Worsened | 0 | 3 (7.5) |
| Not Worsened | 40 (100) | 37 (92.5) |
| Unchanged | 31 (77.5) | 29 (72.5) |
| Improved | 9 (22.5) | 8 (20.0) |
| Number of subjects imputed | 0 | 3 (7.5) |
| due to death or PH-related disease progression (by Class IV) | 0 | 2 (5.0) |
| by last post-baseline OCF | 0 | 1 (2.5) |

WHO functional class worsened, remained unchanged or improved if the class level increased, did not change or decreased, respectively
OCF=observation carried forward
The percentages are based on N.
Source: Modified from Table 15-62, Output: T_WHO_FAS, Produced by biarnal1 on 31OCT2016

**Table 15-63 WHO functional class: Number (%) of subjects who worsened and between-group comparisons by time point, Full Analysis set**

ACT-064992
Protocol: AC-055E201
WHO functional class: Number (%) of subjects who worsened and between-group comparisons by time point
Analysis Set: Full analysis set

| Time Point | Macitentan 10 mg N=40 | | Placebo N=40 | | Between-Treatment Groups Odds Ratio | | |
|---|---|---|---|---|---|---|---|
| | n / Nn (%) | 95% CL | n / Nn (%) | 95% CL | OR | 95% CL | P-value |
| Week 8 | 1 / 40 (2.5) | 0.0006, 0.1316 | 0 / 40 | 0.0000, 0.0881 | 1.179 | 0.062, >999.999 | 0.4590 |
| Week 16 | 0 / 40 | 0.0000, 0.0881 | 2 / 40 (5.0) | 0.0061, 0.1692 | 0.298 | <0.001, 2.610 | 0.1803 |
| Week 24 | 0 / 40 | 0.0000, 0.0881 | 3 / 40 (7.5) | 0.0157, 0.2039 | 0.212 | <0.001, 1.464 | 0.0962 |

CL=Confidence Limit, OR=Odds Ratio
n is the number of subjects who worsened at the corresponding time point.
N is the total number of subjects in the treatment group.
Nn is the total number of subjects with non-missing or imputed data at the corresponding time point.
Confidence limits are calculated using exact Clopper-Pearson formula.
Logistic regression is used for Treatment Group vs. Placebo comparison to generate odds ratio, CL, and p-values with treatment and WHO functional class at baseline as factors in the model.
Output: T_WHOLR_FAS, Produced by biarnal1 on 31OCT2016 15:46 (CET), SDTM production date: 31OCT2016
Program: val_csr/program_output/who03.sas
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**Change in RHC variables other than PVR from baseline to Week 16**

For cardiac index (CI) and cardiac output (CO), clinically meaningful mean increases of 0.43 L/min/m2 or 0.78 L/min from baseline were observed on macitentan at Week 16. On placebo, no change from baseline was observed for cardiac index. For CO, a mean decrease from baseline of 0.02 L/min with placebo was observed [Table 11-11]. The LS mean difference of change from baseline to Week 16 for cardiac index (macitentan vs placebo) of 0.43 was statistically significant (95% CL: 0.18, 0.67; p = 0.0008). The LS mean difference of change from baseline to Week 16 for CO (macitentan vs placebo) of 0.78 was statistically significant (95% CL: 0.35, 1.20; p = 0.0005).

The LS mean difference of change from baseline to Week 16 (macitentan vs placebo) for SvO2 (95% CL: –0.42, 6.85; p = 0.0822) and TPR (95% CL: –345.05, 20.63; p = 0.0812) favored macitentan. However the difference was not statistically significant.

For other variables including for mRAP, mPAP, there was a trend in the change from baseline to Week 16 favoring macitentan, but these changes were not statistically significant.

**Table 11-11 Summary of change from baseline to Week 16 in RHC variables other than PVR, FAS**

| Variables<br>Mean ± SD | n | Macitentan 10 mg (N = 40) | n | Placebo (N = 40) | Between treatment analysis<br>LS mean (macitentan–placebo), 95% CLs<br>Type III analysis of effects p-value |
|---|---|---|---|---|---|
| mRAP (mmHg) | 40 | –2.63 ± 8.41 | 36 | –0.11 ± 3.46 | –1.47 (–3.77, 0.84), p = 0.2093 |
| mPAP (mmHg) | 40 | –3.45 ± 8.30 | 36 | –1.67 ± 8.96 | –1.93 (–5.88, 2.02), p = 0.3341 |
| mSAP (mmHg) | 40 | –3.65 ± 9.59 | 36 | –6.03 ± 11.58 | 1.39 (–3.12, 5.91), p = 0.5400 |
| Cardiac index ($L/min/m^2$) | 40 | 0.43 ± 0.65 | 36 | 0 ± 0.41 | 0.43 (0.18, 0.67), p = 0.0008 |
| $SvO_2$ (%) | 39 | 2.54 ± 10.02 | 35 | –1.37 ± 7.33 | 3.21 (–0.42, 6.85), p = 0.0822 |
| TPR ($dyn.sec/cm^5$) | 40 | –200.50 ± 506.43 | 36 | –66.51 ± 330.75 | –162.21 (–345.05, 20.63), p = 0.0812 |
| SVR ($dyn.sec/cm^5$) | 40 | –221.75 ± 771.21 | 36 | –204.43 ± 528.48 | –103.76 (–377.53, 170.01), p = 0.4525 |
| PSI | 40 | –0.051 ± 0.138 | 36 | –0.001 ± 0.152 | –0.05 (–0.12, 0.02), p = 0.1455 |
| PAWP or LVEDP (mmHg) | 40 | 1.43 ± 5.28 | 36 | 1.92 ± 6.36 | –1.45 (–3.77, 0.88), p = 0.2192 |
| Cardiac Output (L/min) | 40 | 0.76 ± 1.14 | 36 | –0.02 ± 0.68 | 0.78 (0.35, 1.20), p = 0.0005 |
| PVR/SVR | 40 | –0.051 ± 0.138 | 36 | –0.001 ± 0.152 | –0.049 (–0.116, 0.017), p = 0.1455 |

CL = confidence limit; FAS = Full Analysis Set; LVEDP = left ventricular end diastolic pressure; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; mSAP = mean systemic arterial pressure; PAWP = pulmonary arterial wedge pressure; PSI = pulmonary selectivity index; PVR = pulmonary vascular resistance; RHC = right heart catheterization; $SvO_2$ = mixed venous oxygen saturation; SVR = systemic vascular resistance; TPR = total pulmonary resistance.

**PH-related disease progression**

There were a total of 9 disease progression events in the study. 2 events occurred in the macitentan group, and 7 events occurred in the placebo group. No subject died in the macitentan group. The distribution of events is shown in

**Table 7**.

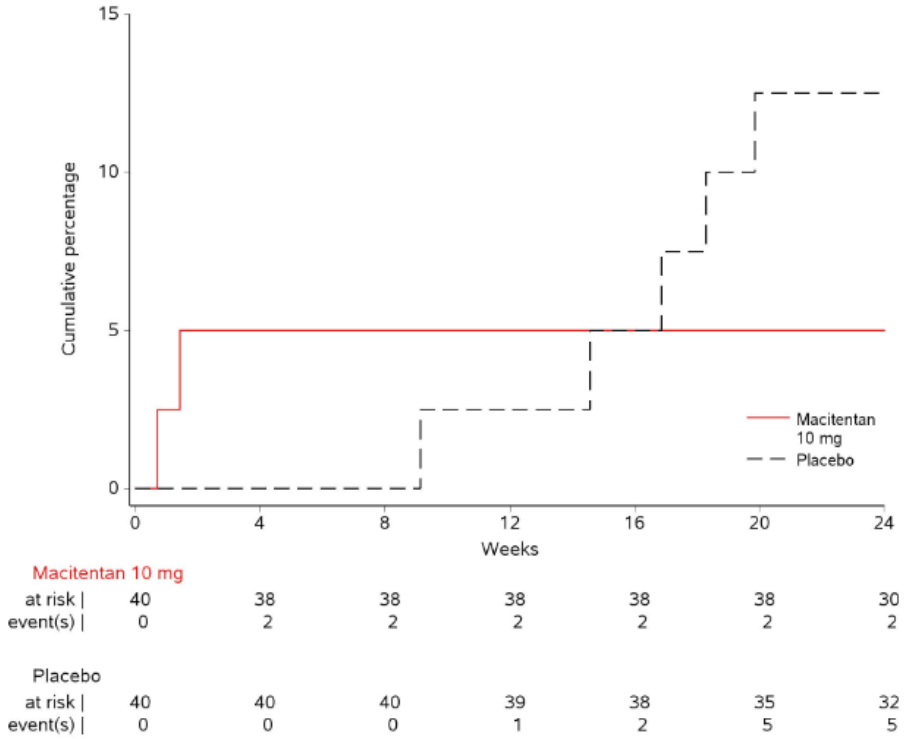
**Table 7. PH-related disease progression event components, FAS**

| | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) |
|---|---|---|
| PH-related disease progression | 2 (5.0) | 7 (17.5) |
| All-cause death | 0 | 1 (2.5) |
| Hospitalization due to PH | 2 (5.0) | 4 (10.0) |
| Other PH-related disease progression | 0 | 2 (5.0) |

Source: Table 15-73(Output: T_REASPHRDP_FAS, Date 01NOV2016)

The 2 disease progression events in the macitentan group were 2 hospitalizations due to PH, while the 7 events in the placebo group corresponded to (4 hospitalizations due to PH, 1 death due to hemorrhagic stroke and 2 other PH-related disease progressions qualified as AE of PH worsening on day 171 and a SAE of CTEPH progression on day 119. However, The Kaplan-Meier curve only included 5 events in the placebo group, whereas 7 placebo subjects were reported to have PH-related disease progression. The applicant is requested to clarify (LOQ).

PH-related disease progression events were reported early in treatment with macitentan in the 2 subjects (Day 6 and Day 11, respectively) with no further events reported during the remaining treatment period up to 24 weeks. At Week 24, PH-related disease progression free survival rate was 95.0% (95% CL: 81.5, 98.7) for macitentan and 87.5% (95% CL: 72.5, 94.6) for placebo [Module 5.3.5.1, table 15-72].




**NT-proBNP**

Baseline NT-proBNP (mean ± SD) was 2204.4 ± 2943.18 in the macitentan group and 1793.1 ± 2075.25 in the placebo group [Table 15-74 of the MERIT-1 CSR]. NT-proBNP decreased to a greater extent on macitentan than on placebo at Week 24. Significant reductions in NT-proBNP of 26%, 32% and 20% in the macitentan group vs the placebo group were observed at Weeks 8, 16, and 24, respectively. The treatment effect (geometric mean ratio macitentan/placebo) over a period of 24 weeks, analyzed by the repeated measure model was 0.73 (95% CL: 0.64, 0.84, $p < 0.0001$), i.e., a 27% reduction favoring macitentan over placebo [Table 11-16 of the MERIT-1 CSR].

**Table 11-16 Summary of change from baseline over time in NT-proBNP, FAS**

| NT-proBNP (pg/mL) | n | Geometric mean ratio (macitentan/placebo), 95% CLs | Between treatment analysis<br>LS mean (macitentan–placebo), 95% CLs<br>Type III analysis of effects p-value |
|---|---|---|---|
| **Week 8** | 78 | 0.74 (0.59, 0.93) | –0.31 (–0.52, –0.10), p = 0.0050 |
| **Week 16** | 78 | 0.68 (0.52, 0.89) | –0.39 (–0.65, –0.12), p = 0.0045 |
| **Week 24** | 78 | 0.80 (0.63, 1.01) | –0.24 (–0.46, –0.01), p = 0.0398 |
| **Overall Repeat measure analysis** | n | **Geometric mean ratio (macitentan/placebo), 95% CLs, p-value** | |
| | 78 | 0.73 (0.64, 0.84), p < 0.0001 | |

Source: Table 15-74 (Output: T_BNP_FAS, Date 27JAN2017), Table 15-75 (Output: T_BNPAC_FAS, Date 27JAN2017), and Table 15-76 (Output: T_BNPACRM_FAS, Date 27JAN2017)
CL = confidence limit; FAS = Full Analysis Set; LS = least squares; NT-ProBNP = N-terminal ProB-type Natriuretic Peptide.

**Quality of life assessments**
Scores of PAH-SYMPACT™ ranged from 0 "no symptom at all" to 4 "very severe" for the symptom part and 0 "yes, with no difficulty at all" to 4 "no, not able at all" / "yes, with extreme difficulty" / "extremely" / "very much" for the impact part of the questionnaire. The EQ-5D-3L consists of a descriptive system (the questionnaire), and the EQ VAS. In general, QoL assessed by PAH-SYMPACT™ symptom and impact part scores and EQ-5D scores did not show differences in clinical significance between macitentan and placebo [Table 11-17 and Table 11-18 of the MERIT-1 CSR].

***OPUS Registry (AC-055-503)***
In the OPUS Registry, each enrolled patient is followed up for at least 1 year from enrollment until Opsumit discontinuation, loss to follow-up, withdrawal of consent, death, or study end, whichever occurs first. Consistent with the observational study design, no specific schedule of visits and no mandatory investigations or assessments are planned. OPUS collects clinical outcomes (e.g., hospitalization) and clinical/laboratory assessments (e.g., functional assessments such as WHO FC and 6MWT). All clinical/laboratory assessments are performed per routine clinical practice at each study site, and at intervals determined by the treating physician.

The CTEPH Follow-up set (n = 45) of the OPUS Registry was predominantly White, female, and ranged from 18–87 years old [Module 5.3.5.4]. The CTEPH population of the OPUS Registry is broadly comparable to the MERIT population: predominance of inoperable patients (79.5% in OPUS vs 100% in MERIT-1), similar gender distribution (64.4% of females in OPUS vs 63.8% in MERIT-1), except OPUS CTEPH patients were slightly older compared to those in MERIT-1 (mean age: 64.8 and 57.5 years, respectively).

In the CTEPH Follow-up set, up to the data cut-off date of 17 April 2018, the median exposure to Opsumit was 9.9 months (range: 0.2–40.2 months), with 18 patients exposed to Opsumit for more than 12 months [Module 5.3.5.4, table 11].

**Clinical outcomes**
In order to assess outcomes in CTEPH patients treated with macitentan as monotherapy or in combination with other PH-specific therapies including riociguat, 6MWD and WHO FC data were analyzed for Opsumit with sGC stimulator (any time during Opsumit exposure, n = 27) and Opsumit without sGC stimulator (n = 18) cohorts [Table 8]. The 2 cohorts were considered generally

comparable with regard to demographic and disease characteristics [Module 5.3.5.4, table 3]. The clinical condition of most patients in both cohorts remained stable or improved as evidenced by the majority of patients who did not have a worsening in WHO FC (82.4% and 75.0%, respectively) or a decrease of ≥ 15% in 6MWD [Table 8]. The 6MWD and WHO FC results in the CTEPH Follow-up set are consistent with those in the PAH Follow-up set in the OPUS Registry [Module 5.3.5.4].

**Table 8. 6MWD and WHO FC results during Opsumit exposure in the CTEPH Follow-up set - OPUS Registry**

| | CTEPH Follow-up set N = 45 | | | |
|---|---|---|---|---|
| | Opsumit with sGCS N = 27 | | Opsumit without sGCS N = 18 | |
| **WHO FC** | | | | |
| WHO FC | Baseline | Last available follow-up assessment | Baseline | Last available follow-up assessment |
| n | 17 | 17 | 8 | 8 |
| Class I | 0 | 1 (5.9%) | 0 | 1 (12.5%) |
| Class II | 5 (29.4%) | 6 (35.3%) | 3 (37.5%) | 2 (25.0%) |
| Class III | 10 (58.8%) | 10 (58.8%) | 2 (25.0%) | 4 (50.0%) |
| Class IV | 2 (11.8%) | 0 | 3 (37.5%) | 1 (12.5%) |
| Time from baseline to last available WHO FC follow-up assessment (days), median (range) | 267.0 (75.0–807.0) | | 470.0 (49.0–1185.0) | |
| Absence of worsening in WHO FC | 14 (82.4%) (95% CI: 56.6, 96.2) | | 6 (75.0%) (95% CI: 34.9, 96.8) | |
| **6MWD** | | | | |
| n | 10 | | 5 | |
| Time from baseline to last available 6MWD follow-up assessment (days), median (range) | 344.0 (71.0–751.0) | | 455.0 (140.0–1076.0) | |
| Decrease in 6MWD ≥ 15% | 1 (10.0%) (95% CI: 0.3, 44.5) | | 2 (40.0%) (95% CI: 5.3, 85.3) | |

6MWD = 6-minute walk distance; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; FC = functional class; sGCS = soluble guanylate cyclase stimulator; WHO = World Health Organization.
n = number of patients with baseline and last available follow-up assessments
% based on n
95% exact confidence interval (Clopper Pearson)
Source: Modified from Module 5.3.5.4 table 18, table 20.

Hospitalizations are also collected in the OPUS Registry. The proportion of patients with hospitalization in the CTEPH (including the 2 cohorts of Opsumit with/without sGC stimulator) and PAH Follow-up sets are summarized in Table 9. The proportions of first and all hospitalizations in the CTEPH Follow-up set (31.1% and 62.2%, respectively) were similar to those observed in the PAH Follow-up set (33.3% and 69.8%, respectively).

The hospitalization data in the CTEPH Follow-up set are consistent with those observed in the SERAPHIN study. As described in the Opsumit SmPC, "*The risk of PAH related death or hospitalisation for PAH up to EOT was reduced by 50% (HR 0.50; 97.5%CI: 0.34 to 0.75; logrank p < 0.0001) in patients receiving macitentan 10 mg (50 events) compared to placebo (84 events). At 36 months, 44.6% of patients on placebo and 29.4% of patients on macitentan 10 mg (Absolute Risk Reduction = 15.2%) had been hospitalised for PAH or died from a PAH-related cause"* [section 5.1].

**Table 9. Hospitalizations during Opsumit exposure in the CTEPH and PAH Follow-up sets - OPUS Registry**

| | CTEPH Follow-up set N = 45 | CTEPH Follow-up set N = 45 | | PAH Follow-up set N = 1455 |
|---|---|---|---|---|
| | | Opsumit with sGCS N = 27 | Opsumit without sGCS N = 18 | |
| **First hospitalization** | | | | |

| | | | | |
|---|---|---|---|---|
| Number of first hospitalizations | 14 (31.1%) | 10 (37%) | 4 (22.2%) | 485 (33.3%) |
| Exposure time (patient-years) | 37.9 | 20.6 | 17.2 | 1318.8 |
| First event of hospitalization rate per 100 patient-years (95% CI) | 36.9 (21.9, 62.4) | 48.6 (26.2, 90.3) | 23.3 (8.7, 62.0) | 36.8 (33.6, 40.2) |
| **All hospitalizations** | | | | |
| Number of all hospitalizations | 28 (62.2%) | 16 (59.3%) | 12 (66.7%) | 1015 (69.8%) |
| Exposure time (patient-years) | 46.8 | 23.0 | 23.8 | 1673.1 |
| All hospitalizations rate per 100 patient-years (95% CI) | 59.8 (41.3, 86.6) | 69.7 (42.7, 113.8) | 50.4 (28.6, 88.7) | 60.7 (57.0, 64.5) |

CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; sGCS = soluble guanylate cyclase stimulator.

Source: Module 5.3.5.4, table 21– table 23.

In summary, and with the limitations of real-world data, the outcome results from the OPUS Registry show a positive effect of macitentan alone or in combination with sGC stimulator on WHO FC and 6MWD; most notably, there is a similar proportion of CTEPH patients with a hospitalization relative to that observed in PAH patients in OPUS. These observations are consistent with the findings from the SERAPHIN study, which illustrated the positive effect of macitentan on hospitalization compared to placebo in PAH patients.

## *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table. Summary of Efficacy for trial MERIT-1**

| **Title: MERIT-1: Macitentan in the treatment of inoperable chronic thromboembolic pulmonary hypertension** | | | |
|---|---|---|---|
| Study identifier | **AC-055E201** | | |
| Design | **Phase II, prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study** | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 24 weeks (PEP assessed at week 16)<br>not applicable<br>30-day safety follow-up | |
| Hypothesis | Superiority | | |
| Treatments groups | Experimental | | Macitentan 10 mg OD for 24 weeks (n= <treatment>. <duration>, <number randomized> |
| | Control | | Placebo |
| Endpoints and definitions | Primary endpoint | PVR | Change in pulmonary vascular resistance (PVR) from baseline to week 16. |
| | Secondary endpoint | 6MWD | Change in 6-minute walk distance (6MWD) from baseline to week 24. |
| | Secondary endpoint | BDI | Change in Borg Dyspnoea Index (BDI) from baseline to week 24. |
| Database lock | N/A (between final SAP dated on 21-oct 2016 and post-hoc SAP dated on 17 May 2017). | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | **PVR:** Full Analysis Set [FAS] (i.e., all randomized subjects) at week 16 (change from baseline). ANCOVA model ANCOVA model including treatment group and baseline value as covariates.<br>**6MWD** and **BDI**: FAS at week 24 (change from baseline). ANCOVA model including treatment group and baseline value as covariates. | | |
| Descriptive statistics and estimate variability | Treatment group | Macitentan 10 mg | Placebo |
| | Number of subject | n=40 | N=40 |
| | Mean Change from baseline in PVR at week 16 | -206.1 dyn.sec/cm$^5$ | -85.8 dyn.sec/cm$^5$ |
| | (±SD) | ±450.39 | ±301.7 |
| | Mean Change from baseline in 6MWD at week 24 | 35.0 m | 1.0 m |
| | (±SD) | ± 52.52 | ± 83.24 |
| | Mean Change from baseline in BDI at week 24 (±SD) | −0.1 points<br>± 1.86 | +0.3 points<br>± 2.04 |
| Effect estimate per comparison | **Change in PVR at week 16**, Primary endpoint | Comparison groups | Macitentan vs. Placebo |
| | | Mean ratio | 0.84 |
| | | 95%CI | 0.70 to 0.99 |
| | | P-value | 0.041 |
| | **Change in 6MWD at week 24**, Secondary endpoint | Comparison groups | Macitentan vs. Placebo |
| | | Mean difference of change | 34.04 m |
| | | 95%CI | 2.9 to 65.2 |
| | | P-value | 0.0326 |
| | **Borg Dyspnoea Index (BDI)** , Secondary endpoint | Comparison groups | Macitentan vs. Placebo |
| | | Mean difference of change | −0.39 points |
| | | 95%CI | −1.21 to 0.43 |
| | | P-value | 0.3492 |
| **Analysis description** | **Secondary analysis (in the per protocol set, PPS)** | | |
| Mean change in PVR at week 16 | The mean decrease in PVR (± SD) from baseline to Week 16 was 206.1 ± 450.39 dyn.sec/cm$^5$ on macitentan and 112.9 ± 305.36 dyn.sec/cm$^5$ on placebo. The ratio of means (macitentan/placebo) was 0.87 (95%CI: 0.73 to 1.04), p = 0.1302. | | |
| Mean change in 6MWD at week 24 | The mean change from baseline to Week 24 was 35.0 ± 52.52 m on macitentan and 17.40 m ± 44.79 m on placebo. The mean difference for the change from baseline to Week 24 (macitentan vs. placebo) was 18.03 (95% CI: −4.90 to 40.96), p=0.1212. | | |
| Mean change in BDI at week 24 | The mean change from baseline to Week 24 was -0.14 on macitentan and 0.31 on placebo. The mean difference for the change from baseline to Week 24 (macitentan vs. placebo) was -0.44 points (95%CI: −1.32 to 0.43). | | |

6MWD = 6-minute walk distance; BDI = Borg Dyspnoea Index; CI = confidence interval; PEP = primary endpoint; PVR = Pulmonary Vascular Resistance; SD = standard deviation.

## *Analysis performed across trials (pooled analyses and meta-analysis)*

**Longitudinal assessment of 6MWD from baseline to each study visit in MERIT-1 and MERIT-2:**

To investigate the persistence of the macitentan treatment effect on 6MWD beyond the 24 weeks (6 months) of treatment in the MERIT-1 DB study and to assess the potential benefit of macitentan on 6MWD for subjects who were on placebo in the MERIT-1 study, the following cohorts were defined:

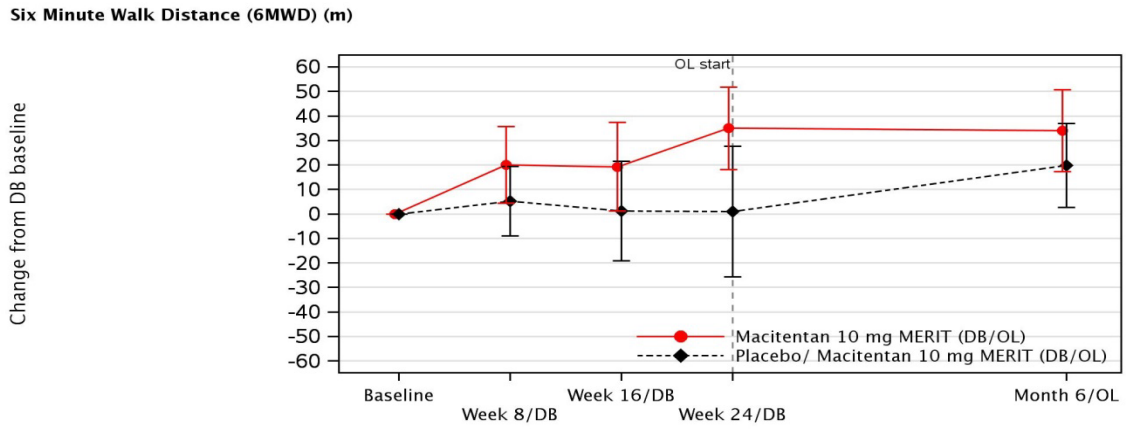
- **Macitentan 10 mg MERIT DB/OL (n = 40):** This cohort included subjects who received macitentan in MERIT-1 and MERIT-2; the median time on treatment was 23.5 months (range: 6.7–37.4 months) [Module 5.3.5.3 appendix 1 table 2].
- **Placebo/macitentan 10 mg MERIT DB/OL (n = 40):** This cohort received placebo during MERIT-1 (for a median of 5.6 months, Module 5.3.5.1 table 12-1) and macitentan during MERIT-2; the median time on treatment was 18.7 months (range: 1.2–31.8 months) [Module 5.3.5.3 appendix 1 table 2].

Figure 8 shows the mean change from baseline in 6MWD over 12 months in the long-term macitentan cohort (macitentan 10 mg MERIT DB/OL) and the placebo/macitentan 10 mg MERIT DB/OL cohort.

In the macitentan 10 mg MERIT DB/OL cohort, the change from DB observed at the end of MERIT-1 persisted in MERIT-2, i.e., 34 m at Month 6 of MERIT-2 (i.e., 12 months overall), while an improvement in 6MWD (a mean change from DB baseline of 19.8 m) after 6 months on macitentan in MERIT-2 was observed in subjects who had received placebo in MERIT-1 (placebo/macitentan 10 mg MERIT DB/OL cohort) [Figure 10 and Table 13 of the Integrated Summary of Efficacy, Module 5.3.5.3].

Notably, the time since diagnosis of CTEPH was 0.44 years in the macitentan group and 0.56 years in the placebo group of the MERIT-1 study. The Applicant is requested to discuss if this can have influenced the efficacy results

**Figure 8. 6MWD (including imputed values): Mean (95% CL) change from DB baseline to Week 8, Week 16, and Week 24 in MERIT-1 and Month 6 in MERIT-2 in the DB/OL pooled cohorts, FAS**




DB: Double blind; OL: Open-Label
CL=Confidence Limit. Subjects who had both the baseline assessment and the relevant post-baseline assessment are included

Source: Module 5.3.5.3 figure 10 (F_I6MWD_TIME_FAS).

**Table 13. Change from DB baseline to Month 6 in 6MWD - DB/OL (imputed), Full analysis set**

| | Macitentan 10 mg MERIT (DB/OL) N=40 | Placebo/ Macitentan 10 mg MERIT (DB/OL) N=36 |
|---|---|---|
| 6MWD (m) | | |
| Baseline | | |
| n | 40 | 36 |
| Mean | 353.0 | 352.0 |
| SD | 87.90 | 75.52 |
| Median | 388.0 | 362.5 |
| Q1, Q3 | 285.5, 420.0 | 288.5, 414.5 |
| Min, Max | 160, 455 | 162, 467 |
| Month 6 / MERIT-2 | | |
| n | 40 | 36 |
| Mean | 387.1 | 371.9 |
| SD | 85.73 | 106.52 |
| Median | 402.0 | 374.0 |
| Q1, Q3 | 338.5, 455.5 | 318.5, 456.0 |
| Min, Max | 180, 516 | 0, 567 |
| Total number of subjects with imputation of missing values [n (%)] | 4 (10.0) | 4 (11.1) |
| due to death (by 0m) | 0 | 1 (2.8) |
| by last post-baseline OCF | 4 (10.0) | 3 (8.3) |
| Change from DB baseline to Month 6 / MERIT-2 | | |
| n | 40 | 36 |
| Mean | 34.0 | 19.8 |
| SD | 52.36 | 50.81 |
| Median | 21.0 | 23.5 |
| Q1, Q3 | 6.0, 66.5 | 4.0, 42.5 |
| Min, Max | -45, 170 | -214, 100 |
| Treatment difference based on change from DB baseline to Month 6 / MERIT-2 | | |
| Mean | 14.2 | |
| SD | 51.63 | |
| 95% CL | -9.4, 37.8 | |

DB: Double blind; OL: Open-Label
CL=Confidence limit, OCF=Observation carried forward, SD=Standard Deviation
Output: T_I6MWD_DBB_FAS, Produced by verbiol1 on 28FEB2018 13:26 (CET), SDTM production date: 19JAN2018 - Cutoff date: 17OCT2017
Program: val_csr/program_output/smwd01.sas
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Table 14 of the Integrated Summary of Efficacy [Module 5.3.5.3], not discussed by the Applicant in the Summary of Clinical Efficacy, shows a mean 2.0 m (median 5 m) improvement during MERIT-2 in those patients who were switched from placebo ("Previously on DB placebo" group, n=36), taking the baseline 6MWD value as the one measured at the start of the open-label phase (i.e.: just before switching from placebo).

**Table 14. Change from OL baseline to Month 6 in 6MWD - OL (imputed), Full analysis set**

| | Macitentan 10 mg MERIT-2 (OL) | | |
|---|---|---|---|
| | Previously on DB Macitentan 10 mg N=40 | Previously on DB Placebo N=36 | All subjects N=76 |
| 6MWD (m) | | | |
| Baseline | | | |
| n | 40 | 36 | 76 |
| Mean | 388.0 | 369.9 | 379.4 |
| SD | 83.31 | 91.25 | 87.05 |
| Median | 391.5 | 366.0 | 378.0 |
| Q1, Q3 | 358.0, 448.0 | 314.8, 439.0 | 319.0, 441.0 |
| Min, Max | 180, 523 | 156, 565 | 156, 565 |
| Month 6 / MERIT-2 | | | |
| n | 40 | 36 | 76 |
| Mean | 387.1 | 371.9 | 379.9 |
| SD | 85.73 | 106.52 | 95.79 |
| Median | 402.0 | 374.0 | 390.0 |
| Q1, Q3 | 338.5, 455.5 | 318.5, 456.0 | 328.0, 455.5 |
| Min, Max | 180, 516 | 0, 567 | 0, 567 |
| Total number of subjects with imputation of missing values [n (%)] | 4 (10.0) | 4 (11.1) | 8 (10.5) |
| due to death (by 0m) | 0 | 1 (2.8) | 1 (1.3) |
| by last OCF | 4 (10.0) | 3 (8.3) | 7 (9.2) |
| Change from OL baseline to Month 6 / MERIT-2 | | | |
| n | 40 | 36 | 76 |
| Mean | -1.0 | 2.0 | 0.4 |
| SD | 40.89 | 63.58 | 52.51 |
| Median | 0.0 | 5.0 | 1.0 |
| Q1, Q3 | -13.5, 17.5 | -12.5, 34.0 | -13.5, 23.5 |
| Min, Max | -123, 85 | -271, 84 | -271, 85 |
| Treatment difference based on change from OL baseline to Month 6 / MERIT-2 | | | |
| Mean | -2.9 | | |
| SD | 52.85 | | |
| 95% CL | -27.1, 21.3 | | |

DB: Double blind; OL: Open-Label
CL=Confidence limit, OCF=Observation carried forward, SD=Standard Deviation
Output: T_I6MWD_OLB_FAS, Produced by verbiol1 on 28FEB2018 13:26 (CET), SDTM production date: 19JAN2018 - Cutoff date: 17OCT2017
Program: val_csr/program_output/smwd01.sas
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### *Clinical studies in special populations*

N/A.

### *Supportive study(ies)*

N/A.

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

The MERIT-1 study was a Phase 2 exploratory study designed with pulmonary vascular resistance (PVR) as primary endpoint in the restricted population of inoperable patients (i.e.: excluding patients with recurrent/persistent pulmonary hypertension following intervention) and excluding background therapy with riociguat). The study was not powered to show a robust effect on clinically relevant endpoints like exercise capacity, symptoms or to address morbidity-mortality.

From the ambiguous GCG statement provided by the applicant, it cannot inferred whether in the applicant's view, all studies, or only a part of them are GCP compliant. This issue should be clarified. In addition, the results of any audits or inspections available for this clinical trial should be submitted (see RSI). In the Rapporteur's view, as the body of the data provided is clearly insufficient to grant the pursued indication, a triggered inspection of the MERIT-2 study is not needed.

**Inclusion criteria:** The MERIT-1 study enrolled adult patients in WHO FC II-III with inoperable CTEPH (due to the localization of obstruction being surgically inaccessible, i.e., distal disease), as adjudicated by Country-Specific and Central Adjudication Committee. Originally, medical therapy had been developed for technically inoperable patients. Classification of a patient into the CTEPH subset with distal disease is subjective and in MERIT required a majority vote from the adjudication committee experts. This adjudication is important mostly because of concerns that medical therapy might be erroneously perceived as a valid alternative to potentially curative pulmonary endarterectomy. According to the studied population, the indication proposed by the applicant includes adult patients with inoperable CTEPH in FC II to III.

**Exclusion criteria:** MERIT-1 excluded the other subset of patients with CTEPH tested within randomised trials with riociguat (i.e.: patients who had already had unsuccessful pulmonary endarterectomy), which is the only orphan drug indicated in CTEPH.

**Concomitant treatments:** Administration of endothelin receptor antagonists (ERA), guanylate cyclase stimulators, L-arginine, intravenous or subcutaneous prostanoids, or any investigational drug (other than study drug) was not permitted from 1 month prior to baseline RHC and Randomization (excluding acute administration during a catheterization procedure to test vascular reactivity). However, subjects in WHO FC III/IV were allowed to take phosphodiesterase-5 inhibitors or oral / inhaled prostanoids provided that the dose had been stable for at least 1 month prior to baseline. These protocol features are consistent with the frequent off-label use of PAH-specific drugs (ERA, PDE5-inh), alone or in combination, in clinical practice, with data extrapolated from mainly idiopathic PAH. Finally, as concomitant treatment with riociguat was not allowed, no data with the macitentan-riociguat combination are available.

Therefore, paradoxically, the applicant has generated data with the off-label use of macitentan-PDE5inh combination, but not with the combination of macitentan with the only approved drug in this indication (i.e.: riociguat). From a regulatory standpoint, this issue makes challenging to include some statement about combination therapy in the product labelling.

The primary objective was to evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) at rest in comparison with placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Secondary objectives were to evaluate the effects

of macitentan 10 mg in comparison with placebo on: Exercise capacity, Dyspnea (assessed by the Borg dyspnea index) and WHO functional class (FC).

The main analysis of the primary endpoint( percent of baseline PVR at rest at Week 16) was performed using the Full Analysis Set ([FAS] i.e., all subjects assigned to a study treatment). The null hypothesis was tested on the primary endpoint by means of an analysis of covariance (ANCOVA) model on the $\log_e$ transformed percent of baseline PVR at rest at Week 16, as the primary endpoint was assumed to be log-normally distributed. Covariates included in the primary model were randomized treatment and the $\log_e$ transformed baseline PVR at rest value. For the main analysis and sensitivity analyses on PVR, imputation methods pre-specified in the MERIT-1 protocol were applied to subjects with missing PVR values at Week 16 (all 4 in the placebo group; 3 imputed by the median value in the placebo group, i.e., 12% improvement, 1 imputed [due to death] by the largest percent deterioration in the placebo group, i.e., 55%) (MERIT-1 Statistical Analysis Plan; Module 5.3.5.1.).

For the secondary endpoint, 6MWD, the change from baseline to Week 24 was analyzed by an ANCOVA model, including treatment group and 6MWD baseline value as covariates. Least Squares (LS) estimates for each treatment group and treatment difference were estimated from the model with corresponding means, 95% confidence limits (CLs), and p-value. For 6MWD analyses, imputation methods pre-specified in the MERIT-1 protocol were applied to subjects with missing values at Week 24 (all 4 in the placebo group; 2 imputed with last observation carried forward [LOCF] and 2 imputed with 0 m due to death [Module 5.3.5.1]). The Summary of Clinical Efficacy also presents additional sensitivity analyses conducted on 6MWD, encompassing repeated measure analysis, multiple imputation methods (Method 1 and 2), single imputation methods (LOCF, baseline observation carried forward, and Median), analysis of variance, non-parametric analysis (Hodges Lehmann estimator), and the extended model [Module 5.3.5.1, appendix 2]. The objective of these analytical approaches was to provide estimates of the treatment effect using different ways of handling missing data and different statistical models, thereby evaluating the robustness of the conclusions from the main analysis.

The applicant also submitted data from the MERIT-2 open label extension and the OPUS registry with macitentan, that includes a subset of patients with CTEPH. In standard practice, 80% of CTEPH cases can be treated with PEA, and only about 20% of CTEPH are inoperable. An additional 30% of patients refuse PEA [Quadery et al. Eur Respir J. 2018], and receive pharmacological treatment. The applicant is invited to discuss about the potential off-label use of the product in operable patients who refuse surgery, and to clarify if some of the patients recruited into the OPUS registry correspond to this patients subset (RSI).

## Efficacy data and additional analyses

**Change in PVR (main study endpoint):** The main analysis for the primary endpoint was the ANCOVA model on log-transformed percent of baseline PVR at Week 16 adjusted by treatment as a factor and log-transformed PVR at baseline as a covariate in the full analysis set (FAS, randomized patients). From the adjusted model, the treatment effect at Week 16 (ratio of geometric means macitentan/placebo) was 0.84 (95% CL: 0.70, 0.99), p = **0.041**, i.e., a 16% relative reduction in PVR with macitentan compared to placebo. The median ratio was 0.82 (95%CI: 0.71 to 0.94). However, the adjusted model in PPS showed no statistically significant results at Week 16 (mean ratio macitentan/placebo: 0.87; 95% CI: 0.73, 1.04; p = **0.1302**] [Table 15-34]. The median ratio macitentan/placebo at week 16 was 0.85 (95% CI: 0.74, 0.98) [Table 15-34]. There was no statistically significant indication of heterogeneity of treatment effect across the predefined subgroups based on the interaction tests. The treatment effect was similar in the subgroup of subjects who were receiving PH advanced therapy at baseline. Due to the low number of subjects in some subgroups, e.g., male, Asia, Western Europe and WHO FC II, wider 95% CIs (higher variability around the point estimates of treatment effect) were observed. For sensitivity analyses of PVR with corrected values and excluding 4 subjects with incorrect values, the treatment effect at Week 16 was 0.81 (95% CL: 0.69, 0.95) and 0.79 (95% CL: 0.67, 0.93), respectively [Table 5; Module 5.3.5.1].

In absolute terms, the placebo-corrected improvement (decrease) in PVR with macitentan (-120 dyn·s/cm$^5$) is subject to wide variability due to the small study sample size, and it was not statistically significant in the per protocol set, probably due to lack of statistical power after excluding patients with protocol deviations. Despite having in mind this important limitation, the absolute 120 dyn·s/cm$^5$ placebo-corrected decrease in PVR with macitentan is very similar to the -127 dyn·s/cm$^5$ decrease in PVT observed with bosentan in the BENEFiT study [Jais et al, *J Am Coll Cardiol.* 2008;52:2127–34]

(that was not sufficient to grant an indication for bosentan), and much lower than the - 246 dyn·s/cm$^5$ decrease in PVT achieved by riociguat in the CHEST-1 study [Ghofrani et al, *N Engl J Med.* 2013;369: 319–29].

**Change in 6MWD (secondary endpoint):** At week 24, the secondary endpoint of 6-min walk distance (6MWD) had increased from baseline by a mean of 35.0 m (SD 52.52) in the macitentan group versus 1.0 m (83·24) in the placebo group (least squares mean difference: 34.0 m; 95% CI 2.9–65.2, p=0.033). There was no statistical heterogeneity in the treatment effect on exercise capacity across the pre-specified subgroups. The main sponsor's analysis of 6MWD in MERIT-1 focused on the LS mean difference of the change from baseline to week 24 using an ANCOVA test. This approach does not provide a good estimate of the treatment effect, as change in 6MWD does not follow a normal distribution. The wide range of sensitivity analyses using different tests and imputation models show that the applicant's primary analysis (placebo-corrected 34 m improvement) is very close to the best-case estimation of the effect (36 m), which is 2-fold better than the worst-case estimation (17 m). The use of a non-conservative analysis for an application based on a single pivotal trial, in which the primary analysis should be conservative and the results particularly compelling, is not the preferred situation for taking regulatory decisions. As the primary outcome does not follow a normal distribution, an appropriate test for the analysis of 6MWD should assume that the data are not normally distributed, are subject to high inter-individual variability and would be based on median rather than mean values. Therefore, a better estimate would be the Hodges-Lehmann estimate associated with the stratified Wilcoxon test, included in one of the sensitivity analyses. The Hodges-Lehman estimate shows a 17 meter median difference that is not statistically significant. Similar non-significant results are obtained in sensitivity analyses using BOCF and LOCF imputation methods and also in the per protocol analysis without imputation.

With respect to internal consistency, from subgroup analyses it is apparent that most part of the effect on 6MWD is driven by results in Eastern Europe (36 subjects from Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine). In Western Europe the between-treatment difference is of only 6 metres (n=11 patients). However, given the low sample sizes, statistical heterogeneity between subgroups is not statistically significant. The applicant is requested to show the disaggregated data on 6MWD by country and center, in order to ascertain if there is an outlier center driving the positive trend on 6MWD (see RSI). In addition, as ERA have a well defined AE profile, it should be ruled out that patients with recognizable ERA-related AEs have no better performance in the 6MWD than those patients without these AEs due to unblinding (i.e.: ascertainment bias). The applicant is invited to provide sensitivity analyses in patients with and without ERA-related AEs (see RSI).

Regarding the clinical relevance of the effect, a 17 m difference using the Hodges-Lehman estimate, or 18 m using the per protocol population, or 19 m difference in median values, which is probably closer to the real effect than the primary outcome estimation, is difficult to put into the perspective of clinical relevance and correlation with patient outcome. In order to assess the clinical relevance of the effect of macitentan in the MERIT-1 study, the applicant is invited to provide exploratory analyses of the said study using different responder threshold criteria according to a previous analysis published with riociguat in the CTEPH indication [D'Armini, et al. Use of responder threshold criteria to evaluate the response to treatment in the phase III CHEST-1 study. J Heart Lung Transplant. 2015;34:348-55] (see RSI).

Although direct comparisons of the results of different clinical trials require caution, the placebo-corrected improvement in 6MWD with macitentan (point estimate between 17 m to 36 m depending on the test/imputation method used) is lower than the 46 m improvement achieved by riociguat in the CHEST-1 study [Ghofrani et al. *N Engl J Med.* 2013;369: 319–29]. In addition, the results with riociguat were highly statistically significant in the ITT analysis (Difference: 45.69 m; 95% CI: 24.74 m to 66.63 m; p<0.0001), in the Per Protocol analysis (52.24 m; 95% CI: 30.53 m to 73.95 m, p<0.0001) and in sensitivity analyses [Adempas EPAR. EMA/CHMP/734750/2013]. These results are much more robust than those achieved with macitentan in the MERIT-1 study. In the other available clinical trial in CTEPH (BENEFiT study) bosentan only achieved a 2.2 m improvement in 6MWD compared with placebo [Jais et al, *J Am Coll Cardiol.* 2008;52:2127–34].

The applicant has also provided an analysis of 6MWD during the MERIT-2 open-label cohort. In the macitentan 10 mg MERIT DB/OL cohort, the change from DB observed at the end of MERIT-1 persisted in MERIT-2 (i.e., 12 months overall), which means that no additional improvement or worsening in 6MWD was achieved during the OL period in those patients that had received macitentan 10 mg during MERIT-1.

The applicant states that an improvement in 6MWD (a mean change from DB baseline of 19.8 m) after 6 months on macitentan in MERIT-2 was observed in subjects who had received placebo in MERIT-1 (placebo/macitentan 10 mg MERIT DB/OL cohort). However, the said analysis is misleading, as the baseline values chosen to justify a 19.8 m mean increase in 6MWD during MERIT-2 study are the baseline values of the MERIT-1 study. Baseline values of the open-label MERIT-2 should have been used instead. Table 14 of the Integrated Summary of Efficacy (Module 5.3.5.3) shows that the mean improvement from OL baseline in patients that were on placebo and are switched to macitentan is of only 2 metres (mean) or 5 metres (median) at 6 months after switching. Therefore, the analysis of MERIT-2 suggests no effect of macitentan in 6MWD after switching from placebo. The applicant is invited to comment (see RSI).

**Borg dyspnea index (BDI):** From adjusted model, the mean change from baseline to Week 24 did not show a statistically significant difference between treatment groups at week 24 (–0.39, 95% CL: –1.21, 0.43, p = 0.3492). The point estimate was far beyond the 0.9 units that are considered the minimal important difference in BDI in patients with PAH [Khair RM, et al. Ann Am Thorac Soc. 2016;13(6):842-9], which is against a meaningful effect in relief of symptoms. The company is invited to provide a post-hoc responder analysis showing the rate of patients with a >0.9 unit improvement vs. baseline (i.e.: above the minimal) per treatment group (see RSI).

**Change in WHO FC from baseline:** From baseline to Week 24, the majority of subjects (31 patients on macitentan and 29 patients on placebo) did not show a change in the status of WHO FC, while a small number of subjects improved in WHO FC (9 subjects on macitentan and 8 subjects on placebo). Worsening of WHO FC at end of study (week 24) was reported for 0 patients on macitentan and for 3 subjects on placebo (two deaths that were imputed as worsening WHO FC and one patient who worsened from FC III to FC IV). The odds ratio for the proportion of subjects with worsening WHO FC at Week 24 (macitentan 0 patients vs. placebo 3 patients: 0.21; 95%CI: 0 to 1.46, p = 0.0962) favored macitentan. However, this result needs to be interpreted with caution due to small number of subjects with worsening of WHO FC.

**Quality of life assessments:** QoL assessed by PAH-SYMPACT symptom and impact part scores and EQ-5D scores did not show differences in clinical significance between macitentan and placebo.

**RHC variables other than PVR from baseline to Week 16:** For cardiac index and CO, clinically meaningful mean increases of 0.43 L/min/m2 or 0.78 L/min from baseline were observed on macitentan at Week 16. On placebo, no change from baseline was observed for cardiac index. The mean change from baseline to Week 16 for cardiac index (macitentan vs placebo) of 0.43 was statistically significant (95% CL: 0.18, 0.67). The LS mean difference of change from baseline to Week 16 for cardiac output (CO) (macitentan vs placebo) of 0.78 was also statistically significant (95% CL: 0.35, 1.20). For other variables including mRAP, mPAP, SvO2 and TPR there was a trend in the change from baseline to Week 16 favoring macitentan, but these changes were not statistically significant.

**PH-related disease progression:** There were a total of 2 disease progression events in the macitentan group (2 PH-hospitalizations), and 7 events in the placebo group (4 PH-hospitalizations, 1 death due to hemorrhagic stroke and 2 other PH-related disease progressions qualified as AE of PH worsening on day 171 and a SAE of CTEPH progression on day 119). It is unknown why a death due to hemorrhagic stroke was qualified as a PH-related disease progression (see RSI).

**Supportive data from the OPUS registry:** The company has provided data from the CTEPH Follow-up set (n = 45) of the OPUS Registry. Population in the OPUS registry is approximately 10 years older than the one included in the MERIT-1 study (mean age: 65 years in OPUS vs. 58 years in MERIT-1). There is a significant amount of missing data in the OPUS registry, with only 25 of 45 patients (55%) having data available on WHO FC and only 15 of 45 patients (33%) having data on 6MWD. Rates of first hospitalisations per 100 patient-years were 38% in 27 patients on macitentan plus sGC and 17% in patients on macitentan without sGC. These rates are higher than the 5% to 10% 24-week hospitalization rate observed in the MERIT-1 study with macitentan and placebo, respectively (approximately 10% to 20% pt-yr rate). Probably those patients on macitentan plus sGC in the OPUS registry that had a 38% hospitalization rate are older and sicker patients on FC III-IV, which may justify the higher rate of hospitalisations compared with those not on sGC in the OPUS registry or those on macitentan or placebo in the MERIT-1 study. Anyway, the information is very limited to draw any meaningful conclusion.

**Labelling issues:** Regarding the Applicant's intention of including a claim about improvement in exercise capacity in the indication, in the absence of morbidity-mortality data, this could be feasible

provided that the results on exercise capacity are finally considered robust and clinically relevant. The initial Company's intention to request the claim of combination therapy in the indication, as discussed during the pre-submission meeting, was not endorsed, mainly due to the lack of data in combination with the single approved therapy in this indication (riociguat). It would be a regulatory challenge to indicate macitentan to be used in patients treated with an unapproved therapy (i.e., off label use of PDE 5 inhibitors in many patients in the MERIT-1 study). The Company has also submitted a brief analysis of patients on macitentan plus SGC (n=27) in the OPUS registry compared with those on macitentan without sGC (n=18). PH hospitalisations were higher in patients on macitentan+sGC (38%) than in patients on macitentan only (17%), which could be related to a more advanced disase in patients needing combination therapy. Anyway, the information is very scarce to draw any meaningful conclusion about the efficacy and safety of macitentan with or without concomitant riociguat. Regarding combination therapy, it could be possible to mention in section 5.1 that macitentan showed efficacy on 'top of PAH background therapy' in the MERIT-1 study, provided that the data of the MERIT-1 phase II study are finally considered sufficient to conclude that the benefit-risk of macitentan in this indication is positive.

At this stage, the Rapporteur is of the opinion that the results of the MERIT-1 study are not robust enough to be included in the SmPC, either as a new indication in section 4.1, or even only described in section 5.1.

### Additional expert consultation

N/A.

### Assessment of paediatric data on clinical efficacy

N/A.

## 2.4.4. Conclusions on the clinical efficacy

The MERIT-1 study, which has been submitted as the single pivotal supporting this variation application in CTEPH, was adequately designed as a Phase 2 exploratory study with pulmonary vascular resistance (PVR) as primary endpoint. It was conducted in a restricted population [i.e., inoperable CTEPH patients only, excluding patients with recurrent/persistent pulmonary hypertension following intervention, and excluding background therapy with riociguat) and it was not adequately powered to show a consistent benefit in the endpoints of clinical relevance (i.e.: mortality, PH clinical worsening and exercise capacity) according to the EMA guideline applicable (EMEA/CHMP/EWP/356954/2008).

Some hemodynamic endpoints (i.e.: PVR, cardiac index), laboratory measurements (i.e.: NT-proBNP), and 6MWD suggest a trend towards a beneficial effect of macientan versus placebo. However, the results of PVR and 6MWD in the per protocol population (not significant) and sensitivity analyses (significance obtained using non-conservative tests and some imputation methods, but not achieved when conservative tests, no imputation or imputation based on BOCF or LOCF were applied) shows that the main results are not robust. In addition, the macitentan effect on symptoms (BDI) were neither statistically nor clinically relevant.

The lack of robustness of the main results in PVR and 6MWD is a major concern. According to the EMA guideline on applications based on one pivotal study (CPMP/EWP/2330/99), in cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling in terms of internal and external validity, clinical relevance and degree of statistical significance. In this respect, there should be no indications of potential bias, the estimated size of treatment benefit must be large enough to be clinically valuable and a degree of statistical significance considerably stronger than $p<0.05$ is usually required, accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. None of these features are entirely applicable to the MERIT-1 study. In addition, the point estimates for the effects of macitentan on PVR and 6MWH are quite modest compared with those obtained with riociguat, the only approved drug in the CTEPH indication.

In summary, the MERIT-1 phase II study does not provide robust data for exercise capacity, symptoms or morbidity-mortality that would eventually support an indication of macitentan in patients with inoperable CTEPH.

**Rapporteur's view:**
Despite some similarities, PAH and CTEPH are different diseases due to different causes (i.e.: primary or secondary vasoconstriction in PAH versus thromboembolism in CTEPH). Although safety can be extrapolated to some extent from PAH to CTEPH, dedicated pivotal study/ies using a morbidity/mortality or exercise capacity primary endpoint are needed to assess the efficacy of the compound in CTEPH. In the Rapporteur's view, the data provided are not robust enough to grant an indication in patients with CTEPH.

**Co-Rapporteur's view:**
In the opinion of the Co-Rapporteur, submission of only one pivotal study in support of the current extension of the indication application for CTEPH is sufficient considering that CTEPH has the same pathophysiologic and clinical features as the approved PAH indication. The main clinical data of the MERIT-1 study are limited, which is expected due to the rarity of the disease, but do show a significant effect on exercise time after 24 weeks. Additionally, improvements in haemodynamic parameters, NT-proBNP and a positive trend in time to PH-related disease progression worsening in WHO FC have been observed. These beneficial effects are further supported by the clinical studies on the use of macitentan in patients with PAH. Therefore, the Co-Rapporteur considers that this pivotal study does not need to fulfill the requirements as presented in the guideline on applications based on one pivotal study (CPMP/EWP/2330/99),
Furthermore, in the opinion of the Co-Rapporteur, the deviation from the normal distribution of the 6MWD data is not large, and the ANCOVA test is valid as it is robust to some deviation of normality. Therefore, the primary analysis and the sensitivity analyses using multiple imputation are considered the most important analyses and these show a statistically significant effect. Most of the sensitivity analyses that did not provide in a statistically significant result, used single imputation (LOCF, BOCF, median). These use strong assumptions which are hard to test. Therefore, these are considered of less importance. Focusing on the analysis with the smallest effect size (Hodges-Lehmann) may be over-conservative.

## *2.5. Clinical safety*

## Introduction

The initial safety profile of macitentan was established with studies in subjects with pulmonary arterial hypertension (PAH) presented in the initial MAA in 2013 [Opsumit EPAR: EMA/CHMP/457699/2013], and is reflected in the current macitentan Summary of Product Characteristics (SmPC). Overall, macitentan showed a safety profile similar to other ERAs. The adverse events (regardless of causality relationship with study drug) most frequently reported in clinical trials were right heart failure, PAH (both in principle related to the underlying condition), oedemas, upper tract infection, anaemia and liver abnormalities. The most common adverse reactions with Opsumit, reported in more than 10% of patients, included nasopharyngitis, anaemia and headache. Oedema and fluid retention were frequent adverse reactions. Most side effects were mild to moderate in severity. Although there were no major safety concerns related to macitentan, a potential association between macitentan and risk of liver toxicity could not be definitively ruled out. The SmPC of Opsumit was aligned with that of ambrisentan regarding hepatic safety (contraindication in patients at risk, and recommendation for regular monitoring), as the hepatotoxicity risk seems comparable. In addition, in view of the teratogenicity observed in non-clinical studies, macitentan was contraindicated during pregnancy. Furthermore, the need for reliable contraception and monthly pregnancy tests during treatment was reflected in section 4.6 of the SmPC with corresponding warnings in section 4.4 of the SmPC [Opsumit EPAR: EMA/CHMP/457699/2013].

For this new indication, data from subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) enrolled in AC-055E201/MERIT-1 (a completed, double-blind [DB], placebo-controlled, Phase 2 study in 80 subjects who received macitentan 10 mg or placebo) of whom

76 enrolled in AC-055E202/MERIT-2 (an ongoing, macitentan 10 mg open-label [OL], uncontrolled, Phase 2, extension study of MERIT-1 with a data cut-off date of 17 October 2017). MERIT-1 is completed and MERIT-2 is ongoing; the data cut-off date used for the SCS was 17 October 2017. In addition, safety data on macitentan (Opsumit) use in CTEPH are available from the OPUS Registry and post-marketing sources**.** The Safety Set includes all subjects from clinical studies in CTEPH who received at least 1 dose of study treatment, and comprises the same subjects as the Full Analysis Set. In order to provide long-term follow-up data in subjects with inoperable CTEPH who were exposed to macitentan in the DB phase and/or in the OL extension phase, data from MERIT-1 and MERIT-2 were integrated, meaning that the data from the same subjects randomized in MERIT-1 were concatenated with their data from the OL extension study MERIT-2.

Safety data from the clinical pharmacology studies of macitentan in healthy subjects were summarized in the initial submission for macitentan in the treatment of subjects with PAH. In this SCS, safety data from 2 additional clinical pharmacology studies in healthy subjects are presented as appropriate in the relevant sections of the document. The safety profile of macitentan in patients with PAH is described in the SmPC. Additional sources of safety data for macitentan are available from the 7th macitentan Periodic Benefit-Risk Evaluation Report / Periodic Safety Update Report (PBRER/PSUR; cut-off date of 17 October 2017 and are briefly described in this document; serious adverse event (SAE) reports for ongoing clinical studies are available in the Actelion Drug Safety database, Argus Safety™ [Argus].

**Definition of cohorts for safety data**

| | | Safety observation period | | |
|---|---|---|---|---|
| **Studies/Cohorts** | **Definition** | **From** | **Until** | **Description** |
| **MERIT-1 DB**<br>Macitentan 10 mg (n = 40)<br>Placebo (n = 40) | All subjects enrolled and treated with macitentan 10 mg or placebo in MERIT-1 | Start of macitentan treatment in MERIT-1. | Study completion of MERIT-1 | Comparative safety assessment based on randomized placebo-controlled data. |
| **MERIT-2 OL**<br>Previously on DB Macitentan 10 mg (n = 40)<br>Previously on DB Placebo (n = 36)<br>All subjects (n = 76) | All subjects enrolled and treated with macitentan 10 mg in MERIT-2 displayed overall and by prior MERIT-1 treatment group | Start of macitentan treatment in MERIT-2. | Data cut-off date in MERIT-2 (17 October 2017 inclusive) | Uncontrolled safety data of MERIT-2 |
| **MERIT DB/OL**<br>Macitentan 10 mg (n = 40) | All subjects treated with macitentan 10 mg in MERIT-1 and received at least 1 dose of macitentan 10 mg in MERIT-2 | Start of macitentan treatment in MERIT-1. | Data cut-off date in MERIT-2 (17 October 2017 inclusive) | Longitudinal assessment of safety representing the longest exposure to macitentan across MERIT-1 and MERIT-2 |
| **Macitentan 10 mg Pool**<br>(n = 76) | All subjects treated with macitentan 10 mg in MERIT-1 and/or MERIT-2 | Start of macitentan treatment in MERIT-1 or MERIT-2. | Data cut-off date in MERIT-2 (17 October 2017 inclusive) | Largest body of macitentan safety data based on cumulative exposure to macitentan from MERIT-1 and MERIT-2 |
| **OPUS Registry**<br>CTEPH Follow-up Set (n = 45) | All follow-up patients who had only CTEPH reported as a reason for Opsumit prescription | First CTEPH patient enrolled in the OPUS Registry (15 September 2014) | Data cut-off date of 17 April 2018 | Opsumit safety data in the post-marketing setting |

CTEPH = chronic thromboembolic pulmonary hypertension, DB = double-blind; OL = open-label.

## Patient exposure

During the 4 years since the International Birth Date (IBD) of Opsumit® (macitentan) for the treatment of PAH (18 October 2013), based on the first approval in the United States, an estimated 40,724 patients have been exposed to commercial macitentan worldwide. In addition, an estimated 3099 subjects have been exposed to macitentan in ongoing and completed interventional clinical studies since the Development IBD (DIBD; 6 September 2004).

In MERIT-1, the median (range) duration of study treatment (including interruptions) was similar for macitentan (5.6 [5.4–5.7] months) and for placebo (5.6 [3.5–6.1] months). This corresponded to a total exposure of 18.6 subject-years (SY) in the macitentan group and 18.4 SY in the placebo group.
In MERIT-2, all subjects received macitentan 10 mg. Up to the data cut-off date (17 October 2017), the median (range) duration of study treatment was 18.4 (1.1–31.8) months, corresponding to a total exposure of 117.7 SY.

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the median (range) duration of study treatment was 23.5 (6.7–37.4) months. The majority of subjects (90.0%) were treated up to 18 months, and the total exposure was 81.2 SY.

Supportive safety data from the OPUS registry on CTEPH patients treated with macitentan are also described. Up to the data cut-off date of 17 April 2018, the median (range) exposure to Opsumit was 9.9 (0.2–40.2) months, with 18 patients exposed to Opsumit for more than 12 months.

**Table 10. Study treatment exposure, Safety Set**

| | MERIT-1 DB | | Macitentan 10 mg MERIT DB/OL | MERIT-2 OL | | | Macitentan Pool |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | (N = 76) |
| Duration of study treatment (months) | | | | | | | |
| N | 40 | 40 | 40 | 40 | 36 | 76 | 76 |
| Mean | 5.59 | 5.51 | 24.37 | 18.78 | 18.36 | 18.58 | 21.53 |
| SD | 0.11 | 0.41 | 6.69 | 6.69 | 6.86 | 6.73 | 7.37 |
| Median | 5.6 | 5.6 | 23.5 | 17.9 | 18.7 | 18.4 | 21.9 |
| Q1, Q3 | 5.5, 5.7 | 5.5, 5.7 | 20.4, 28.3 | 14.9, 22.6 | 14.9, 22.3 | 14.9, 22.6 | 17.3, 26.4 |
| Min, Max | 5.4, 5.7 | 3.5, 6.1 | 6.7, 37.4 | 1.1, 31.7 | 1.2, 31.8 | 1.1, 31.8 | 1.2, 37.4 |
| Cumulative duration of study treatment [n (%)] | | | | | | | |
| At least 6 months | 0 | 1 (2.5) | 40 (100) | 38 (95.0) | 33 (91.7) | 71 (93.4) | 73 (96.1) |
| At least 12 months | 0 | 0 | 37 (92.5) | 36 (90.0) | 32 (88.9) | 68 (89.5) | 69 (90.8) |
| At least 18 months | 0 | 0 | 36 (90.0) | 20 (50.0) | 20 (55.6) | 40 (52.6) | 56 (73.7) |
| At least 24 months | 0 | 0 | 19 (47.5) | 8 (20.0) | 4 (11.1) | 12 (15.8) | 23 (30.3) |
| At least 30 months | 0 | 0 | 8 (20.0) | 3 (7.5) | 1 (2.8) | 4 (5.3) | 9 (11.8) |
| At least 36 months | 0 | 0 | 3 (7.5) | 0 | 0 | 0 | 3 (3.9) |
| Subject-years (total) | 18.6 | 18.4 | 81.2 | 62.6 | 55.1 | 117.7 | 136.3 |

DB = double-blind; OL = open-label; SD = standard deviation.
Duration of study treatment is including potential treatment interruptions. Data cut-off date: 17 OCT 2017.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 2 (T_EXP_SS) and table 31 (T_AESI_ADJEXPO_SS).

## Adverse events

An overview of treatment-emergent AEs is shown in Table 8.

**Table 11 Overview of treatment-emergent adverse events, Safety Set.**

| Subjects with at least 1 of the | MERIT-1 DB | Macitentan 10 mg MERIT | MERIT-2 OL | Macitentan Pool |
|---|---|---|---|---|

| following | Macitentan 10 mg (N = 40) | Placebo (N = 40) | DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | (N = 76) |
|---|---|---|---|---|---|---|---|
| AE | 30 (75.0) | 32 (80.0) | 37 (92.5) | 34 (85.0) | 29 (80.6) | 63 (82.9) | 66 (86.8) |
| Severe AE | 0 | 5 (12.5) | 12 (30.0) | 11 (27.5) | 11 (30.6) | 22 (28.9) | 23 (30.3) |
| Drug-related AE | 10 (25.0) | 5 (12.5) | 14 (35.0) | 8 (20.0) | 9 (25.0) | 17 (22.4) | 23 (30.3) |
| AE leading to study drug discontinuation | 0 | 2 (5.0) | 2 (5.0) | 2 (5.0) | 4 (11.1) | 6 (7.9) | 6 (7.9) |
| SAE | 3 (7.5) | 7 (17.5) | 13 (32.5) | 11 (27.5) | 12 (33.3) | 23 (30.3) | 25 (32.9) |
| Drug-related SAE | 0 | 1 (2.5) | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Fatal SAE | 0 | 2 (5.0) | 4 (10.0) | 4 (10.0) | 5 (13.9) | 9 (11.8) | 9 (11.8) |

AE = adverse event; DB = double-blind; OL = open-label; SAE = serious adverse event.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 11 (T_AE_SUMMARY_SS).

**MERIT-1 DB**

A total of 30 (75.0%) subjects in the macitentan group and 32 (80.0%) subjects in the placebo group had at least 1 treatment-emergent AE [Table 8]. The incidence of SAEs in the macitentan group was lower than in placebo-treated subjects (3 [7.5%] subjects and 7 [17.5%] subjects, respectively). There were no deaths or discontinuations in the macitentan group compared to 2 deaths and 2 discontinuations due to AEs reported in the placebo group.

Overall, no AEs of severe intensity were reported in the macitentan group. Severe AEs were reported for 5 (12.5%) subjects in the placebo group, with each one reported as an SAE.
In the macitentan group, 10 (25%) subjects had AEs reported as drug-related, whereas in the placebo group 5 (12.5%) subjects had AEs reported as drug-related.

**MERIT-2 OL treatment with macitentan**

In MERIT-2, up to the cut-off date of 17 October 2017, a total of 63 (82.9%) subjects (34 DB macitentan and 29 DB placebo) had at least 1 treatment-emergent AE [Table 8]. Overall, death, SAEs, and AEs leading to discontinuation were reported in 9 (11.8%), 23 (30.3%), and 6 (7.9%) subjects, respectively.
No new or unexpected safety observations were made for the cohort with the longest exposure to macitentan (macitentan 10 mg MERIT DB/OL), or for subjects who received macitentan 10 mg at any time (macitentan pool, representing the largest exposed cohort).

## Common adverse events

A summary of treatment-emergent AEs by PT in more than 2 subjects in any treatment group is provided in
Table 9.

**Table 12. Summary of treatment-emergent adverse events by Preferred Term in more than 2 subjects in any treatment group, Safety Set**

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Subjects with at least 1 AE | 30 (75.0) | 32 (80.0) | 37 (92.5) | 34 (85.0) | 29 (80.6) | 63 (82.9) | 66 (86.8) |
| Oedema peripheral | 9 (22.5) | 4 (10.0) | 11 (27.5) | 2 (5.0) | 4 (11.1) | 6 (7.9) | 15 (19.7) |
| Haemoglobin decreased | 6 (15.0) | 0 | 8 (20.0) | 4 (10.0) | 5 (13.9) | 9 (11.8) | 13 (17.1) |
| Pain in extremity | 3 (7.5) | 0 | 4 (10.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 5 (6.6) |
| Upper respiratory tract infection | 3 (7.5) | 0 | 6 (15.0) | 4 (10.0) | 2 (5.6) | 6 (7.9) | 8 (10.5) |
| Cough | 2 (5.0) | 3 (7.5) | 5 (12.5) | 3 (7.5) | 4 (11.1) | 7 (9.2) | 9 (11.8) |
| Dizziness | 2 (5.0) | 1 (2.5) | 5 (12.5) | 3 (7.5) | 1 (2.8) | 4 (5.3) | 6 (7.9) |
| Dyspnoea | 2 (5.0) | 2 (5.0) | 3 (7.5) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 4 (5.3) |

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Urinary tract infection | 2 (5.0) | 1 (2.5) | 5 (12.5) | 3 (7.5) | 2 (5.6) | 5 (6.6) | 7 (9.2) |
| Abdominal discomfort | 1 (2.5) | 0 | 3 (7.5) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 4 (5.3) |
| Anaemia | 1 (2.5) | 1 (2.5) | 2 (5.0) | 1 (2.5) | 5 (13.9) | 6 (7.9) | 7 (9.2) |
| Arthralgia | 1 (2.5) | 3 (7.5) | 2 (5.0) | 1 (2.5) | 3 (8.3) | 4 (5.3) | 5 (6.6) |
| Blood alkaline phosphatase increased | 1 (2.5) | 1 (2.5) | 1 (2.5) | 0 | 2 (5.6) | 2 (2.6) | 3 (3.9) |
| Cardiac failure | 1 (2.5) | 1 (2.5) | 3 (7.5) | 2 (5.0) | 2 (5.6) | 4 (5.3) | 5 (6.6) |
| Diarrhoea | 1 (2.5) | 1 (2.5) | 2 (5.0) | 1 (2.5) | 4 (11.1) | 5 (6.6) | 6 (7.9) |
| Haemoptysis | 1 (2.5) | 1 (2.5) | 1 (2.5) | 0 | 3 (8.3) | 3 (3.9) | 4 (5.3) |
| Haemorrhoids | 1 (2.5) | 0 | 2 (5.0) | 1 (2.5) | 1 (2.8) | 2 (2.6) | 3 (3.9) |
| Nasopharyngitis | 1 (2.5) | 4 (10.0) | 3 (7.5) | 3 (7.5) | 2 (5.6) | 5 (6.6) | 5 (6.6) |
| Right ventricular failure | 1 (2.5) | 3 (7.5) | 4 (10.0) | 3 (7.5) | 1 (2.8) | 4 (5.3) | 5 (6.6) |
| Weight decreased | 1 (2.5) | 0 | 2 (5.0) | 1 (2.5) | 4 (11.1) | 5 (6.6) | 6 (7.9) |
| Alanine aminotransferase increased | 0 | 3 (7.5) | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Aspartate aminotransferase increased | 0 | 3 (7.5) | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Back pain | 0 | 3 (7.5) | 2 (5.0) | 2 (5.0) | 2 (5.6) | 4 (5.3) | 4 (5.3) |
| Blood bilirubin increased | 0 | 1 (2.5) | 1 (2.5) | 1 (2.5) | 2 (5.6) | 3 (3.9) | 3 (3.9) |
| Bronchitis | 0 | 1 (2.5) | 4 (10.0) | 4 (10.0) | 4 (11.1) | 8 (10.5) | 8 (10.5) |
| C-reactive protein increased | 0 | 1 (2.5) | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Cardiac failure acute | 0 | 0 | 1 (2.5) | 1 (2.5) | 2 (5.6) | 3 (3.9) | 3 (3.9) |
| Cataract | 0 | 0 | 0 | 0 | 3 (8.3) | 3 (3.9) | 3 (3.9) |
| Chest discomfort | 0 | 1 (2.5) | 1 (2.5) | 1 (2.5) | 2 (5.6) | 3 (3.9) | 3 (3.9) |
| Cystitis | 0 | 0 | 0 | 0 | 3 (8.3) | 3 (3.9) | 3 (3.9) |
| Fall | 0 | 0 | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Hyperuricaemia | 0 | 0 | 3 (7.5) | 3 (7.5) | 0 | 3 (3.9) | 3 (3.9) |
| Iron deficiency | 0 | 0 | 0 | 0 | 3 (8.3) | 3 (3.9) | 3 (3.9) |
| Large intestine polyp | 0 | 0 | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Oropharyngeal pain | 0 | 0 | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Pneumonia | 0 | 0 | 2 (5.0) | 2 (5.0) | 2 (5.6) | 4 (5.3) | 4 (5.3) |
| Pulmonary embolism | 0 | 0 | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Pulmonary hypertension | 0 | 4 (10.0) | 2 (5.0) | 2 (5.0) | 5 (13.9) | 7 (9.2) | 7 (9.2) |
| Sleep apnoea syndrome | 0 | 0 | 3 (7.5) | 3 (7.5) | 0 | 3 (3.9) | 3 (3.9) |
| Syncope | 0 | 3 (7.5) | 2 (5.0) | 2 (5.0) | 0 | 2 (2.6) | 2 (2.6) |

AE = adverse event; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label.
Frequencies represent the number of subjects with the event. Preferred Terms are based on MedDRA version 19.0.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 12 (T_AE_PT_SS).

***MERIT-1 DB***

The most frequently reported AE in the macitentan group compared with placebo was peripheral edema (9 subjects, 22.5% and 4 subjects, 10.0%, respectively) [
Table 9]. AEs only reported in the macitentan group included decreased hemoglobin (15.0%), pain in extremity and upper respiratory tract infection (3 subjects each, 7.5% each), bone pain, fatigue, and pharyngitis (2 subjects each, 5.0% each) [Module 5.3.5.3 ISS Appendix 1 table 12]. AEs reported in the macitentan group were consistent with the known safety profile of macitentan in PAH.

AEs that were reported more frequently in the placebo group compared with macitentan included nasopharyngitis (2.5% macitentan, 10.0% placebo), cough (5.0% macitentan, 7.5% placebo), arthralgia (2.5% macitentan, 7.5% placebo), right ventricular failure (2.5% macitentan, 7.5% placebo). AEs only reported in the placebo group included PH (10.0%) and increased ALT, increased AST, back pain, and syncope (7.5% each). AEs reflecting manifestations of the underlying disease

(such as PH progression/worsening, right ventricular failure, syncope) were reported more frequently in the placebo group.

***MERIT-2 OL treatment with macitentan***

In MERIT-2 up to the cut-off date of 17 October 2017, the most frequently reported AEs were decreased hemoglobin (11.8%), bronchitis (10.5%), cough (9.2%), and PH (9.2%) [
Table 9]. Other frequently reported AEs included peripheral edema (7.9%), upper respiratory tract infection (7.9%), and anemia (7.9%).

In general, the types of AEs reported during macitentan treatment in MERIT-1 and during long-term treatment in MERIT-2 were consistent. Overall, the proportion of subjects with AEs was higher during the MERIT-2 study (82.9%) compared to MERIT-1, which is consistent with the longer treatment duration and observation in MERIT-2. Overall, 86.8% of subjects in the macitentan pool had at least 1 AE.

## Treatment-emergent adverse events suspected to be drug-related

***MERIT-1 DB***
A total of 10 (25%) subjects in the macitentan group and 5 (12.5%) subjects in the placebo group had at least 1 drug-related AE [Table 8]. The most frequently reported drug-related AEs in the macitentan group were decreased hemoglobin (12.5%), peripheral edema (7.5%), and bone pain (5.0%).

***MERIT-2 OL treatment with macitentan***
In MERIT-2 up to the cut-off date, 17 (22.4%) subjects had at least 1 drug-related AE [Table 8]. The most frequently reported drug-related AEs were decreased hemoglobin (7.9%) and anemia (5.3%).
For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg DB/OL), the proportion of subjects with at least 1 drug-related AE was 35.0% [Table 8]. The most frequently reported drug-related AEs were the same as those reported in MERIT-1 (decreased hemoglobin and peripheral edema). In general, the types of drug-related AEs reported following macitentan treatment in MERIT-1 were consistent with those reported during long-term treatment in MERIT-2.
For subjects who received macitentan 10 mg at any time (macitentan pool), the proportion of subjects with at least 1 drug-related AE was 30.3% [Table 8]. The most frequently reported drug-related AEs were the same as those reported during MERIT-1 (decreased hemoglobin and peripheral edema)

## Treatment-emergent adverse events of severe intensity

The incidence of AEs reported as severe intensity is provided in Table 8.

***MERIT-1 DB***

No subjects in the macitentan group had AEs of severe intensity [Table 8]. In the placebo group, 5 (12.5%) subjects had at least 1 AE of severe intensity. These were sepsis and worsening of PH (1 subject), right ventricular failure and embolism (1 subject), and hemorrhagic stroke, worsening of PH, and cardiac failure (1 subject each). All these AEs of severe intensity in the placebo group were reported as SAEs.

***MERIT-2 OL treatment with macitentan***

In MERIT-2 up to the cut-off date, 22 (28.9%) subjects (11 DB macitentan and 11 DB placebo) had at least 1 AE of severe intensity [Table 8]. The severe AEs reported in more than 1 subject were PH (3 subjects), right ventricular failure (3 subjects), acute cardiac failure (3 subjects), pneumonia (3 subjects), cardiac failure (2 subjects), septic shock (2 subjects), and pulmonary embolism (2 subjects). These types of severe AEs are consistent with the progressive nature of CTEPH. For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg DB/OL), 12 (30.0%) subjects had at least 1 AE of severe intensity. For subjects who received macitentan 10 mg at any time (macitentan pool), 23 (30.3%) subjects had at least 1 AE of severe intensity.

**Treatment-emergent adverse events in clinical pharmacology studies**
In AC-055-122, the most frequently reported AE was headache, which was reported for 3/19 subjects (15.8%) when macitentan was administered alone, and 4/18 subjects (22.2%) when macitentan and rosuvastatin were administered concomitantly. When rosuvastatin was administered alone, none of the

20 subjects reported an AE of headache. In AC-055-123, the most frequently reported AE was headache, which was reported for 2/20 subjects (10.0%) when riociguat was administered alone, 2/20 subjects (10.0%) when macitentan was administered alone, and 6/20 subjects (30.0%) when macitentan and riociguat were administered concomitantly. In both studies, no severe intensity AEs were reported. The AE profiles were consistent with the known safety profiles of macitentan, rosuvastatin, and riociguat.

## Deaths

**MERIT-1 DB**

No deaths were reported in the macitentan group. In the placebo group, 2 subjects died: 1 due to hemorrhagic stroke (on Day 172), and 1 due to right ventricular failure (on Day 129) with embolism reported as a secondary cause of death.

**MERIT-2 OL treatment with macitentan**

In MERIT-2, up to the cut-off date, the median (range) duration of study treatment (including interruptions) for all subjects was 18.4 (1.1–31.8) months [Table 3]. In MERIT-2 up to the cut-off date of 17 October 2017, a total of 9 (11.8%) subjects (4 DB macitentan and 5 DB placebo) died. Deaths in MERIT-2 by macitentan exposure period are presented in Table 10.

**Table 13. Deaths in MERIT-2 by macitentan exposure period.**

| Primary cause of death | Day of death with respect to macitentan initiation (in MERIT-1 or MERIT-2) | 0–6 months (N = 76) | 6–12 months (N = 71) | 12–18 months (N = 68) | > 18 months (N = 40) |
|---|---|---|---|---|---|
| Acute cardiac failure | 727 | | | | x |
| Cardiac failure | 675 | | | | x |
| Acute cardiac failure | 636 | | | | x |
| Cardiac failure | 576 | | | | x |
| Multiple organ dysfunction syndrome | 557 | | | | x |
| Intracranial hemorrhage | 472 | | | x | |
| Sepsis with septic shock | 412 | | | x | |
| Pulmonary hypertension | 355 | | x | | |
| Acute cardiac failure | 63 | x | | | |

Source: Modified from Module 5.3.5.3 ISS Appendix 1 listing 1 (L_EXP_FAS), listing 6 (L_DTH_FAS), listing 5 (L_AE_FAS), listing 3 (L_DISC_FAS).

The most frequent cause of death was (acute) heart failure (5 subjects). One subject of the 5 subjects who died due to (acute) heart failure also had pulmonary embolism reported as a fatal AE. Other causes of death included multiple organ dysfunction syndrome in a subject with sepsis, sepsis with septic shock, PH, and intracranial hemorrhage (1 subject each).

Of the 9 deaths, 1 death (DB placebo) was reported within 6 months (Day 63) and 1 was reported between 6 and 12 months (Day 355) of treatment start with macitentan. All other deaths were reported after at least 12 months of treatment with macitentan.

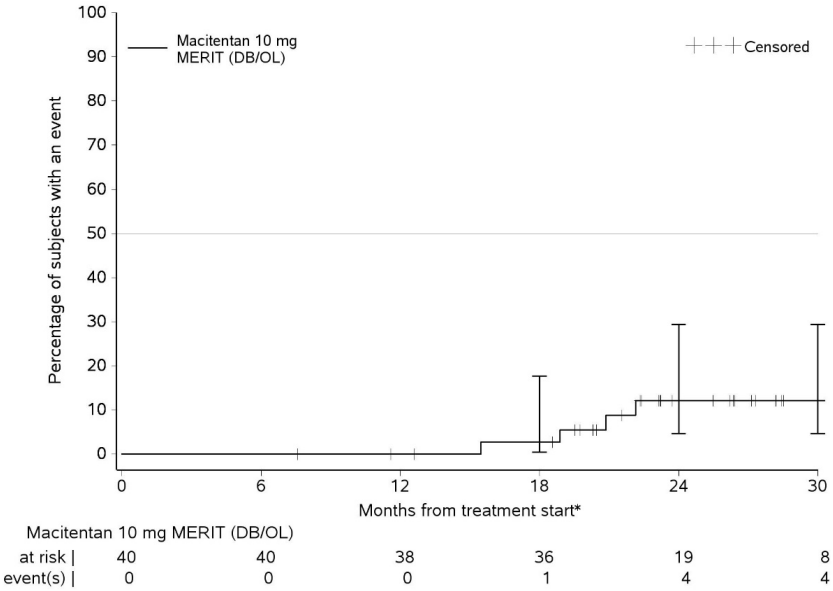
Most of these subjects had multiple confounding comorbidities. All subjects who died due to worsening of heart failure and/or CTEPH worsening or acute heart failure had right ventricular failure/cardiac failure reported in their medical history at the time of enrollment in MERIT-1. These subjects had severely impaired pulmonary hemodynamics (PVR 735–1730 dyn.sec/cm$^5$, mean right atrial pressure 7–22 mmHg, mean pulmonary artery pressure 45–73 mmHg, cardiac index 1.5–2.6 L/min/m$^2$), and increased N-terminal ProB-type natriuretic peptide levels ranging from 2088 to 11417 pg/mL at macitentan treatment start. 7 of the 9 subjects who died were in WHO FC III.

All 9 deaths were considered by the investigator as not related to the study treatment. Overall, deaths reported in MERIT-2 were consistent with the severity of the underlying disease and comorbidities reported in these subjects, and for the CTEPH population in general.

After the cut-off date, an additional death was reported in the MERIT-2 study clinical database by the time of the data extraction. A 65-year old subject was hospitalized with fever and dyspnea and died in hospital. The cause of death was reported as unknown. Previously the subject had SAEs of streptococcal sepsis and congestive cardiac failure.

For subjects who received macitentan in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the median (95% CI) follow-up was 26.2 (23.1, 27,1) months. Up to the data cut-off date, 4 deaths (10.0%) were reported in this cohort [Table 8]. Of the 4 deaths, 1 was reported between 12 and 18 months after treatment start with macitentan. The other deaths were reported between 18 and 24 months after macitentan treatment initiation. The KM estimates for survival in the macitentan 10 mg MERIT DB/OL cohort at 1 and 2 years were 100% and 87.9%, respectively.

**Figure 9 Time to death for the macitentan 10 mg MERIT DB/OL cohort, Full Analysis Set**




Event curves are presented up to 30 months which corresponds to the time when more than 10% of the subjects are still at risk.
*Treatment start corresponds to the start of double-blind Macitentan 10mg in AC-055E201.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 figure 1 (F_KM_T2DTH_FAS).

## Other serious adverse events

The incidence of subjects with SAEs is provided in Table 8. Treatment-emergent SAEs are available by PT in Table 11.

**Table 14 Summary of treatment-emergent serious adverse events by Preferred Term, Safety Set**

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Subjects with at least 1 SAE | 3 (7.5) | 7 (17.5) | 13 (32.5) | 11 (27.5) | 12 (33.3) | 23 (30.3) | 25 (32.9) |
| Acute right ventricular failure | 1 (2.5) | 0 | 1 (2.5) | 0 | 0 | 0 | 1 (1.3) |

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | **Macitentan 10 mg (N = 40)** | **Placebo (N = 40)** | **Macitentan 10 mg MERIT DB/OL (N = 40)** | **Previously on DB macitentan (N = 40)** | **Previously on DB placebo (N = 36)** | **All subjects (N = 76)** | **Macitentan Pool (N = 76)** |
| Oedema peripheral | 1 (2.5) | 0 | 1 (2.5) | 0 | 0 | 0 | 1 (1.3) |
| Weight increased | 1 (2.5) | 0 | 1 (2.5) | 0 | 0 | 0 | 1 (1.3) |
| Acute myocardial infarction | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Acute respiratory failure | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Air embolism | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Angina pectoris | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Angiogram pulmonary | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Angioplasty | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Appendiceal abscess | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Arteriovenous malformation | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Asthma | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Atrial fibrillation | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Atrial flutter | 0 | 0 | 1 (2.5) | 1 (2.5) | 1 (2.8) | 2 (2.6) | 2 (2.6) |
| Back pain | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Basal cell carcinoma | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Cardiac arrest | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Cardiac failure | 0 | 1 (2.5) | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Cardiac failure acute | 0 | 0 | 1 (2.5) | 1 (2.5) | 2 (5.6) | 3 (3.9) | 3 (3.9) |
| Cardiac failure congestive | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Cataract | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Catheterisation cardiac | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Diplegia | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Dyspnoea | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Embolism | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Fall | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Gastric polyps | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Haematuria | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Haemoptysis | 0 | 0 | 0 | 0 | 2 (5.6) | 2 (2.6) | 2 (2.6) |
| Haemorrhage intracranial | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Haemorrhagic stroke | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Head injury | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Hypercapnia | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Infective exacerbation of chronic obstructive airways disease | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Large intestine polyp | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Lumbar vertebral fracture | 0 | 0 | 2 (5.0) | 2 (5.0) | 0 | 2 (2.6) | 2 (2.6) |
| Multiple organ dysfunction syndrome | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Neutropenic sepsis | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Pickwickian syndrome | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Pneumonia | 0 | 0 | 1 (2.5) | 1 (2.5) | 2 (5.6) | 3 (3.9) | 3 (3.9) |
| Pneumonia parainfluenzae viral | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Pulmonary artery therapeutic | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| procedure | | | | | | | |
| Pulmonary embolism | 0 | 0 | 1 (2.5) | 1 (2.5) | 1 (2.8) | 2 (2.6) | 2 (2.6) |
| Pulmonary endarterectomy | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Pulmonary hypertension | 0 | 2 (5.0) | 1 (2.5) | 1 (2.5) | 1 (2.8) | 2 (2.6) | 2 (2.6) |
| Pyelonephritis acute | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Right ventricular failure | 0 | 2 (5.0) | 2 (5.0) | 2 (5.0) | 1 (2.8) | 3 (3.9) | 3 (3.9) |
| Sepsis | 0 | 1 (2.5) | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Septic shock | 0 | 0 | 1 (2.5) | 1 (2.5) | 1 (2.8) | 2 (2.6) | 2 (2.6) |
| Sleep apnoea syndrome | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Streptococcal sepsis | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Supraventricular tachycardia | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Systemic lupus erythematosus | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |

DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label; SAE = serious adverse event.
Frequencies represent the number of subjects with the event. Preferred terms are based on MedDRA version 19.0.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 22 (T_SAE_PT_SS).

**MERIT-1 DB**

A total of 3 (7.5%) subjects in the macitentan group and 7 (17.5%) subjects in the placebo group had at least 1 SAE [Table 8]. In the macitentan group, the SAEs were acute right ventricular failure, peripheral edema, and weight increase; none of which were considered by the investigator to be related to the study treatment. Weight increase was of mild intensity and resolved spontaneously with no change to study treatment; acute right ventricular failure resolved after adjusting the diuretic treatment regimen; peripheral edema requiring interruption of the study treatment and hospitalization, which resolved following additional diuretic treatment while the study treatment was restarted. None of these SAEs led to premature discontinuation of study treatment.

In the placebo group, the SAEs were (worsening) PH (2 subjects, concomitant with sepsis in 1 subject), right ventricular failure (2 subjects, concomitant with dyspnea, back pain, and embolism in 1 subject) and supraventricular tachycardia, cardiac failure, and a hemorrhagic stroke (1 subject each). One subject had an SAE (PH) that was reported as drug-related. Two subjects had SAEs with a fatal outcome: 1 subject died due to hemorrhagic stroke and 1 subject died due to right ventricular failure with embolism reported as a secondary cause. Physician decision due to worsening of PH led to premature discontinuation of study treatment for 1 subject.

**MERIT-2 OL treatment with macitentan**

In MERIT-2 up to the cut-off date, 23 (30.3%) subjects (11 DB macitentan and 12 DB placebo) had at least 1 SAE [Table 11]. The most frequently reported SAEs were cardiac failure, acute cardiac failure, pneumonia, and right ventricular failure, all of which were reported in 3 subjects each. Of all SAEs reported during MERIT-2, 1 SAE of hematuria was considered by the investigator to be treatment-related. Although considered as treatment-related, hematuria has not been proposed as ADR in section 4.8. The MAH is requested to clarify.

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg DB/OL), 13 (32.5%) subjects had at least 1 SAE [Table 11]. None of the SAEs were reported in more than 2 subjects each. The SAEs reported in 2 subjects each were cardiac failure, lumbar vertebral fracture, and right ventricular failure. In general, the types of SAEs reported during the long-term treatment in MERIT-2 were consistent with those reported in MERIT-1.

For subjects who received macitentan 10 mg at any time (**macitentan pool**), 25 (32.9%) subjects had at least 1 SAE [Table 11]. The most frequently reported SAEs were cardiac failure, acute cardiac failure, pneumonia, and right ventricular failure, all of which were reported in 3 subjects each.

## Other significant adverse events

### Adverse events leading to discontinuation of study treatment

The incidence of AEs leading to discontinuation of study treatment is provided in Table 8. A summary of AEs leading to premature discontinuation of study treatment is available by PT in Table 12.

**Table 15. Summary of treatment-emergent adverse events leading to discontinuation by Preferred Term, Safety Set**

| | MERIT-1 DB | | | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Subjects with at least 1 AE leading to discontinuation | 0 | 2 (5.0) | 2 (5.0) | 2 (5.0) | 4 (11.1) | 6 (7.9) | 6 (7.9) |
| Anaemia | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Asthenia | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Cardiac arrest | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Cardiac failure acute | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Fall | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Haemoglobin decreased | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Haemorrhage intracranial | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Head injury | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Pneumonia | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Pulmonary embolism | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Pulmonary endarterectomy | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Pulmonary hypertension | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Right ventricular failure | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Somnolence | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |

AE = adverse event; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label.
Frequencies represent the number of subjects with the event. Preferred Terms are based on MedDRA version 19.0.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 28 (T_AE_DISC_PT_SS).

***MERIT-1 DB***
AEs leading to premature discontinuation of study treatment were only reported in the placebo group (2 subjects). One subject prematurely discontinued study treatment based on physician's decision due to an AE of anemia. Another subject was discontinued by the physician from study treatment due to an AE of (worsening) PH. Both AEs were reported as resolved.

***MERIT-2 OL treatment with macitentan***
In MERIT-2 up to the cut-off date, 6 (7.9%) subjects had at least 1 AE leading to discontinuation of study treatment [Table 12]. This included 1 subject who discontinued study treatment following PEA. No PT of AEs leading to discontinuation of study treatment was reported in more than 1 subject.
Adverse events leading to discontinuation of study treatment in clinical pharmacology studies
In AC-055-122, no subject discontinued study treatment due to an AE when macitentan was administered alone or concomitantly with rosuvastatin. One subject discontinued study treatment due to AEs of toothache and tooth abscess when rosuvastatin was administered alone (prior to macitentan administration).
In AC-055-123, no subject discontinued study treatment due to AEs

## Safety topics of special interest

Safety topics of special interest include those which are considered expected based on the current prescribing information for the PAH indication, in addition to those potentially relevant for the CTEPH indication:

- Established safety topics for the PAH indication:
  - Edema/fluid retention
  - Anemia
  - Hepatotoxicity.
- Relevant topics specific to the CTEPH indication:
  - Hypotension (due to patient population being older than PAH)
  - Bleeding events (due to recommended anticoagulant usage).

**Edema and fluid retention**

Edema and fluid retention has been associated with the use of ERAs and has been reported as a frequent AE with macitentan treatment; therefore, these types of AEs were evaluated for MERIT-1 and MERIT-2. Treatment-emergent AEs pertaining to edema or fluid overload were assessed using the respective Standardized MedDRA Query (SMQ), namely the *Haemodynamic oedema, effusions and fluid overload* SMQ, or containing the string 'pulmonary congestion' with the exception of PTs containing 'site'.

The AESIs of edema or fluid retention and the corresponding exposure-adjusted incidence rate are provided in Table 13.

**Table 13 Treatment-emergent adverse events of special interest and exposure-adjusted incidence rate: edema or fluid retention, Safety Set**

| | MERIT-1 DB | | Macitentan | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Subjects with at least 1 AE of special interest: edema and fluid retention | 10 (25.0) | 4 (10.0) | 15 (37.5) | 6 (15.0) | 5 (13.9) | 11 (14.5) | 20 (26.3) |
| Total time (years) | 18.6 | 18.4 | 81.2 | 62.6 | 55.1 | 117.7 | 136.3 |
| Adjusted incidence rate per 100-SY | 53.658 | 21.770 | 18.463 | 9.584 | 9.077 | 9.347 | 14.671 |
| 95% CI | 28.871, 99.726 | 8.171, 58.005 | 11.131, 30.626 | 4.306, 21.333 | 3.778, 21.808 | 5.176, 16.878 | 9.465, 22.740 |
| Oedema peripheral | 9 (22.5) | 4 (10.0) | 11 (27.5) | 2 (5.0) | 4 (11.1) | 6 (7.9) | 15 (19.7) |
| Hydrothorax | 1 (2.5) | 0 | 2 (5.0) | 1 (2.5) | 0 | 1 (1.3) | 2 (2.6) |
| Oedema | 1 (2.5) | 0 | 2 (5.0) | 2 (5.0) | 0 | 2 (2.6) | 2 (2.6) |
| Ascites | 0 | 1 (2.5) | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Pericardial effusion | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |
| Peripheral swelling | 0 | 0 | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Pleural effusion | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |

AE = adverse event; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label, SY = subject-years.
Preferred Terms are based on MedDRA version 19.0.
Adjusted incidence rate per 100-SY = 100*(number of subjects with at least 1 AE) / (sum of treatment time in days / 365.25)
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 30 (T_AESIPR_SS) and table 31 (T_AESI_ADJEXPO_SS).

***MERIT-1 DB***

A total of 10 (25.0%) subjects in the macitentan group and 4 (10.0%) subjects in the placebo group had an edema or fluid retention AESI. The most frequently reported edema AESI was peripheral edema (9 and 4 subjects on macitentan and placebo, respectively). Other AEs concerning edema or fluid retention were reported in 1 subject each. The exposure-adjusted incidence rate for edema or fluid retention AESIs was higher in the macitentan group (53.7 per 100 SY) compared to placebo (21.8 per 100 SY). In the macitentan group, the onset of edema or fluid retention was within 8 weeks of the start of treatment for 6 out of the 10 subjects; on placebo, the onset of edema or fluid overload occurred on Day 20, Day 106, Day 113, and Day 167. A majority of subjects (7 out of 10) with edema or fluid retention AESIs did not have an associated weight increase (based on body weight measurements) during the double-blind study period. There was a decrease in mean body weight over the study period in the macitentan group, whereas a small increase was observed in the placebo group. For 5 of the 10 subjects in the macitentan group, the AEs were transient and resolved spontaneously or after a 13-day study treatment interruption (in 1 subject). Out of these 5 subjects with a resolving edema or fluid retention event, 1 subject had a second episode, which remained

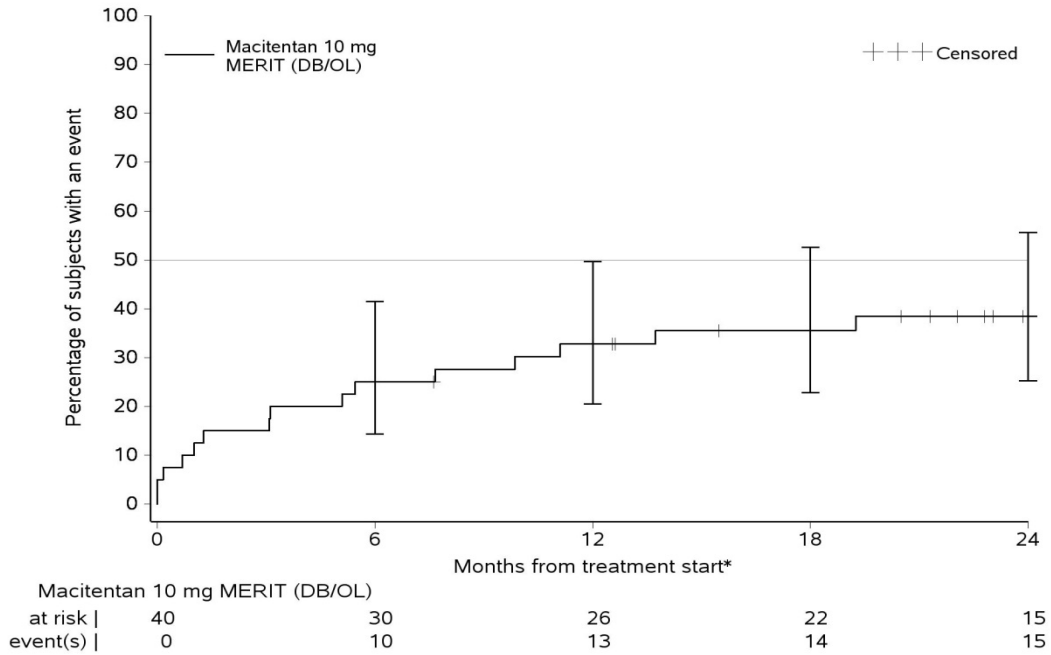
unresolved at the end of MERIT-1 and during MERIT-2. Overall, edema remained unresolved in 6 subjects. The AE for the subject with the study treatment interruption was reported as an SAE. None of the cases led to premature discontinuation of study treatment. For all 4 subjects in the placebo group, the AEs were transient and resolved spontaneously, including the AE of ascites. None of the AEs associated with edema on placebo were SAEs or led to premature discontinuation of study treatment.

***MERIT-2 OLtreatment with macitentan***

In MERIT-2 up to the cut-off date, AESI concerning edema or fluid retention were reported less frequently (14.5%) compared with the macitentan group in MERIT-1 (25.0%). Similarly, the exposure-adjusted incidence rate for an edema or fluid retention AESI was lower in MERIT-2 (9.3 per 100 SY) compared to the macitentan group in MERIT-1 (53.7 per 100 SY). In MERIT-2, peripheral edema (6 [7.9%] subjects; 2 DB macitentan and 4 DB placebo) and edema (2 [2.6%] subjects; both DB macitentan) were reported in more than 1 subject; other AEs concerning edema or fluid retention were reported in 1 subject each. There was no difference in the reported frequency of edema or fluid retention AEs between subjects who had previously received placebo or macitentan in MERIT-1. None of the cases were serious or led to premature discontinuation of study. A KM curve of time to first occurrence of edema or fluid retention AESI is available in Module 5.3.5.3 ISS Appendix 1 figure 8. Changes in body weight from baseline to Month 6 were unremarkable, with no trend observed for an increase in body weight. For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the proportion of subjects with an AESI of edema or fluid retention was higher (37.5%) than in the macitentan group in MERIT-1 (25.0%). However, the exposure-adjusted incidence rate for these AEs in the macitentan 10 mg MERIT DB/OL cohort was lower (18.5 per 100 SY) compared to the macitentan group in MERIT-1 (53.7 per 100 SY). A KM curve of time to first occurrence of edema or fluid retention AESI is presented in Figure 10. At Month 12, the event-free KM estimate for edema or fluid retention AESI was 67.2% in the macitentan 10 mg DB/OL cohort, and from Month 24 it was 61.5%. Changes in body weight from MERIT-1 DB baseline to each MERIT-2 post-baseline assessment up to Month 6 were unremarkable. There was no trend indicating an increase in body weight post-baseline.
For subjects who received macitentan 10 mg at any time (macitentan pool), the exposure-adjusted incidence rate for an edema or fluid retention AESI was also lower (14.7 per 100 SY) compared to the macitentan group in MERIT-1. A KM curve of time to first occurrence of edema or fluid retention AESI (similar to the one for macitentan 10 mg DB/OL, Figure 10) is available in Module 5.3.5.3 ISS Appendix 1 figure 9. Changes in body weight from macitentan baseline to Month 6 assessment were unremarkable, with no trend observed for an increase in body weight [see Section 0].

The KM curves of time to first occurrence of edema or fluid retention AESIs for MERIT-1, MERIT-2 and long-term macitentan pooled data show that these AEs had a tendency to occur early after macitentan start [Module 5.3.5.3 ISS Appendix 1 figure 6–figure 9], which is consistent with the decreasing exposure-adjusted incidence rate of these AEs with long-term exposure.

**Figure 10** **Kaplan-Meier curve of time to first occurrence of AESI of edema and fluid retention for macitentan 10 mg DB/OL, Safety Set**




Event curves are presented up to 24 months which corresponds to the time when more than 10% of the subjects are still at risk.
*Treatment start corresponds to the start of double-blind Macitentan 10mg in AC-055E201.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 figure 7 (F_TIMETOAE_SS).

**Anemia**

Anemia and/or hemoglobin decrease has been established as an expected AE with ERAs and macitentan treatment; therefore, these types of AEs were evaluated for MERIT-1 and MERIT-2. Treatment-emergent AEs pertaining to anemia were assessed with the SMQs Haematopoietic erythropenia or Haematopoietic cytopenias affecting more than 1 type of blood cell (with the exception of 2 non-specific PTs, namely, 'blood disorder' and 'blood count abnormal') or an event with any MedDRA PT containing 'anaemia'. Laboratory data supporting the discussion on anemia are presented along with the AE data. The AESIs concerning anemia and the exposure-adjusted incidence rate are provided in Table 14.

The proportion of subjects with hemoglobin abnormalities is presented in Table 15.

**Table 14** **Treatment-emergent adverse events of special interest and exposure-adjusted incidence rate: anemia, Safety Set**

| | MERIT-1 DB | | Macitentan | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | 10 mg MERIT DB/OL (N = 40) | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | Macitentan Pool (N = 76) |
| Subjects with at least 1 AE of special interest: anemia | 7 (17.5) | 1 (2.5) | 9 (22.5) | 5 (12.5) | 10 (27.8) | 15 (19.7) | 19 (25.0) |
| Total Time (years) | 18.6 | 18.4 | 81.2 | 62.6 | 55.1 | 117.7 | 136.3 |
| Adjusted incidence rate per 100-SY | 37.561 | 5.443 | 11.078 | 7.987 | 18.154 | 12.746 | 13.937 |
| 95% CI | 17.906, 78.787 | 0.767, 38.637 | 5.764, 21.291 | 3.324, 19.188 | 9.768, 33.741 | 7.684, 21.142 | 8.890, 21.850 |
| Haemoglobin decreased | 6 (15.0) | 0 | 8 (20.0) | 4 (10.0) | 5 (13.9) | 9 (11.8) | 13 (17.1) |
| Anaemia | 1 (2.5) | 1 (2.5) | 2 (5.0) | 1 (2.5) | 5 (13.9) | 6 (7.9) | 7 (9.2) |
| Hypochromic anaemia | 0 | 0 | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |

AE = adverse event; DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label, SY = subject-year.
Preferred terms are based on MedDRA version 19.0.
Adjusted incidence rate per 100-SY = 100*(number of subjects with at least 1 AE) / (sum of treatment time in days / 365.25)
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 30 (T_AESIPR_SS) and table 31 (T_AESI_ADJEXPO_SS).

**Table 15 Proportion of subjects with hemoglobin abnormalities, Safety Set**

| Laboratory Parameter Criterion | MERIT-1 DB | | Macitentan 10 mg MERIT DB/OL (N = 40) | MERIT-2 OL | | | Macitentan Pool (N = 76) |
|---|---|---|---|---|---|---|---|
| | Macitentan 10 mg (N = 40) | Placebo (N = 40) | | Previously on DB macitentan (N = 40) | Previously on DB placebo (N = 36) | All subjects (N = 76) | |
| Hemoglobin ≤ 80 g/L | | | | | | | |
| n (%) of subjects | 0 | 1 (2.5) | 0 | 0 | 0 | 0 | 0 |
| 95% CI | 0.0, 8.8 | 0.1, 13.2 | 0.0, 8.8 | 0.0, 8.8 | 0.0, 9.7 | 0.0, 4.7 | 0.0, 4.7 |
| n*/ T | 0/18.64 | 1/18.37 | 0/81.24 | 0/62.60 | 0/55.08 | 0/117.69 | 0/136.33 |
| Adjusted incidence rate per 100-SY | 0.000 | 5.443 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 95% CI | NE | 0.767, 38.637 | NE | NE | NE | NE | NE |
| Hemoglobin ≤ 100 g/L | | | | | | | |
| n (%) of subjects | 1 (2.5) | 0 | 2 (5.0) | 2 (5.0) | 3 (8.3) | 5 (6.6) | 5 (6.6) |
| 95% CI | 0.1, 13.2 | 0.0, 8.8 | 0.6, 16.9 | 0.6, 16.9 | 1.8, 22.5 | 2.2, 14.7 | 2.2, 14.7 |
| n*/ T | 1/18.64 | 0/18.37 | 2/81.24 | 2/62.60 | 3/55.08 | 5/117.69 | 5/136.33 |
| Adjusted incidence rate per 100-SY | 5.366 | 0.000 | 2.462 | 3.195 | 5.446 | 4.249 | 3.668 |
| 95% CI | 0.756, 38.092 | NE | 0.616, 9.843 | 0.799, 12.774 | 1.757, 16.887 | 1.768, 10.207 | 1.527, 8.812 |

CI = confidence interval; DB = double-blind; NE = not evaluable; OL = open-label; SY = subject-years; ULN = upper limit of normal

The incidence was calculated as number of subjects with at least 1 post-baseline abnormality/ number of subjects in safety population (%). The 2-sided 95% CI based on the incidence using a binomial proportion. n is the number of subjects with at least 1 incidence of abnormal hemoglobin; T is the total subjects time on study drug in years.

Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 47 (T_HGBA_SS).

***MERIT-1 DB***

A total of 7 (17.50%) subjects in the macitentan group and 1 subject (2.5%) in the placebo group had an anemia AESI. Decreased hemoglobin was reported in 6 subjects in the macitentan group only; an AE of anemia was reported in 1 (2.5%) subject in each of the 2 groups. None of the anemia AESIs were reported as SAEs [Table 11]. No subject in the macitentan group discontinued study treatment due to an AE of anemia [Table 12]. At Month 6, the event-free KM estimate for anemia AESI was 82.5% in the macitentan group compared to 97.4% in the placebo group [Module 5.3.5.3 ISS Appendix 1 table 32, figure 2].

None of the subjects in the macitentan group who were reported to have an AE of anemia or decreased hemoglobin had a decrease in hemoglobin to < 100 g/L. According to laboratory assessments, 1 subject treated with macitentan had a decrease in hemoglobin to < 100 g/L (113 g/L at baseline to 97 g/L at Week 8 increasing to 105 g/L by Week 16 and 119 g/L by Week 24), which was not reported as an AE. No subject on macitentan had a decrease in hemoglobin to ≤ 80 g/L.

In the placebo group, the subject with an anemia AE had a decrease in hemoglobin from a baseline value of 143 g/L to 80 g/L (local laboratory measurement) on Day 160 and prematurely discontinued study treatment. A total of 17 subjects (10 macitentan, 7 placebo) had hemoglobin decreases from baseline of ≥ 20 g/L and < 50 g/L. However, in all 17 subjects, hemoglobin values remained > 100 g/L. Two subjects (1 in each group) had a hemoglobin decrease from baseline of ≥ 50 g/L: the subject in the macitentan group had a decrease in hemoglobin to 143 g/L at Week 16; the subject in the placebo group is discussed above.

None of the subjects in the macitentan group required a transfusion or administration of erythropoietin.
In the macitentan group, there was a mean decrease (± SD) in hemoglobin from baseline at Week 16 of 12.6 ± 22.8 g/L. At Week 24, the decrease was less pronounced (9.2 ± 22.5 g/L). In the placebo group, hemoglobin concentrations were relatively stable over time (mean changes of –2.7 ± 10.7 g/L at Week 16 and 0.5 ± 11.6 g/L at Week 24)
Narratives for subjects who had an AE of hemoglobin decrease or anemia in MERIT-1 are provided in Module 5.3.5.1, section 15.4.4.

***MERIT-2 OL treatment with macitentan***

In MERIT-2 up to the cut-off date, 15 (19.7%) subjects had an AESI of anemia. The exposure-adjusted incidence rate for an anemia AESI was 12.7 per 100 SY in MERIT-2 compared to 37.6 per 100 SY in the macitentan group in MERIT-1. None of the anemia AESIs were reported as SAEs.

In MERIT-2, of the 15 subjects with anemia AESIs, 4 (1 DB macitentan, 3 DB placebo) had decreases in hemoglobin to ≤ 100 g/L. In addition, 1 DB macitentan subject who had a decrease in hemoglobin to < 100 g/L (97 g/L) during MERIT-1 (described above) had a second episode of decrease in hemoglobin to 100 g/L during MERIT-2. No anemia AESI was reported for this subject. No subject had a decrease in hemoglobin to ≤ 80 g/L.

One subject with an AE of decreased hemoglobin discontinued study treatment due to the pre-specified study discontinuation criterion of hemoglobin decrease from baseline of > 50 g/L. The subject's hemoglobin decreased to 93 g/L on Day 37 from the MERIT-2 baseline value of 164 g/L. After withdrawal, hemoglobin subsequently increased to 103 g/L.

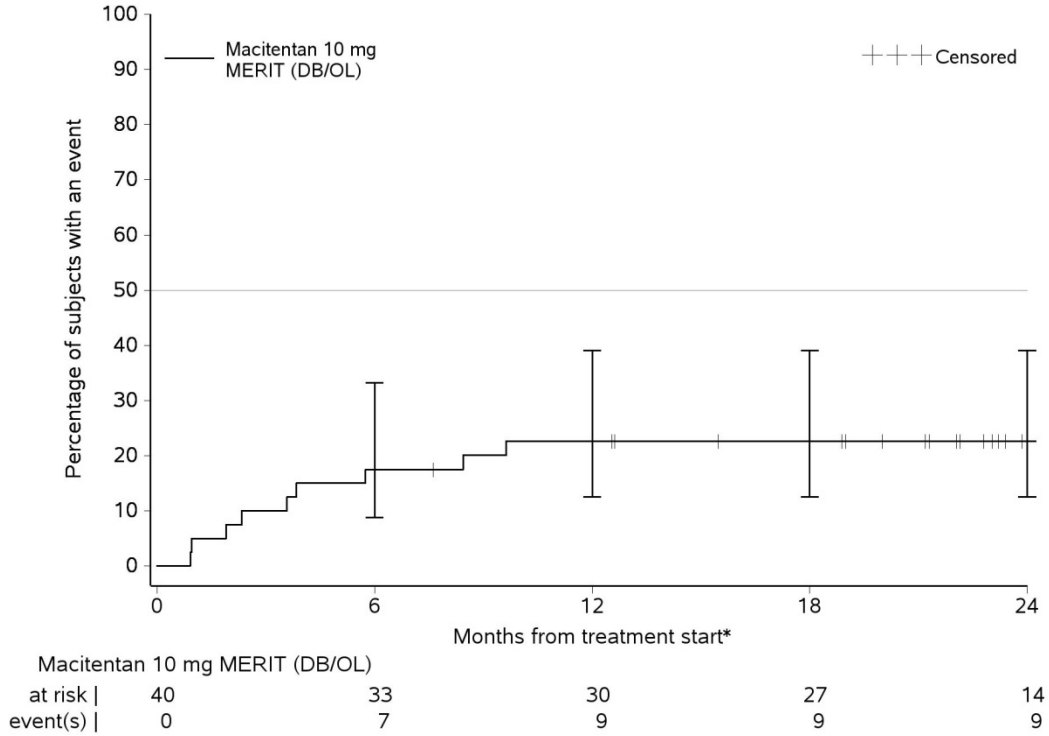
No study subject required transfusion or administration of erythropoietin for an AESI of anemia or decreased hemoglobin.

Narratives for subjects who had an AESI in MERIT-2 are available in Module 5.3.5.3 ISS Appendix 2 sections 4 and 5.

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the exposure-adjusted incidence rates for the anemia AESIs and for a decrease in hemoglobin to ≤ 100 g/L were lower (11.1 and 2.5 per 100 SY, respectively) compared to the macitentan group in MERIT-1. From Month 12, the event-free KM estimate for anemia AESIs was 77.3% in the macitentan 10 mg DB/OL cohort [Figure 11; Module 5.3.5.3 ISS Appendix 1 table 32].

For subjects who received macitentan 10 mg at any time (macitentan pool), the exposure-adjusted incidence rate for an anemia AESI and for a decrease in hemoglobin to ≤ 100g/L was also lower than in the macitentan group in MERIT-1 [. A KM curve of time to first occurrence of anemia AESI (similar to the one for macitentan 10 mg DB/OL, Figure 11) is available in Module 5.3.5.3 ISS Appendix 1 figure 5.

**Figure 11 Kaplan-Meier curve of time to first occurrence of AESI of anemia for macitentan 10 mg DB/OL, Safety Set**




Event curves are presented up to 24 months which corresponds to the time when more than 10% of the subjects are still at risk.
*Treatment start corresponds to the start of double-blind Macitentan 10mg in AC-055E201.

Source: Modified from Module 5.3.5.3 ISS Appendix 1 figure 3 (F_TIMETOAE_SS).

The KM curves of time to first occurrence of anemia AESIs for MERIT-1, MERIT-2 and long-term macitentan pooled data show that these AEs had a tendency to occur relatively early, mostly during the first 6 months after macitentan start, [Module 5.3.5.3 ISS Appendix 1 figure 2–figure 5], which is consistent with the decreasing exposure-adjusted incidence rate of these AEs with long-term exposure.

**Hepatotoxicity**

Hepatotoxicity has been associated with the use of ERAs; therefore, liver test abnormalities were evaluated for MERIT-1 and MERIT-2. AEs associated with hepatotoxicity (increased ALT, increased AST, or increased blood bilirubin) were considered. Laboratory data supporting the discussion on liver tests are presented along with the AE data.

The proportion of subjects with ALT, AST, or bilirubin abnormalities (laboratory data) is presented in Table 16.

**Table 16 Treatment-emergent marked laboratory abnormalities in liver tests, Safety Set**

| Laboratory Parameter Criterion | MERIT-1 DB Macitentan 10 mg (N = 40) | MERIT-1 DB Placebo (N = 40) | Macitentan 10 mg MERIT DB/OL (N = 40) | MERIT-2 OL Previously on DB macitentan (N = 40) | MERIT-2 OL Previously on DB placebo (N = 36) | MERIT-2 OL All subjects (N = 76) | Macitentan Pool (N = 76) |
|---|---|---|---|---|---|---|---|
| ALT or AST > 3 × ULN | | | | | | | |
| n(%) of subjects | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Bilirubin > 2 × ULN | | | | | | | |
| n(%) of subjects | 2 (5.0) | 2 (5.0) | 5 (12.5) | 5 (12.5) | 1 (2.8) | 6 (7.9) | 6 (7.9) |
| 95% CI | 0.6, 16.9 | 0.6, 16.9 | 4.2, 26.8 | 4.2, 26.8 | 0.1, 14.5 | 3.0, 16.4 | 3.0, 16.4 |
| n*/ T | 2/18.64 | 2/18.37 | 5/81.24 | 5/62.60 | 1/55.08 | 6/117.69 | 6/136.33 |
| Adjusted incidence rate per 100-SY | 10.732 | 10.885 | 6.154 | 7.987 | 1.815 | 5.098 | 4.401 |
| 95% CI | 2.684, 42.910 | 2.722, 43.523 | 2.562, 14.786 | 3.324, 19.188 | 0.256, 12.888 | 2.290, 11.348 | 1.977, 9.797 |
| (ALT > 3 × ULN) or (AST > 3 × ULN) and (Total Bilirubin > 2 × ULN at any time) | | | | | | | |
| n(%) of subjects | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; DB = double-blind; NE = not evaluable; OL = open-label; SY = subject-years; ULN = upper limit of normal

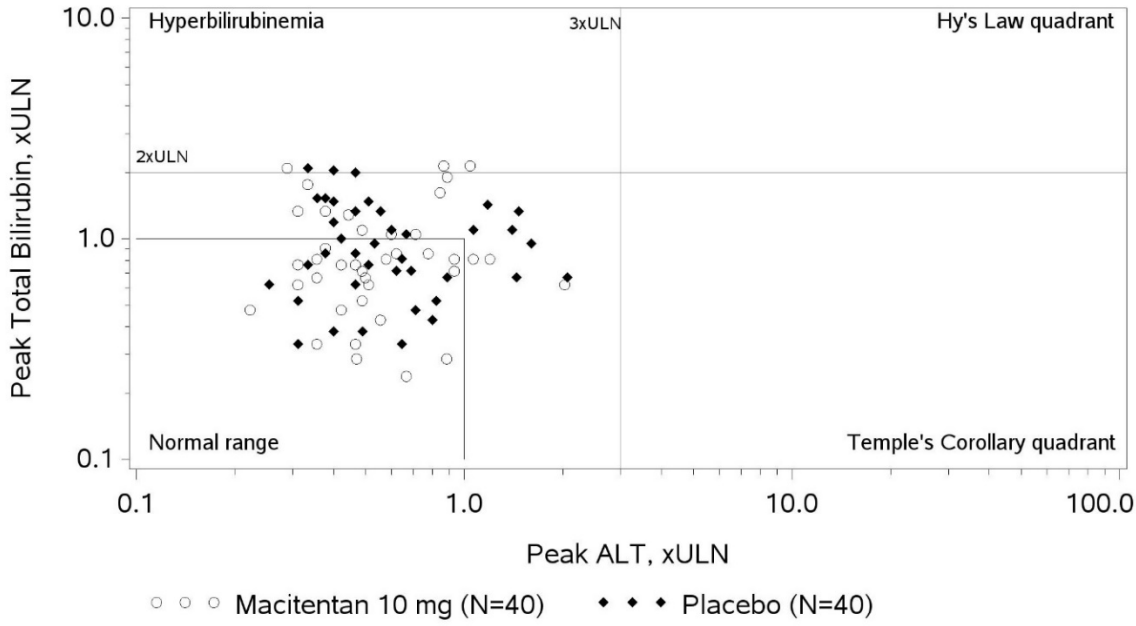
The incidence was calculated as number of subjects with at least 1 post-baseline abnormality/ number of subjects in safety population (%). The 2-sided 95% CI based on the incidence using a binomial proportion. n is the number of subjects with at least 1 incidence of abnormal liver test; T is the total subjects time on study drug in years.

Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 48 (T_LTA_SS).

***MERIT-1 DB***

No liver failure / liver insufficiency AEs were reported in MERIT-1. Liver test AEs were reported only in the placebo group, and included AEs of increased ALT and increased AST (3 [7.5%] subjects each), and increased blood bilirubin (1 [2.5%] subject). There were no subjects with marked increases in aminotransferases (ALT/AST> 3 × ULN). Treatment-emergent increases in bilirubin to > 2 × ULN were reported for 2 subjects in each treatment group. No subject met the search criteria for Hy's Law, i.e., ALT/AST > 3 × ULN, total bilirubin > 2 × ULN [Figure 12].

**Figure 12 Peak total bilirubin versus peak ALT in MERIT-1, Safety Set**




Source: Modified from Module 5.3.5.3 ISS Appendix 1 figure 10 (F_EDISH_SS).

***MERIT-2 OL treatment with macitentan***

**In MERIT-2 up to the cut-off date, no liver failure / liver insufficiency AEs were reported.** Liver test AEs were reported, and included AEs of increased ALT and increased AST in 1 (1.3%) subject each [Module 5.3.5.3 ISS Appendix 1 table 12]. Three (3.9%) subjects had an AE of increased blood bilirubin. None of these AEs were reported as serious or required discontinuation. There were no subjects with marked increases in aminotransferases. Treatment-emergent increases in bilirubin to > 2 × ULN were reported for 6 (7.9%) subjects. No subject met the search criteria for Hy's Law, i.e., ALT/AST > 3 × ULN, total bilirubin > 2 × ULN [Module 5.3.5.3 ISS Appendix 1 figure 12]. For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the exposure-adjusted incidence rate of increase in total bilirubin to > 2 × ULN was 6.2 per 100 SY in the macitentan 10 mg DB/OL cohort compared to 10.7 per 100 SY in the macitentan group in MERIT-1. For subjects who received macitentan 10 mg at any time (macitentan pool), the exposure-adjusted incidence rate of increase in total bilirubin to > 2 × ULN was 4.4 per 100 SY in the macitentan pool compared to 10.7 per 100 SY in the macitentan group in MERIT-1.

**Hypotension**
Hypotension has been associated with the use of ERAs and may represent a potential risk for the CTEPH population based on age, comorbidities, and concomitant treatments, and therefore was evaluated for MERIT-1 and MERIT-2. AEs associated with hypotension (AE PTs of blood pressure decreased, hypotension, and orthostatic hypotension) and vital sign data were considered.

The AEs of hypotension are provided in Table 17.

**Table 16 Treatment-emergent hypotension adverse events by Preferred Term, Safety Set**

| | MERIT-1 DB | | Macitentan | MERIT-2 OL | | | |
|---|---|---|---|---|---|---|---|
| **Preferred term** | **Macitentan 10 mg (N = 40)** | **Placebo (N = 40)** | **10 mg MERIT DB/OL (N = 40)** | **Previously on DB macitentan (N = 40)** | **Previously on DB placebo (N = 36)** | **All subjects (N = 76)** | **Macitentan Pool (N = 76)** |
| Blood pressure decreased [a] | 0 | 0 | 2 (5.0) | 1 (2.5) | 0 | 1 (1.3) | 2 (2.6) |
| Hypotension | 0 | 2 (5.0) | 1 (2.5) | 1 (2.5) | 0 | 1 (1.3) | 1 (1.3) |
| Orthostatic hypotension | 0 | 1 (2.5) | 0 | 0 | 1 (2.8) | 1 (1.3) | 1 (1.3) |

DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities: OL = open-label.
Frequencies represent the number of subjects with the event. Preferred Terms are based on MedDRA version 19.0.
[a] A case of decreased blood pressure was reported for MERIT-1 after MERIT-1 DB closure (see description in the text).
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 12 (T_AE_PT_SS).

***MERIT-1 DB***
During MERIT-1, no subject in the macitentan group had a hypotension AE; in the placebo group, AEs of hypotension (2 [5.0%] subjects) and orthostatic hypotension (1 [2.5%] subject) were reported [Table 17]. Subsequently, 1 subject in the macitentan group had an AE of decreased blood pressure, which was reported with a start date in the MERIT-1 study while the subject was in the MERIT-2 study. Of the 3 subjects with hypotension AEs in the placebo group, 2 were receiving PH advanced therapy at baseline. Changes in systolic and diastolic blood pressure (SBP, DBP) during MERIT-1 were unremarkable in both treatment groups. Of note, most subjects (60.0% of subjects on macitentan and 72.5% on placebo) were receiving PH advanced therapy, specifically PDE-5 inhibitors, at baseline or during the study.

***MERIT-2 OL treatment with macitentan***
In MERIT-2 up to the cut-off date, individual AEs of decreased blood pressure (1 [2.5%] subject), hypotension (1 [2.5%] subject), and orthostatic hypotension (1 [2.5%] subject) were reported [Table 17]. None of the hypotension AEs were reported as serious or resulted in discontinuation of study treatment. No effect of age, sex, or race was observed on the occurrence of hypotension AEs. Changes in SBP and DBP from baseline to Month 6 were unremarkable [see Section 0].

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), AEs concerning hypotension were similar to that observed in MERIT-1. Changes in vital signs from MERIT-1 baseline to each MERIT-2 post-baseline assessment up to Month 6 were unremarkable [Section 0 of the Summary of Clinical Safety]. For subjects who received macitentan 10 mg at any time (macitentan pool), AEs concerning hypotension were similar to those observed in MERIT-1. Changes in SBP and DBP from macitentan baseline to the Month 6 assessment were unremarkable [Section 0 of the Summary of Clinical Safety]. Of note, most subjects (48 out of the 76 in the macitentan pool) were receiving PH advanced therapy, specifically PDE-5 inhibitors, at MERIT-1 baseline.

**Bleeding events**
Although macitentan has not been associated with increased risk of bleeding, 100% anti-coagulant use in this population warrants description of bleeding events, specifically hemoptysis and pulmonary hemorrhage, which may represent a risk for the CTEPH population; therefore, bleeding events were evaluated for MERIT-1 and MERIT-2.

***MERIT-1 DB***
Hemorrhage AEs were reported in both treatment groups. PTs reported in more than 1 subject were epistaxis (1 on macitentan, 2 on placebo), hemoptysis (1 subject each), and menorrhagia (1 subject each). Of all hemorrhage AEs reported, 1 AE (hemorrhagic stroke) was reported as serious and resulted in a fatal outcome in a subject in the placebo group [Module 5.3.5.1 table 15-99]. None of the hemorrhage AEs in the macitentan group were reported as serious or resulted in discontinuation of study treatment [Module 5.3.5.1, table 15-95, table 15-102].

***MERIT-2 OL treatment with macitentan***

In MERIT-2 up to the cut-off date, an AE of hemoptysis was reported in 3 subjects, all of whom had received placebo during MERIT-1. Hemorrhage AEs reported in 2 subjects each were epistaxis, hemorrhoidal hemorrhage, and contusion. One subject who had received macitentan during MERIT-1 died due to an SAE of intracranial hemorrhage following a fall and head injury; [Module 5.3.5.3 ISS Appendix 1 table 18, table 22, table 28]. The remaining SAEs during MERIT-2 were hemoptysis (2 subjects) and hematuria (1 subject) [Module 5.3.5.3 ISS Appendix 1 table 22]. Of the 2 subjects with the hemoptysis SAE, 1 was diagnosed with arteriovenous malformation, underwent surgery and did not experience hemoptysis thereafter; the other subject had multiple asthma attacks preceding hemoptysis. The subject with an SAE of hematuria was diagnosed with urocystitis. Apart from the subject who died due to an SAE of intracranial hemorrhage, no other bleeding AEs required discontinuation.

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (macitentan 10 mg MERIT DB/OL), the incidence of subjects with hemorrhage AEs was similar to what was observed in MERIT-1.

Consistent with the increased exposure and observation time for subjects who received macitentan 10 mg at any time (macitentan pool), the incidence of subjects with hemorrhage AEs was slightly higher than what was observed in the MERIT-1, however, most of these AEs were neither reported as SAEs nor resulted in discontinuation of study treatment [Module 5.3.5.3 ISS Appendix 1 table 22, table 28].

***Clinical pharmacology studies***
No bleeding events were reported in AC-055-122 or AC-055-123 for subjects treated with macitentan [Module 5.3.3.4 table 12-2 and table 12-1].

## *Safety data from the OPUS Registry (AC-055-503)*

The OPUS Registry collects AE data on all patients. For the analysis of AEs in the OPUS Registry, comprehensive AE information is sourced from the OPUS Registry CRF and the Argus safety database.
In order to compare the CTEPH and PAH populations in the OPUS Registry (N = 45 and 1455, respectively), all-cause death and AE data are included for these two patient sets in

Table 17. Overall in this observational registry, supportive safety data from the OPUS Registry contributes an additional exposure period of 24.1 patient-years at risk for an AE, and 46.8 patient-years at risk for death for CTEPH patients treated with Opsumit [

Table 17].

Reported rates for the occurrence of AE and all-cause death per 100 patient-years, and overall AEs for the CTEPH and the PAH Follow-up Sets do not suggest any incremental risk associated with Opsumit in CTEPH patients compared to PAH patients [

Table 17]. No liver test abnormalities were reported during the exposure period in the CTEPH Follow-up Set [Module 5.3.5.4 table 21].

**Table 17 Rates of AE and death per 100 patient-years during the exposure period in the CTEPH Follow-up Set and PAH Follow-up Set – OPUS Registry**

| | CTEPH Follow-up Set N = 45 | PAH Follow-up Set N = 1455 |
|---|---|---|
| **Death** | | |
| Number of deaths | 1 | 145 |
| Exposure time (patient-years) | 46.8 | 1673.1 |
| All cause death per 100 patient-years (95% CI) | 2.1 (0.3, 15.2) | 8.7 (7.4, 10.2) |
| **AEs** | | |
| Patient experienced at least 1 AE | 32 (71.1%) | 1076 (74.0%) |
| Exposure time (patient-years) | 24.1 | 703.5 |
| Rate of AE per 100 patient-years (95% CI) | 132.6 (93.8, 187.6) | 153.0 (144.1, 162.4) |

AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Source: Module 5.3.5.4, table 28, table 30, table 32, table 33.

## Laboratory findings

Laboratory abnormalities that occurred after the study treatment start and up to 30 days after the end of study treatment in MERIT-1 are discussed in detail in the MERIT-1 CSR [Module 5.3.5.1] and are briefly described in the section below. The incidence of abnormal hematology variables (i.e., hemoglobin) and abnormal liver tests (ALT, AST, and total bilirubin) are discussed above.

***Hematology***

Hemoglobin laboratory assessments and AEs have been discussed in previous section about AESIs. In MERIT-1, mean leukocyte count (± SD) showed a greater decrease in the macitentan group (−1.424 ± 1.519 × $10^9$/L) than in the placebo group (−0.846 ± 1.999 × $10^9$/L) at Week 16. At Week 24, change from baseline in leukocyte counts was −0.830 ± 1.745 × $10^9$/L in the macitentan group and −0.461 ± 2.000 × $10^9$/L in the placebo group. Two subjects in the macitentan group had marked decreases in leukocyte counts [Module 5.3.5.1, section 12.4.2]. For platelet count, a small decrease in mean (± SD) platelet count, which was similar in both treatment groups (macitentan, −11.5 ± 37.4 × $10^9$/L; placebo, −11.7 ± 35.8 × $10^9$/L) was observed at Week 16. At Week 24, the change from baseline in

mean platelet count was −8.7 ± 37.1 × $10^9$/L in the macitentan group and −0.8 ± 34.9 × $10^9$/L in the placebo group. International normalized ratio and activated partial thromboplastin time values fluctuated in both treatment groups, with no consistent difference between the treatment groups over 24 weeks. Changes in the other laboratory hematology variables showed no clinically relevant mean changes from baseline [Module 5.3.5.1 section 12.4.1].

***Clinical chemistry***
Treatment-emergent marked laboratory abnormalities in liver tests are provided in Table 16 and Figure 12 as part of the discussion on liver test abnormalities and hepatotoxicity/liver failure.

Other clinical chemistry variables showed no clinically relevant mean changes from baseline in MERIT-1 [Module 5.3.5.1 section 12.4].

## Vital signs, physical findings, and other observations related to safety

Vital signs (SBP, DBP, pulse rate) and body weight were evaluated in MERIT-1 and MERIT-2. A listing of vital signs and body weight is available in Module 5.3.5.3 ISS Appendix 1 listing 14.

***MERIT-1 DB***
Changes in vital signs were unremarkable in both treatment groups. Mean absolute changes (± SD) in SBP/DBP from baseline to Week 24 (end of treatment) were –3.5 ± 11.1 / –3.2 ± 9.0 mmHg on macitentan and –1.2 ± 14.5 / −1.2 ± 9.5 mmHg on placebo [Module 5.3.5.1, table 15-120]. The mean absolute change (± SD) in pulse rate from baseline to Week 24 (end of treatment) was –0.6 ± 11.0 beats per minute (bpm) on macitentan and –3.1 ± 12.9 bpm on placebo.

There was a decrease in mean body weight over the study period in the macitentan group, whereas a small increase was observed in the placebo group. One subject in the macitentan group who experienced an SAE of acute right ventricular failure had a mild intensity AE of decreased weight (loss of 12 kg within 12 weeks) following adjustment of diuretic treatment.

***Long-term treatment with macitentan***
In **MERIT-2** up to the cut-off date, changes in vital signs and body weight from baseline to Month 6 were unremarkable. There was no trend in weight increase post-baseline. Mean absolute changes (± SD) in SBP/DBP were –0.2 ± 13.2 / –2.7 ± 9.5 mmHg. The mean absolute change (± SD) in pulse rate was –1.2 ± 8.7 bpm. The mean absolute change (± SD) in body weight was −0.338 ± 2.852 kg [Module 5.3.5.3 ISS Appendix 1 table 50].

For subjects who received macitentan 10 mg in both MERIT-1 and MERIT-2 (**macitentan 10 mg MERIT DB/OL**), changes in vital signs and body weight from MERIT-1 baseline were small and similar to those reported in MERIT-1 [Module 5.3.5.3 ISS Appendix 1 table 49].

For subjects who received macitentan 10 mg at any time (**macitentan pool**), changes in vital signs and body weight from macitentan baseline to Month 6 assessment were small and similar to those described above in MERIT-1 [Module 5.3.5.3 ISS Appendix 1 table 51].

## Safety in special populations

***Intrinsic factors***
The effect of intrinsic factors on treatment with macitentan in subjects with PAH is available in the SmPC. This section describes results in subjects with inoperable CTEPH from MERIT-1 and the macitentan pool.

**Age**
AEs by age subgroup (< 65 years and ≥ 65 years) are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 33. SAEs by age subgroup are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 43. AEs of special interest by age subgroup are available by PT in Module 5.3.5.3 ISS Appendix 1 table 37. Taking into consideration the disparities in the numbers of subjects in the different age categories (52 subjects aged < 65 years treated with macitentan and placebo [26 subjects each] vs 28 subjects aged ≥ 65 years treated with macitentan and placebo [14 subjects each]), the proportions of subjects with at least 1 AE were generally similar across the age subgroup in MERIT-1. There were no apparent age-associated differences in the incidence of AEs across SOCs in the macitentan and placebo groups in MERIT-1. Overall, in the macitentan pool the proportion of

subjects with AEs was 96.4% and 81.3% in subjects aged ≥ 65 years and < 65 years, respectively. The most frequently reported AEs in the subjects aged ≥ 65 years compared with < 65 years respectively were in the SOCs Gastrointestinal disorders (53.6% and 25.0%), Infections and infestations (53.6% and 41.7%), and General disorders and administration site conditions (39.3% and 29.2%). The Respiratory, thoracic and mediastinal disorders and Cardiac disorder AEs AEs were reported in a similar proportion of subjects aged ≥ 65 years (35.7% and 25.0%, respectively) and < 65 years (37.5% and 25.0%, respectively). The incidence of SAEs in the macitentan pool was comparable in subjects aged ≥ 65 years and < 65 years, with the most frequently reported SAEs in the SOC Cardiac disorders in both subgroups. The proportion of subjects with edema and fluid retention AESIs was 35.7% and 20.8% in subjects aged ≥ 65 years and < 65 years, respectively. The proportion of subjects with anemia AESIs was 14.3% and 31.3% in subjects aged ≥ 65 years and < 65 years, respectively. Incidences of hypotension, hemoptysis and epistaxis AEs were not higher in subjects aged ≥ 65 years compared with those < 65 years.

**Sex:** AEs by sex are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 36. SAEs by sex are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 46. AEs of special interest by sex are available by PT in Module 5.3.5.3 ISS Appendix 1 table 40. There were 51 female subjects (26 treated with macitentan and 25 treated with placebo) vs 29 male subjects (14 treated with macitentan and 15 treated with placebo) in MERIT-1. The overall AE frequency was 76.9% and 71.4% in the macitentan group and 88.0% and 66.7% in the placebo group for female and male subjects, respectively. AEs denoting anemia were reported more frequently in female subjects treated with macitentan (5 [19.2%] subjects) compared with male subjects (2 [14.3%] subjects) [Module 5.3.5.3 ISS Appendix 1 table 40].
In the macitentan pool, the AE profile by sex was comparable with that observed in the MERIT-1 study. The proportion of subjects with an SAE was similar in the female (31.3%) and male (35.7%) subgroups. However, Cardiac disorder SAEs were reported more frequently in male subjects (25.0%) compared to females (12.5%). Edema and fluid retention AESIs were reported more frequently in female subjects (14 [29.2%] subjects) compared with male subjects (6 [21.4%] subjects). AESIs denoting anemia were reported more frequently in female subjects treated with macitentan (14 [29.2%] subjects) compared with male subjects (5 [17.9%] subjects). All 4 hemoptysis AEs were reported in female subjects.

**Race:** AEs by race are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 35. SAEs by race are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 45. AEs of special interest by race are available by PT in Module 5.3.5.3 ISS Appendix 1 table 39. MERIT-1 comprised 50 (62.5%) White subjects and 30 (37.5%) Asian subjects. Subgroup differences in AEs on the basis of race were unremarkable. In White subjects, the frequency of edema and fluid retention AEs was 32.0% in the macitentan group and 16.0% in the placebo group. In Asian subjects, the frequency was 13.3% and 0% in the macitentan and placebo groups, respectively [Module 5.3.5.3 ISS Appendix 1 table 39]. Overall, in the macitentan pool, 91.8% of White subjects and 77.8% of Asian subjects had at least 1 AE. The proportion of subjects with edema and fluid retention AESIs was 34.7% and 11.1% in White and Asian subjects, respectively. No imbalance for anemia AESIs was observed by race. All 4 hemoptysis AEs were reported in Asian subjects.

***Extrinsic factors***
The effect of extrinsic factors on treatment with macitentan in subjects with PAH is available in the SmPC. This section describes results from MERIT-1 in subjects with inoperable CTEPH.

AEs by PH advanced therapy at baseline (with or without) are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 34. SAEs by PH advanced therapy at baseline are available by SOC and PT in Module 5.3.5.3 ISS Appendix 1 table 44. AESI by PH advanced therapy at baseline are available by PT in Module 5.3.5.3 ISS Appendix 1 table 38. Cause of death and treatment-emergent death by PH advanced therapy at baseline are available in Module 5.3.5.3 ISS Appendix 1 table 41 and table 42. There were 49 subjects (24 treated with macitentan and 25 treated with placebo) and 31 subjects (16 treated with macitentan and 15 treated with placebo) with or without PH advanced therapy at baseline, respectively, in MERIT-1. The incidence and types of AEs and SAEs were generally similar in subjects with or without PH therapy at baseline. A higher proportion of subjects with PH advanced therapy at baseline in both treatment groups had edema/fluid retention AESIs (29.2% macitentan, 12.0% placebo) compared to subjects without PH advanced therapy (18.8% macitentan, 6.7% placebo) [Module 5.3.5.3 ISS Appendix 1 table 38]. There was no notable difference in the occurrence of the anemia AESIs by PH advanced therapy at baseline [Module 5.3.5.3 ISS Appendix 1 table 38]. AESIs were also evaluated by SY exposure and are discussed in Section 0 (edema and fluid retention) and Section 0 (anemia).

### *Immunological events*

No new data provided.

## Safety related to drug-drug interactions and other interactions

Details of drug-drug interactions of macitentan are available in the SmPC. No pharmacokinetic interaction was observed between macitentan and rosuvastatin or riociguat (see PK section of this assessment report)

## Post marketing experience

Macitentan (Opsumit) was first approved in 2013 for the treatment of PAH to delay disease progression. It was approved in Brazil for the treatment of CTEPH on 9 July 2018. Similar to other PAH therapies, off-label use in CTEPH is documented in the post-marketing section and below and registry data.

Post-marketing information is available in the Opsumit PBRER/PSUR (cut-off date of 17 October 2017) and SAE reports for ongoing clinical studies in the Actelion Drug Safety database. Additional safety data on macitentan (Opsumit) use in CTEPH is available from the OPUS registry. Safety findings from this registry are described in Section 0.

**Information from the safety database (Argus)**
A total of 25,581 cases have been received cumulatively for macitentan-treated patients between the IBD (18 October 2013) and 17 October 2017, of which 241 had a reported medical history of CTEPH. In 2170 out of the 25,581 cases concomitant use of riociguat was reported.

Based on worldwide post-marketing experience (i.e., all AEs received from patients exposed in real medical practice and long-term use in the post-authorization phase), the review below presents a summary of cumulative data on macitentan, in cases with/without a medical history of CTEPH, and with/without concomitant use of riociguat.

Despite limitations inherent to comparison of safety data based on post-marketing sources, overall, the nature and distribution of events reported in cases with/without riociguat are consistent, and reflect both the known safety profile of macitentan (headache, anemia, decrease in hemoglobin, fluid retention, peripheral edema, hypotension) and events expected in a patient population suffering from PAH and associated comorbidities (dyspnea, PH, right ventricular failure), as well as the known events expected with riociguat as per labeling document. No unusual pattern of AE distribution was observed, and no concerns were identified.

As no patient exposure data are available for patients concomitantly treated with macitentan and riociguat, it is important to highlight that the analysis was based on the nature of AEs reported and the proportional distribution of these AEs among all events reported in cases with documented concomitant use of these medications (i.e., estimation of reporting rates was not possible).

The results of the analyses of available data (up to 17 October 2017) should be interpreted with caution, due to limitations imposed by the relatively low number of cases received for patients concomitantly receiving macitentan and riociguat, the very low number of cases with a medical history of CTEPH, and the limited information provided in cases arising from post-marketing sources, i.e., regarding treatment start and stop dates, and an inability to assess temporal association of the reported AEs and concomitant treatments.

## Identification of potential adverse drug reactions

The safety profile of macitentan was initially established through clinical studies in subjects with PAH.

No treatment-emergent drug-related SAEs with fatal outcome occurred in MERIT-1 or MERIT-2 [Module 5.3.5.3 ISS Appendix 1 table 27].

To identify potential ADRs in subjects with inoperable CTEPH, a list of the AE PTs reported in at least 3% of subjects in the macitentan group and at a frequency more than 3% greater than placebo

(occurring from treatment start up to 30 days from end of treatment by PT) in MERIT-1 was produced [Table 18]. The choice of the threshold of 3% and the difference versus placebo of 3% is felt to be appropriate given the number of subjects in the CTEPH studies.

**Table 18 Adverse events reported by > 3% more frequently in the macitentan group vs placebo in subjects with inoperable CTEPH in MERIT-1, Safety Set**

| System organ class<br>Preferred term | Double-blind [a]<br>Macitentan 10 mg<br>(N = 40) | Placebo<br>(N = 40) |
|---|---|---|
| General disorders and administration site conditions | | |
| Oedema peripheral | 9 (22.5%) | 4 (10.0%) |
| Fatigue | 2 (5.0%) | 0 |
| Investigations | | |
| Haemoglobin decreased | 6 (15.0%) | 0 |
| Infections and infestations | | |
| Upper respiratory tract infection | 3 (7.5%) | 0 |
| Pharyngitis | 2 (5.0%) | 0 |
| Musculoskeletal and connective tissue disorders | | |
| Pain in extremity | 3 (7.5%) | 0 |
| Bone pain | 2 (5.0%) | 0 |

[a] MERIT-1. CTEPH = chronic thromboembolic pulmonary hypertension.
Source: Modified from Module 5.3.5.3 ISS Appendix 1 table 13 (T_AE_SOC_PT_SS).

Frequency determination does not account for other factors including varying study duration, pre-existing conditions, and baseline subject characteristics; therefore, an individual assessment accounting for medical plausibility, including an evaluation of the incidences of these AEs in the pivotal Phase 3 PAH study (SERAPHIN), has been applied in the final assessment of ADRs.

Anemia, nasopharyngitis/pharyngitis and bronchitis are already included as adverse reactions in the Opsumit SmPC, therefore, hemoglobin decreased, pharyngitis and upper respiratory tract infections that were reported more frequently on macitentan vs placebo in CTEPH subjects do not represent new adverse reactions.

Oedema/fluid retention is also already included as an adverse reaction in the Opsumit SmPC, with edema and fluid retention specified as associated with the use of ERAs.

In MERIT-1, pain in extremity was reported in 3 subjects (7.5%), fatigue and bone pain were reported in 2 subjects each (5.0% each) in the macitentan group. In the pivotal PAH study with morbidity/mortality endpoint (SERAPHIN), incidences of pain in extremity and fatigue in the macitentan 10 mg group were lower compared to the placebo group. One subject in the macitentan 10 mg group had an AE of bone pain in SERAPHIN. Given the low number of events resulting in a numerical imbalance for these AEs in MERIT-1, without an increased frequency reported in SERAPHIN, the AEs of pain in extremity, fatigue and bone pain are not considered ADRs.

Evaluation of results from MERIT-1 in subjects with inoperable CTEPH did not identify any additional ADRs in this patient population compared to the established safety profile of macitentan.
Table 19 lists the ADRs identified in inoperable CTEPH.

**Table 19. Adverse reactions for macitentan in inoperable CTEPH.**

| Preferred term | Frequency |
|---|---|
| Oedema peripheral | Very common |
| Haemoglobin decreased | Very common |
| Upper respiratory tract infection | Common |
| Pharyngitis | Common |

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000)
CTEPH = chronic thromboembolic pulmonary hypertension.
Source: Table 18.

Description of selected adverse reactions
In a DB study in patients with inoperable CTEPH, the incidence of edema or fluid retention AEs was 25.0% in the macitentan 10 mg group and 10.0% in the placebo group.

Laboratory abnormalities

*Liver aminotransferases*
No incidences of aminotransferase elevations (ALT/AST) > 3 × ULN were reported for subjects on macitentan 10 mg or placebo in a DB study in subjects with inoperable CTEPH (MERIT-1).

*Hemoglobin*
In a DB study in subjects with inoperable CTEPH (MERIT-1), a decrease from baseline in hemoglobin of ≥ 20 g/L and < 50 g/L was reported in 25% of subjects treated with macitentan 10 mg and 17.5% of subjects treated with placebo [Module 5.3.5.1, table 12-7].

## 2.5.1. Discussion on clinical safety

The safety evaluation for the new indication (i.e: inoperable patients with CTEPH) is primarily based on 80 subjects enrolled in the MERIT 1, a double-blind, placebo-controlled Phase 2 study. Data from MERIT 1 and MERIT 2 (an open label ongoing study with 76 patients previously recruited into the MERIT-1 study) were integrated in order to provide long-term follow-up data. Some safety data from the OPUS Registry (n=45, CTEPH cohort) and post marketing sources (OPUS registry and Argus Safety Database) were also provided. No comparative studies versus riociguat, or on top of riociguat, the single drug approved for the treatment of CTEPH patients, have been presented within this application. The applicant is invited to provide information about planned studies to further assess the safety profile of macitentan in CTEPH standard practice (i.e.: in comparison with riociguat or on top of riociguat) upon an eventual approval of the new indication (see RSI).

In MERIT-1, the median (range) duration of exposure in the macitentan and placebo groups was similar (24.1 weeks). The proportion of subjects with treatment-emergent AEs in the macitentan group was 30 out of 40 (75.0%) and in the placebo group it was 32 out of 40 (80.0%). Peripheral edema (9 subjects [22.5%] macitentan, 4 subjects, [10.0%] placebo) and hemoglobin decrease (6 subjects [15%] macitentan, no subjects on placebo) were the most frequently reported AEs. In MERIT 2, AESI concerning edema or fluid retention were reported less frequently (14.5%) compared with the macitentan group in MERIT 1 (25.0%). In MERIT-2 up to the cut-off date, 15 (19.7%) subjects had an AESI of anemia.

No deaths were reported on macitentan during MERIT-1. On placebo, 2 subjects died, one due to hemorrhagic stroke on Day 172 and one due to right ventricular failure with embolism reported as a secondary cause of death on Day 129. There were 9 additional deaths reported in open-label extension MERIT-2, none of them were considered by the investigator as not related to macitentan (5 of them were due to acute heart failure, 2 deaths were due to sepsis, one to worsening PH and one due to intracranial hemorrhage). In MERIT-1, the proportion of subjects with SAEs was lower in the macitentan group (3 subjects, 7.5%) than in the placebo group (7 subjects, 17.5%). The most frequently reported SAEs were cardiac failure, acute cardiac failure, pneumonia, and right ventricular failure. None of them was drug-related. In the macitentan group, no subject discontinued treatment due to an AE. In the placebo group, 2 subjects discontinued due to AEs (anemia and worsening of PH). A total of 14 subjects (10 macitentan [25.0%], 4 placebo [10.0%]) had at least one AE associated with edema and fluid overload (defined as AEs of special interest). A total of 8 subjects (7 macitentan [17.5%], 1 placebo [2.5%]) had at least one AE associated with anemia or decreased hemoglobin (also defined as an AE of special interest). None of the 7 subjects treated with macitentan who had an AE of anemia had a decrease in hemoglobin to < 100 g/L, but one subject in the macitentan group had a decrease in hemoglobin to < 100 g/L (from 113 g/L to 97 g/L [i.e., a decrease of 16 g/L]), without anemia or decreased hemoglobin reported as an AE. The subject's hemoglobin value returned to 105 g/L by the subsequent assessment visit (Week 16). There were no subjects with marked liver abnormalities, although AEs for elevations in aminotransferases (< 3 × upper limit of the normal range) were reported for 3 subjects in the placebo group. No liver failure / liver insufficiency AEs were reported in MERIT-1 or MERIT-2. The mean changes in systolic and diastolic blood pressures (mmHg ± SD) from baseline to Week 24 were -3.5 ± 11.1/−3.2 ± 9.0 mmHg on macitentan and −1.2 ± 14.5/−1.2 ± 9.5 mmHg on placebo in MERIT-1.

Respect to intrinsic factors and AE, the rate of patients with AEs was higher in subjects aged ≥ 65 years vs < 65 years (96.4% and 81.3%, respectively), mainly at expenses of gastrointestinal disorders (53.6% vs. 25.0%), Infections and infestations (53.6% vs. 41.7%), and General disorders and administration site conditions (39.3% vs. 29.2%). AEs denoting anemia were reported more frequently in female subjects treated with macitentan compared to male subjects (29.2% vs. 17.9%). The same

imbalance between females and males was found for Edema/fluid retention AESIs (female 29.2% vs. male subjects 21.4%) subjects). The trend of increased rates of AEs in the elderly and in females is consistent with that reported in the PAH. Race subgroup differences in AEs were unremarkable in the MERIT-1 study, where the population comprised 50 (62.5%) White subjects and 30 (37.5%) Asian subjects. Concerning extrinsic factors, the incidence and types of AEs and SAEs were generally similar in subjects with or without PH therapy at baseline. A higher proportion of subjects with PH advanced therapy at baseline in both treatment groups had edema/fluid retention AESIs (29.2% macitentan vs. 12.0% placebo) compared to subjects without PH advanced therapy (18.8% macitentan vs. 6.7% placebo). Patients on concomitant PH therapies represent a higher risk population with a more advanced disease. Increased risk of AESIs is not unexpected. Anyway, the applicant is invited to discuss (see RSI).

Additional safety data from the OPUS registry and Argus safety database did not identify new or unexpected safety observations beyond the established safety profile in the PAH indication. The results of the analyses of available data should be interpreted with caution, due to limitations imposed by the relatively low number of cases with a medical history of CTEPH, and the limited information provided (i.e., regarding important baseline characteristics like WHO FC, 6MWD, and incomplete data regarding treatment start and stop dates, concomitant treatments, as well as an inability to assess temporal association of the reported AEs and concomitant treatments).

### Additional expert consultations

N/A.

### Assessment of paediatric data on clinical safety

N/A.

## 2.5.2. Conclusions on clinical safety

Macitentan is an endothelin receptor antagonist and currently approved for the treatment of pulmonary hypertension; as such, there is previous safety experience. The safety data for macitentan are limited as expected due to the rarity of the disease, however, generally in line with the safety profile of macitentan in PAH. However, some uncertainties exist due to the lack of a systemic presentation of safety in the special populations with respect to age and PH advanced therapy status at baseline, which needs to be addressed by the MAH.

## 2.5.3. PSUR cycle

Not applicable

## 2.5.4. Direct Healthcare Professional Communication

Not applicable

## *2.6. Significance of paediatric studies*

Not applicable

# 3. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

- To update some sections of the RMP (MERIT data and other updates highlighted in yellow) that were outdated and not aligned with the clinical data submitted to the EMA since the initial MA application.

- To update some sections of the RMP in accordance with the GVP module VGVP module V – Risk Management Systems (Rev.2), and the Guidance on the format of the RMP in the EU – in integrated format (Rev.2 EMA/PRAC/613102/2015, dated 30 March 2017).

## *3.1. Safety Specification*

## *Epidemiology of the indications and target population*

The MAH has updated some sections regarding epidemiology in the PAH indication and has also included all data of epidemiology concerning the new proposed indication Chronic thromboembolic pulmonary hypertension as detailed below.

**Indication: Chronic thromboembolic pulmonary hypertension**

**Incidence and prevalence of CTEPH**

*Adults*

Based on information collected in European registries, the incidence of CTEPH is estimated to be 2.0–5.7 patients per million population per year .In the US, approximately 1600 new cases of CTEPH are diagnosed each year.

The Orphanet 2018 report estimates the prevalence of CTEPH in Europe to be about 30 cases per mil. Based on data from European PH registries, prevalence estimates range from 15.7–32.0 cases per million adults for CTEPH.

*Paediatrics*

CTEPH is even rarer in children than in adults. In the Netherlands in 2006, the estimated annual incidence rate was 0.1 cases of CTEPH per million children. The Spanish Registry for Pediatric Pulmonary Hypertension published an annual incidence of CTEPH of 0.076 cases per million and a prevalence of 0.22 cases per million in childhood.

**Demographics of the population in CTEPH and risk factors for the disease**

*Demographics of patients with CTEPH*

A median or mean age of 60.3–70.0 years at diagnosis is commonly reported from CTEPH registries There is a similar-to-higher proportion of females with CTEPH (49.9–69.7%) compared to that of males with CTEPH.

*Risk factors for the disease*

A number of risk factors for the development of CTEPH have been identified. A case-control-study comparing 436 consecutive patients with CTEPH with 158 patients with IPAH found that a clinical history of acute venous thromboembolism (VTE), which was reported in 80.2% of CTEPH patients, large previous pulmonary embolism, blood groups other than O, and older age are associated with

CTEPH. Operability of CTEPH patients is strongly associated with younger age, proximal lesions, and pulmonary vascular resistance (PVR) below 1200 dyn.s.cm-5.

*Main existing treatment options*

*Surgery*: pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH and represents a potentially curative option in eligible patients.

PEA surgery involves clearing all obstructive thromboembolic material from the pulmonary arteries, including the intima and superficial media. The aim is to reduce the PVR, to ameliorate right ventricular compromise, and to improve ventilation/perfusion matching .

Although pulmonary thromboendarterectomy is increasingly successful for the definitive treatment of CTEPH, not all patients have surgically accessible disease. Others are poor surgical candidates because of comorbid illness. Therefore, an alternative interventional strategy of balloon pulmonary angioplasty can be used for patients without surgical potential.

*Medical therapy*: for 10–50% of the patients, surgery is not possible (inoperable CTEPH), either due to the distal pulmonary vascular obstruction being surgically inaccessible or to significant comorbidities that may be associated with unacceptably high risk. Riociguat, a guanylate cyclase stimulator administered orally, demonstrated a significant improvement in exercise capacity and PVR in Phase 3 trials with CTEPH patients who were deemed to be inoperable or who had persistent or recurrent PH after undergoing PEA. Riociguat is approved for the treatment of CTEPH in several countries, including the United States, Canada, Japan, and the European Union. However, riociguat cannot be used concomitantly with PDE-5 inhibitors (contra-indication).

*Supportive therapy*: optimal medical treatment for CTEPH consists of anticoagulants, plus diuretics and oxygen in cases of heart failure or hypoxemia. The aim of anticoagulation in CTEPH is to prevent *in situ* pulmonary artery thrombosis and recurrent VTE. Treatment should be continued throughout the patient's life, even after PEA.

*PAH-specific therapy:* as in PAH, ET-mediated vascular remodelling has been demonstrated in animal models of CTEPH, and increased ET levels and $ET_B$ receptor expression have been observed in CTEPH patients. Hence, ERAs appear to be a potential treatment option for inoperable CTEPH.

**Natural history of the indicated condition in the CTEPH population, including mortality and morbidity**

Without therapeutic intervention, the prognosis of patients with CTEPH is poor and depends on the haemodynamic severity. PEA is the treatment of choice for eligible patients as it is the only therapy that can cure the disease.

*Survival estimates in patients with CTEPH*

1) International CTEPH registry

Estimated survival at 1, 2, and 3 years between 2007 and 2009: operated patients (n = 404) 93%, 91%, and 89%, respectively; non-operated patients (n = 275) 88%, 79%, and 70%, respectively.

2) UK

Survival at 1 and 3 years between 2001 and 2006: 88% and 76% for surgical patients (n =236), respectively; 82%, and 70% for non-surgical patients (n = 148), respectively.

3) Portugal (National PH registry) Survival at 1 year: PEA-operated patients between 2008 and 2010 (n = 5) 100%; non-operated patients (n = 28) 92.9%.

4) Spain (REHAP registry)

Survival at 1, 3, and 5 years between 2006 and 2013: operated patients (n = 122) 97%, 91%, and 86%, respectively; non-operated patients (n = 269) 93%, 81%, and 65%, respectively.

**Important comorbidities**

The associated medical conditions among CTEPH patients include: thrombophilic disorder, previous major surgery, varicose veins, obesity, chronic venous insufficiency, prolonged hospitalisation, history of cancer, coronary disease and/or myocardial infarction, thyroid disorder and hormone replacement therapy, family history of deep venous thrombosis or pulmonary embolism, fracture, non-insulin-dependent diabetes mellitus, congestive heart failure, splenectomy, ventriculoatrial shunt, inflammatory bowel disease, and infection of ventriculoatrial shunt or pacemaker.

*PRAC Rapporteur's assessment comment:*

*The MAH has updated of epidemiology in the PAH indication and has added data of epidemiology concerning the new proposed indication Chronic thromboembolic pulmonary hypertension. All these proposed changes in this section are acceptable.*

## *Clinical trial exposure*

The MAH has updated this section including a brief descriptions of all clinical trials available for macitentan and all tables regarding clinical trial exposure ( duration of exposure, age group and gender, dose, ethnic origin) split by data for all indications, doubled-blind randomised studies in PAH, double-blind randomised study in CTEPH, double-blind randomised studies in cardiopulmonary indications other than PAH and CTEPH and doble blind, randomised studies in DUs associated with SSc.

New Information included regarding the new proposed indications is:

AC-055E201 / MERIT-1 (CTEPH): Prospective, randomised, placebo-controlled, double-blind, multicentre, parallel-group, 24-week study to assess the efficacy, safety, and tolerability of macitentan in subjects with inoperable CTEPH. 80 patients were randomised and were treated with once-daily 10 mg macitentan (40 patients) or matching placebo (40 patients). Patients received study treatment (macitentan 10 mg) for a median duration of 24.2 weeks up to a maximum of 25 weeks.

AC-055E202 / MERIT-2 (CTEPH): Long term, multicentre, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability, and efficacy of macitentan in subjects with inoperable CTEPH. Among the 80 patients randomised in MERIT-1, 76 patients were enrolled and treated in MERIT-2 with once-daily 10 mg macitentan. Up to the cut-off date of 17 October 2017, the median treatment duration in MERIT-2 was 80 weeks up to a maximum of 138.3 weeks.

**Table 20 Duration of exposure**

| **Double-blind, randomised study in CTEPH**<br>AC-055E201 | | |
|---|---|---|
| **Duration of exposure** | **Patients** | **Person time (patient years)** |
| < 1 m | 0 | |
| ≥ 1 m | 40 | 18.6 |
| ≥ 3 m | 40 | 18.6 |
| ≥ 6 m | 0 | |
| Total person time for indication | | 18.6 |

**Table 21 Age group and gender**

| **Double-blind, randomised studies in CTEPH**<br>AC-055E201 | | | | |
|---|---|---|---|---|
| ≥ 12 and < 18 years | 0 | 0 | | |
| ≥ 18 and < 65 years | 9 | 17 | 4.2 | 7.9 |
| ≥ 65 and < 75 years. | 2 | 6 | 0.9 | 2.8 |
| ≥ 75 and < 85 years | 3 | 3 | 1.4 | 1.4 |
| ≥ 85 years | 0 | 0 | | |
| Total | 14 | 26 | 6.5 | 12.1 |

**Table 5 Dose**

| **Double-blind, randomised studies in CTEPH**<br>AC-055E201 | | |
|---|---|---|
| 10 mg | 40 | 18.6 |
| Total | 40 | 18.6 |

**Table 22 Ethnic origin**

| **Double-blind, randomised studies in CTEPH**<br>(AC-055E201) | | |
|---|---|---|
| White | 25 | 11.7 |
| Asian | 15 | 6.9 |
| Black | 0 | |
| Other | 0 | |

**Table 23 Duration of exposure in open-label studies**

| **Ongoing open-label extension CTEPH study**<br>AC-055E202[b] | | |
|---|---|---|
| < 1 m | 0 | |
| ≥ 1 m | 76 | 117.7 |
| ≥ 3 m | 72 | 117.1 |
| ≥ 6 m | 71 | 116.6 |
| ≥ 12 m | 68 | 114.3 |
| ≥ 24 m | 12 | 28.2 |
| Total person time for the study | | 117.7 |

*PRAC Rapporteur's assessment comment:*

*The study AC-055E201 / MERIT-1 (CTEPH) for the proposed indication included only 40 patients in treatment with macitentan whilst 76 patients were enrolled and treated in MERIT-2 (open-label extension of MERIT1) with once-daily 10 mg macitentan. The changes proposed in this section are acceptable.*

### *Populations not studied in clinical trials*

Relevant updated data are:

***Limitations in respect to populations typically under-represented in clinical trial development programmes***

**Table 24 Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | The data from the use of macitentan in pregnant women comprise 55 reports pertaining to maternal exposure during pregnancy, including 24 cases from clinical trials and 31 cases observed in the post-marketing setting (cut-off 17 October 2017). Pregnancy should generally be avoided by women with PAH. |
| Breastfeeding women | Not included in the clinical development programme. |
| Patients with relevant comorbidities:<br>• *Patients with hepatic impairment*<br>• *Patients with renal impairment*<br>• *Immunocompromised patients*<br>• *Patients with a disease severity different from inclusion criteria in clinical trials* | There is no clinical experience with the use of macitentan in PAH or CTEPH patients with moderate or severe hepatic impairment. In Phase 1 studies macitentan was well tolerated by 24 patients with hepatic impairment (Child Pugh classes A–C) and based on PK data no dose adjustment is needed in these patients.<br><br>There is no clinical experience with the use of macitentan in PAH or CTEPH patients with severe renal impairment. In Phase 1 studies, macitentan was well tolerated by 8 subjects with severe renal impairment. Caution is recommended in this population. There is no experience with the use of macitentan in patients undergoing dialysis, therefore Opsumit is not recommended in this population.<br><br>In study AC-055-302 (SERAPHIN), 1% of the patients had PAH associated with HIV infection.<br><br>Clinical trials with macitentan have included patients with all stages of the disease (I–IV). |

*PRAC Rapporteur's assessment comment:*

*The changes included in this section are acceptable.*

## *Post-authorisation experience*

The MAH has included this updated information in this section:

SV.1.2 Exposure

Cumulatively, between International Birth Date (IBD) and 31 October 2017, an estimated 41,549 patients have been exposed to commercial macitentan. Macitentan is currently approved in PAH (WHO group 1), and the overwhelming majority of patients for whom an indication was provided had PAH reported as indication.

Estimates for the split of the treated population according to region, gender, and age groups are based on the most recent Periodic Benefit-Risk Evaluation Report / Periodic Safety Update Report (PBRER/PSUR; data cut-off 17 October 2017):

43% of the patients were located in the US, 31% in the EEA, and 26% in other countries.

The split into gender and age groups was estimated based on data collected in the US in the context of controlled distribution; due to local data privacy regulations, such information cannot consistently be collected outside the US.

According to cumulative exposure data from the US, 72% of the exposed patients were females and 28% were males – this matches the gender distribution for the indication of PAH. Adult and elderly patients were the largest age groups (49% and 50%, respectively). Adolescents (12 and 18 years) accounted for 0.5% and children (below 12 years) for 0.2%.

The indications for the use of macitentan were estimated based on adverse event (AE) cases reported to pharmacovigilance: An off-label indication was reported for 3% of the cases; an additional 0.3% of cases referred to patients whose treatment was considered off-label based on age below 12 years (both labelled and off-label indications were reported in these paediatric patients).

| **Sex** | | **Age (years)** | | | | **Region** | | |
|---|---|---|---|---|---|---|---|---|
| *Male* | *Female* | *< 18 y* | *> 18 to 65 y* | *> 65 to 75 y* | *> 75 y* | *EEA* | *USA* | *Other* |
| **~11592** | ~29957 | ~292 | ~20442 | ~11384 | ~9431 | ~12711 | ~17976 | ~10860 |

*PRAC Rapporteur's assessment comment:*

*The updated data included in this section are acceptable.*

## *Identified and potential risks*

The MAH has updated the details of all safety concerns with data of placebo controlled study in CTEPH ( MERIT ) Phase 2 study in CpcPH ( MELODY) and phase 3 in ES( MAESTRO) in PAH. In addition data from PM exposure have also been updated for all safety concerns. (For detailed information please see RMP v9.2 submitted by MAH).

Moreover, section VII.2 "New safety concerns and reclassification with a submission of an updated RMP" has been updated to reflect the reclassification of "symptomatic hypotension" following the PRAC recommendation based on the assessment of the 6th macitentan PBRER/PSUR [PSUSA00010115-201610]. This update was also included in the 5 year renewal application of Opsumit (macitentan)

[EMEA/H/C/002697/R/0027]. At the time of the submission, the CHMP adopted a positive opinion on 28 June 2018 on the renewal of the marketing authorisation of Opsumit.

| |
|---|
| *PRAC Rapporteur's assessment comment:*<br>*The changes implemented in this section are acceptable.* |

## *3.2. Summary of the safety concerns*

**Table SVIII.1: Summary of the Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | Anaemia, decrease in haemoglobin concentration<br>Hepatotoxicity<br>Teratogenicity<br>Symptomatic hypotension |
| **Important potential risks** | Thrombocytopenia<br>Leukopenia<br>Menstrual disorders (primarily bleeding)<br>Ovarian cysts<br>Pulmonary oedema associated with PVOD<br>Testicular disorders and male infertility<br>Off-label use (including in paediatric patients) |
| **Missing information** | Paediatric patients<br>Elderly patients aged > 75 years<br>Patients with moderate to severe hepatic impairment<br>Patients with severe renal impairment and/or undergoing dialysis |

| |
|---|
| *PRAC Rapporteur's assessment comment*<br>*Within current variation, no new safety concerns have been identified by MAH after review of new safety data from CTEPH trials. Although population exposed in CTEPH CTs is very limited , conclusions on clinical safety in this AR describe that the safety profile of macitentan in CTEPH is generally consistent with that observed in the PAH indication. Moreover, it is noted that according to the safety data cumulatively reviewed regarding off-label use in the PSUSA procedures and the recent Renewal procedure (June 2018), review of ADRs cumulatively reported from PM data sources in group 4 Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions of the* |

*clinical classification of PH [Galiè 2016] did not reveal any new safety concern and the safety profile was consistent with that known for macitentan in the approved indication.*

*This new RMP version submitted is the first according to the GVP module V Rev.2, and the MAH has not proposed any change to the list of safety concerns for macitentan. However, the assessors consider that the safety concerns Thrombocytopenia and Leukocytopenia could be removed from the list of safety concern in line with the GVP V-Rev2. Safety information on both risks is included in section 4.8 of the PI as ADRs with frequency common and no specific monitoring is required. No additional pharmacovigilance activities are ongoing or planned to address these risks. Moreover, safety postmarketing available information for both risks to date (safety data up to 17 October 2018 provided in last PSUR currently under assessment) does not show any new relevant emerging issue. Therefore, we are of the opinion that both risks could be removed from the list of safety concerns of RMP for macitentan. No further changes to the list of safety concerns are considered necessary.*

*The MAH is reminded that new safety information on these potential risks no longer categorised as important in the RMP is expected to be included in the PSURs as per GVP module VII.*

## *3.3. Pharmacovigilance plan*

No new additional pharmacovigilance activities have been proposed on the basis of the new proposed indication. Therefore only routine pharmacovigilance activities are proposed to address all the safety concerns.

*PRAC Rapporteur's assessment comment:*

*The Pharmacovigilance Plan remains unchanged. No additional planned pharmacovigilance activities have been proposed regarding the new proposed indication.*

*Since no new safety concerns have been identified with available data to date (from CT and off-label use in PM), it is accepted that routine pharmacovigilance is sufficient to identify and characterise the risks of the product for the time being.*

*As routine pharmacovigilance activities the MAH has included three specific adverse follow-up forms but FUQ for the safety concern Teratogenicity has not been included in the annex 4 or in the table V.3 Summary of risk minimisation measures. The MAH should amend these discrepancies.*

## *Plans for post-authorisation efficacy studies*

No ongoing or planned imposed post authorisation efficacy studies included in the pharmacovigilance plan.

## *3.4. Risk minimisation measures*

This section has been updated according to the Guidance on the format of the RMP in the EU – in integrated format (Rev.2 EMA/PRAC/613102/2015, dated 30 March 2017). For detailed information please see RMP 9.3 submitted by MAH.

## *Routine risk minimisation measures*

No updates of previous routine risk minimisation measures have been proposed related to the new proposed indication.

### *Additional risk minimisation measures*

No new additional risk minimisation measures have been proposed on the basis of the new proposed indication.

*PRAC Rapporteur's assessment comment:*

*Routine and additional risk minimisation measures proposed remain unchanged.*

*The PRAC Rapporteur, having considered the updated data submitted, is of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the new proposed indication.*

### *3.5. Elements for a public summary of the RMP*

The elements for a public summary of the RMP will requirerevision following the conclusion of the procedure.

### *3.6. Annexes*

The annexes have been updated appropriately.

### *3.7. Overall conclusion on the RMP*

☒ The changes to the RMP and the changes to the conditions and obligations of MA could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

## 4. Changes to the Product Information

Please refer to Attachment 1 which includes the proposed changes to the Product Information with assessor's comments.

### 4.1.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

### 4.1.2. Additional monitoring

Not applicable

# 5. Benefit-Risk Balance (Updated on 20 Feb 2019)

## *5.1. Therapeutic Context*

### 5.1.1. Disease or condition

CTEPH is a rare orphan disease that remains largely underdiagnosed [Delcroix M, et al. Ann Am Thorac Soc. 2016;13Suppl.3: S201–S206]. A recent epidemiological analysis suggests that the incidence of diagnosed CTEPH in the USA and Europe ranges from 4–7 cases per million [Gall H, et al. Eur Respir Rev. 2017;26(143): doi: 10.1183/16000617.0121-2016]. CTEPH is one of the leading causes of severe pulmonary hypertension (PH), defined as precapillary PH (mean pulmonary artery pressure [mPAP] ≥ 25 mmHg, mean pulmonary arterial wedge pressure ≤ 15 mmHg) in the presence of non-resolving organized thromboemboli located proximally or more distally in the pulmonary arterial tree (main, lobar, segmental, subsegmental pulmonary arteries) and persisting at least 3 months after the start of anticoagulant therapy [Gopalan D, et al. Ann Am Thorac Soc. 2016;13Suppl.3:S222–S239]. In the classification of Pulmonary Hypertension, PAH corresponds to Group 1 while CTEPH corresponds to Group 4. They are therefore considered as separate conditions [Galié N, et al. Eur Respir J. 2015;46:903–975]. Both PAH and CTEPH are characterized by vascular remodeling, deregulation in vascular cell proliferation and *in situ* thrombosis, leading to increased pulmonary vascular resistance (PVR), abnormal pulmonary vascular tone, progressive right ventricular dysfunction/failure and, ultimately, premature death [Pepke-Zaba J, et al. Circulation. 2011;124:1973–1981].

### 5.1.2. Available therapies and unmet medical need

The treatment of choice of CTEPH is PEA, which is feasible in about 80% and conducted in about 50% of patients. Medical therapy had been developed for technically inoperable patients [i.e., not candidates for pulmonary endarterectomy (PEA)], who are identified on the basis of vascular imaging that indicates distal disease (20% of patients), or those patients who are operable but refuses to have the procedure (30%) [Quadery et al. Eur Respir J. 2018;52(3):doi:10.1183/13993003.00589-2018.]. The same recent review shows a superior survival in patients undergoing PEA (83%) *versus* technically operable disease patients who refuse to undergo surgery (53%) and inoperable due to disease distribution (59%). Therefore, PEA remains the standard of care in these patients. Classification of a patient into the CTEPH subset with distal disease is subjective and, in clinical trials, normally requires the majority vote from the adjudication committee experts.

Riociguat is the only approved therapy for inoperable and persistent/recurrent CTEPH. The lack of full adoption of riociguat as standard of care in inoperable CTEPH could be attributable to several causes, probably being the contraindication of use in combination with PDE-5 inhibitors the more important one. Other PAH therapies, including PDE-5 inhibitors, endothelin receptor antagonists (ERAs), and prostanoid therapies, are also used in CTEPH, despite little randomised trial data to support their use. The off-label use of other PH advanced (PAH-targeted) therapies in inoperable CTEPH, like ERAs, is also reflected in the PH expert guidelines, despite evidence of their efficacy and safety is limited in CTEPH [Galié N, et al. Eur Respir J. 2015;46:903–975]. In a recent publication of the CTEPH EAS registry of riociguat, in 262 patients, 84 (28%) switched to riociguat monotherapy from previous treatment with PAH-approved therapies [58 (19%) from PDE-5inh, 44 (15%) from ERAs and 7 (2%) from beraprost or iloprost], on which they had shown an insufficient clinical response [McLaughlin, et al. BMC Pulmonary Medicine. 2017;17:216]. Of these patients, 24 (8%) were previously receiving combination therapy, including one patient on triple therapy. 6MWD improved 42 m (36 m in switched patients in and 49 in treatment naive patients).

### 5.1.3. Main clinical studies

## *5.2. Favourable effects*

The sponsor's analysis of the main endpoint in the MERIT-1 phase II study (i.e.: change in PVR at Week 16) showed that the ratio of geometric means macitentan/placebo was 0.84 (95% CL: 0.70, 0.99), p = 0.041, i.e., a 16% relative reduction in PVR with macitentan compared to placebo. The median ratio was 0.82 (95%CI: 0.71 to 0.94). There was no statistically significant indication of heterogeneity of treatment effect across the predefined subgroups based on the interaction tests. The treatment effect was similar in the subgroup of subjects who were receiving PH advanced therapy at baseline. Due to the low number of subjects in some subgroups, e.g., male, Asia, Western Europe and WHO FC II, wider 95% CIs (higher variability around the point estimates of treatment effect) were observed. For sensitivity analyses of PVR with corrected values and excluding 4 subjects with incorrect values, the treatment effect at Week 16 was 0.81 (95% CL: 0.69, 0.95) and 0.79 (95% CL: 0.67, 0.93), respectively.

At week 24, the secondary endpoint of 6-min walk distance (6MWD) had increased from baseline by a mean of 35.0 m (SD 52.52) in the macitentan group versus 1.0 m (83·24) in the placebo group (least squares mean difference, ANCOVA: 34.0 m; 95% CI 2.9–65.2, p=0.033). There was no statistical heterogeneity in the treatment effect on exercise capacity across the pre-specified subgroups.

From baseline to Week 24, the majority of subjects (31 patients on macitentan and 29 patients on placebo) did not show a change in the status of WHO FC, while a small number of subjects improved in WHO FC (9 subjects on macitentan and 8 subjects on placebo). Worsening of WHO FC at end of study (week 24) was reported for 0 patients on macitentan and for 3 subjects on placebo (two deaths that were imputed as worsening WHO FC and one patient who worsened from FC III to FC IV). The odds ratio for the proportion of subjects with worsening WHO FC at Week 24 (macitentan 0 patients vs. placebo 3 patients: 0.21; 95%CI: 0 to 1.46, p = 0.0962) favored macitentan. However, this result needs to be interpreted with caution due to small number of subjects with worsening of WHO FC.

For cardiac index and CO (secondary haemodynamic endpoints), clinically meaningful mean increases of 0.43 L/min/m2 or 0.78 L/min from baseline were observed on macitentan at Week 16. On placebo, no change from baseline was observed for cardiac index. The mean change from baseline to Week 16 for cardiac index (macitentan vs placebo) of 0.43 was statistically significant (95% CL: 0.18, 0.67). The LS mean difference of change from baseline to Week 16 for cardiac output (CO) (macitentan vs placebo) of 0.78 was also statistically significant (95% CL: 0.35, 1.20). For other variables including mRAP, mPAP, SvO2 and TPR there was a trend in the change from baseline to Week 16 favoring macitentan, but these changes were not statistically significant.

There were a total of 2 disease progression events in the macitentan group (2 PH-hospitalizations), and 7 events in the placebo group (4 PH-hospitalizations, 1 death due to hemorrhagic stroke and 2 other PH-related disease progressions qualified as AE of PH worsening on day 171 and a SAE of CTEPH progression on day 119). A death due to hemorrhagic stroke was wrongly qualified as a PH-related disease progression. It should have to be qualified as clinical worsening. Anyway, the wrong qualification of the event does not change the conclusions, given that the study was underpowered to detect differences in disease progression.

The pharmacokinetics of macitentan is comparable between CTEPH patients and the previously investigated PAH population. Taking into account the lack of an interaction with the most relevant drugs and the comparable exposure to macitentan and it's major metabolite, the new pharmacokinetic data in combination with previously collected pharmacokinetic data are considered sufficient to support this application.

## *5.3. Uncertainties and limitations about favourable effects*

The MERIT-1 phase II study was not powered to show a robust effect on clinically relevant endpoints recommended in the EMA guideline (EMEA/CHMP/EWP/356954/2008), like exercise capacity, symptoms or to address morbidity-mortality (i.e.: time to clinical worsening, PH-related hospitalizations, PH-related death, all-cause death).

The effect of macitentan on 6MWD in the primary analyses and the sensitivity analyses based on different missing data imputation techniques shows that the effect estimates statistics are not robust and differences are difficult to interpret (see also assessment of Q3, Q4): a1) The main analysis of change in 6MWD using ANCOVA is biased by high variability (SD in mean change in 6MWD from baseline is more than two-fold higher than the mean value) probably due to the presence of extreme values. Therefore, an analysis focused on median would have been more appropriate. Please, discuss; a2) On the other hand, the applicant is invited to comment about the difference in standard deviations in change in 6MWD between the FAS and PP populations, despite no patient was excluded for the PP population in the macitentan group (see 2nd RSI).

With respect to internal consistency, from subgroup analyses it is apparent that most part of the effect on 6MWD is driven by results in Eastern Europe (36 subjects from Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine). In Western Europe the between-treatment difference is of only 6 metres (n=11 patients). However, given the low sample sizes, statistical heterogeneity between subgroups is not statistically significant. In the response to the first RSI, the applicant has shown the disaggregated data on 6MWD by country and center. The point estimate for the effect in 6MWD favoured placebo in most countries, while the trend towards a benefit was only achieved in Russia, Ukraine and Thailand (see assessment of Q11). Particularly in Ukraine, the difference in favour of macitentan was an impressive 122.5 m improvement versus placebo. In this respect: b1) Please, provide the interaction p-value by country for the effect on 6MWD and analyse the results of 6MWD including country as covariate; b2) The applicant is requested to provide a narrative for patient treated with macitentan in one centre in Ukraine, who improved 160 metres in 6MWD from baseline to week 24. Please, also discuss about the chance for a patient with inoperable CTEPH to improve 160 metres from baseline to week 24; b3) As sensitivity analysis, the applicant is requested to show MERIT-1 study results: by excluding that patient; and by excluding one centre in Ukraine (see 2nd RSI).

The high number of important protocol deviations in more than 50% of patients and the fact that these deviations were not at random (much higher in the placebo group) add uncertainties on whether study conduct and oversight was adequate and goes against the robustness of the results. The applicant is invited to discuss on the potential causes for these not at random protocol deviations (see 2nd RSI).

The main sponsor's analysis of 6MWD in MERIT-1 focused on the LS mean difference of the change from baseline to week 24 using an ANCOVA test. This approach does not provide a good estimate of the treatment effect, as change in 6MWD does not follow a normal distribution. The wide range of sensitivity analyses using different tests and imputation models show that the applicant's primary analysis (placebo-corrected 34 m improvement) is very close to the best-case estimation of the effect (36 m), which is 2-fold better than the worst-case estimation (17 m). The use of a non-conservative analysis for an application based on a single pivotal trial, in which the primary analysis should be conservative and the results particularly compelling, is not the preferred situation for taking regulatory decisions. As the primary outcome does not follow a normal distribution, an appropriate test for the analysis of 6MWD should assume that the data are not normally distributed, are subject to high inter-individual variability and would be based on median rather than mean values. Therefore, a better estimate would be the Hodges-Lehmann estimate associated with the stratified Wilcoxon test, included in one of the sensitivity analyses. The Hodges-Lehman estimate shows a 17 meter median difference that is not statistically significant. Similar non-significant results are obtained in sensitivity analyses using BOCF and LOCF imputation methods and also in the per protocol analysis without imputation.

Regarding the clinical relevance of the effect, a 17 m difference using the Hodges-Lehman estimate, or 18 m using the per protocol population, or 19 m difference in median values, which is probably closer to the real effect than the primary outcome estimation, is difficult to put into the perspective of clinical relevance and correlation with patient outcome. In order to assess the clinical relevance of the effect of macitentan in the MERIT-1 study, the applicant has provided exploratory analyses of the said study using different responder threshold criteria according to a previous analysis published with riociguat in the CTEPH indication [D'Armini, et al. Use of responder threshold criteria to evaluate the response to treatment in the phase III CHEST-1 study. J Heart Lung Transplant. 2015;34:348-55]. The responders' analyses are also supportive of a lack of clinically meaningful effect (see also assessment of Q13 and Q15). The applicant is invited to comment (see 2nd RSI).

The applicant has also provided an analysis of 6MWD during the MERIT-2 open-label cohort. In the macitentan 10 mg MERIT DB/OL cohort, the change from DB observed at the end of MERIT-1 persisted in MERIT-2 (i.e., 12 months overall), which means that no additional improvement or worsening in 6MWD was achieved during the OL period in those patients that had received macitentan 10 mg during MERIT-1.

The applicant states that an improvement in 6MWD (a mean change from DB baseline of 19.8 m) after 6 months on macitentan in MERIT-2 was observed in subjects who had received placebo in MERIT-1 (placebo/macitentan 10 mg MERIT DB/OL cohort). However, the said analysis is misleading, as the baseline values chosen to justify a 19.8 m mean increase in 6MWD during MERIT-2 study are the baseline values of the MERIT-1 study. Baseline values of the open-label MERIT-2 should have been used instead. Table 14 of the Integrated Summary of Efficacy (Module 5.3.5.3) shows that the mean improvement from OL baseline in patients that were on placebo and are switched to macitentan is of only 2 metres (mean) or 5 metres (median) at 6 months after switching. Therefore, the analysis of MERIT-2 suggests no effect of macitentan in 6MWD after switching from placebo.

In the response to the 1st RSI, the applicant has provided a post-hoc exploratory subgroup analysis of the exploratory secondary outcome of 6MWD depending on time since CTEPH diagnosis (≤ 6 months vs. > 6 months). The p-value for interaction is 0.3504, thus far beyond of being statistically significant, and therefore it cannot be concluded whether the effect of macitentan may be lower or higher when there is a delay in starting treatment. The applicant has also provided several post-hoc analyses of the secondary outcome of 6MWD during the open label phase of the MERIT study (MERIT-2). It worth mentioning that there is high variability, as shown by a SD much higher than the point estimate for change in 6MWD in most cases. In addition, four imputed values in the former placebo group (1 death and 3 other missing values) substantially impact the ability to illustrate the treatment effect in this cohort, as comparatively low OL baseline values are carried forward. These limitations prevent from concluding whether there was or there was not an increase in 6MWD when patients were switched from placebo to macitentan. In summary, data on 6MWD from MERIT-2 are not assessable due to important limitations (small sample size, high variability, lack of control group, high dependence on whether imputed or observed data are considered and on the imputation methods applied). Although it is counterintuitive that a sick symptomatic patient with CTEPH can benefit from an early start of treatment, the results of MERIT-1/2 study are exploratory and cannot confirm whether the effect of macitentan is higher when started in patients < 6 months since CTEPH diagnosis or > 6 months since diagnosis. Therefore, the uncertainties about the potential benefit from treatment with macitentan in the MERIT-1 study in terms of statistical significance and clinical relevance are applicable to the overall study population, regardless of time since diagnosis, and also to patients in whom start of treatment is delayed for more than 6 months and then are switched to macitentan (MERIT-2).

There was no symptomatic benefit with macitentan. From adjusted model, the mean change from baseline to Week 24 did not show a statistically significant difference between treatment groups in BDI at week 24 (−0.39, 95% CL: −1.21, 0.43, p = 0.3492). The point estimate was far beyond the 0.9 units that are considered the minimal important difference in BDI in patients with PAH [Khair RM, et al. Ann Am Thorac Soc. 2016;13(6):842-9]. The applicant, in the response to the 1st RSI, has provided additional responders' analyses, which are also supportive of a lack of clinically meaningful effect (see also assessment of Q13 and Q15). The applicant is invited to comment (see 2nd RSI).

Quality of Life assessed by PAH-SYMPACT symptom and impact part scores and EQ-5D scores did not show differences in clinical significance between macitentan and placebo.

With respect to the change in PVR (main endpoint), the adjusted model in PPS showed no statistically significant results at Week 16 (mean ratio macitentan/placebo: 0.87; 95%CI: 0.73 to 1.04; p=0.1302) probably due to lack of statistical power after excluding patients with protocol deviations. Despite having in mind this important limitation, the absolute 120 dyn·s/cm$^5$ placebo-corrected decrease in PVR with macitentan is very similar to the -127 dyn·s/cm$^5$ decrease in PVT observed with bosentan in the BENEFiT study [Jais et al, *J Am Coll Cardiol.* 2008;52:2127–34] (this indication is not approved for bosentan), and lower than the - 246 dyn·s/cm$^5$ decrease in PVT achieved by riociguat in the CHEST-1 study [Ghofrani et al, *N Engl J Med.* 2013;369: 319–29].

The MERIT-1 study excluded patients with persistent or recurrent CTEPH after surgical treatment, and also taking concomitant treatment with riociguat. Therefore, no data on the whole spectrum of patients with CTEPH or in those receiving the only approved therapy for CTEPH are available. The Company has submitted a brief analysis of patients on macitentan plus SGC (n=27) in the OPUS registry compared with those on macitentan without sGC (n=18). PH hospitalisations were higher in patients on macitentan+sGC (38%) than in patients on macitentan only (17%), which could be related to a more advanced disease in patients needing combination therapy. In fact, population in the OPUS registry is approximately 10 years older than the one included in the MERIT-1 study (mean age: 65 years in OPUS vs. 58 years in MERIT-1). Anyway, the information is very scarce to draw any meaningful conclusion about the efficacy and safety of macitentan with or without concomitant riociguat. There is a significant amount of missing data in the OPUS registry, with only 25 of 45

patients (55%) having data available on WHO FC and only 15 of 45 patients (33%) having data on 6MWD.

The applicant has provided clarifications about the ambiguous GCG statement included in the initial submission. The applicant confirms that all studies listed in the GCP statement in Module 1.9 have been *conducted within and outside of the European Union and meet the ethical requirements of Directive 2001/20/EC.* As stated in section 9.7.3 of the MERIT-1 CSR [Module 5.3.5.1 D-17.097], independent auditing was conducted by the Actelion GQM department according to Actelion SOPs. The audit certificates were provided in appendix 16.1.8. of the CSR.

In the Rapporteur's view, as the body of the data provided is clearly insufficient to grant the pursued indication, a triggered inspection of the MERIT-2 study is not needed.

## *5.4. Unfavourable effects*

In MERIT-1, the proportion of subjects with SAEs was numerically lower in the macitentan group (3 subjects, 7.5%) than in the placebo group (7 subjects, 17.5%).

More patients on macitentan had AEs associated with edema and fluid overload (10 subjects, 25.0%) compared with placebo (4 subjects, 10.0%). In addition, more patients on macitentan had at least one AE associated with anemia or decreased hemoglobin (7 subjects, 17.5%) compared with placebo (1 subject, 2.5%). AEs for elevations in aminotransferases (< 3 × upper limit of the normal range) were numerically lower in patients on macitentan (0 subjects) compared with placebo (3 subjects).

Elderly patients had more AEs than patients <65 years old, mainly at expenses of gastrointestinal disorders (53.6% vs. 25.0%), Infections and infestations (53.6% vs. 41.7%), and General disorders and administration site conditions (39.3% vs. 29.2%). AEs denoting anemia were reported more frequently in female subjects treated with macitentan compared to male subjects (29.2% vs. 17.9%). The same imbalance between females and males was found for Edema/fluid retention AESIs (female 29.2% vs. male subjects 21.4%) subjects). The trend of increased rates of AEs in the elderly and in females is consistent with that reported in the PAH.

Analysis of AEs in subpopulations of MERIT-1 shows a higher proportion of subjects with PH advanced therapy at baseline in both treatment groups had edema/fluid retention AESIs (29.2% macitentan vs. 12.0% placebo) compared to subjects without PH advanced therapy (18.8% macitentan vs. 6.7% placebo). Patients on concomitant PH therapies represent a higher risk population with a more advanced disease. Increased risk of AESIs is not unexpected. The low number of events, as well as the presence of concomitant confounding factors (more subjects in the macitentan group presented edema as a concomitant disease at baseline and more subjects in the macitentan group were receiving a dihydropyridine derivative compared to the placebo group) prevent from any meaningful conclusion.

Additional safety data from MERIT-2 1-year open-label extension, OPUS registry and Argus safety database did not identify new or unexpected safety observations beyond the established safety profile in the PAH indication.

## *5.5. Uncertainties and limitations about unfavourable effects*

The number of AEs and patients in MERIT-1 was very limited and therefore the results are subject to high imprecision. Additional safety data provided (MERIT-2 1-year open-label extension, OPUS registry and Argus safety database) are also very limited and lack a control group. Data available suggests a safety profile similar to the PAH indication. However, in the absence of prospective comparison, either in head-to-head or add-on design versus or on top of riociguat, the safety of macitentan in the new indication is difficult to be ascertained.

In the response to the 1st RSI, the MAH has provided the additional safety data analyzed since the CTEPH submission to the EMA on 28 August 2018, which includes: 1) Post-marketing experience (spontaneous AE reporting) up to 18 October 2018 (18 October 2017 in the Summary of Clinical Safety) including reports from the off-label use of macitentan, in particular in the CTEPH population; and 2) Additional safety data from the combined OPUS and OrPHeUS databases. The data provided do not raise new safety concerns with the combination of macitentan with riociguat. In addition, the company has collected 720 cases from the Actelion Drug Safety Database Argus with a medical history of CTEPH "CTEPH population" and concomitant use of riociguat in 143 cases. These data show that an

observational study is not required to further characterise the safety of the product in the proposed indication. But these data also provide information that there are many potential candidates to be included in a confirmatory clinical trial what in our opinion is still considered necessary to demonstrate the efficacy in CTEPH.
It is also important to note that patients with persistent CTEPH after surgery were excluded. Therefore, no safety data are available in this important subgroup, which contrasts with the data available for riociguat in the whole spectrum of CTEPH patients (i.e.: operable and inoperable).

## *5.6. Effects Table*

**Effects Table for Opsumit (macitentan) versus placebo in patients with CTEPH (MERIT-1 study)**

| Effect | Short description | Unit | Macitentan 10 mg OD | Placebo | Uncertainties / Strength of evidence | Refs. |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PVR | Change in Pumonary Vascular Resistance at week 16 vs. baseline | Dyn.sec /cm$^5$ (SD) | -206.1 (±450.39) | -85.8 (±301.7) | Mean ratio vs. placebo: 0.84 (95%CI, 0.70 to 0.99), p=0.041.<br><br>High variability, no statistical significance achieved in the PP analysis. Relevant improvement in cardiac index and pro-BNP but not in other haemodynamic parameters. | * |
| 6MWD | Change in 6-minute walk distance at week 24 vs. baseline | Metres (SD) | 35.0 (±52.52) | 1.0 (±83.24) | Mean difference vs. placebo, metres: 34.04 (95%CI, 2,9 to 65.2), p=0.0326.<br><br>Best-case estimate using ANCOVA and mean, despite data do not follow normal distribution. High variability, lack of robustness with a 16-18 m point estimate and no statistical significance achieved in the PP analysis with no imputation, Hodges-Lehman test with median levels and LOCF and BOCF imputation methods. | * |
| BDI | Change in Borg Dyspnoea Index at week 24 vs. baseline | Score points (SD) | -0.01 (±1.86) | +0.3 (±2.04) | Mean difference vs. placebo, points: -0.39 (95%CI, -1.21 to 0.43), p=0.4392.<br><br>Neither statistically nor clinically relevant improvement. | * |
| **Unfavourable Effects** | | | | | | |
| SAES, including deaths | Serious adverse events | n (%) | 3 (7.5) | 7 (17.5) | High imprecision. Low number of events. None of the SAEs was drug-related. | * |
| Anemia or Hb decrease | Defined as AE of special interest | n (%) | 10 (25) | 4 (10) | High imprecision. Low number of events. Result consistent with macitentan's known safety profile. | * |
| Oedema and fluid overload | Defined as AE of special interest | n (%) | 7 (17.5) | 1 (2.5) | High imprecision. Low number of events. Result consistent with macitentan's known safety profile. | * |
| Transaminase elevations | Defined as AE of special interest | n (%) | 0 (0) | 3 (7.5) | High imprecision. Low number of events. | * |

* MERIT-1 Clinical Study Report. Module 5.3.5.1 [Ghofrani, et al. Lancet Respir Med. 2017;5:785-94]
6MWD = 6-minute walk distance; AE = adverse event; BDI = Borg Dyspnoea Index; CI = confidence interval; Hb = haemoglobin; PVR = Pulmonary Vascular Resistance; SAEs = serious adverse events; SD = standard deviation.

## *5.7. Benefit-risk assessment and discussion*

### 5.7.1. Importance of favourable and unfavourable effects

The efficacy data provided are insufficient to draw any meaningful conclusion about the favourable effects of macitentan in the outcome of patients with CTEPH. The MERIT-1 phase II study, submitted as pivotal in current variation application, was not powered to show a robust effect on clinically relevant endpoints, like exercise capacity, symptoms or to address morbidity-mortality (i.e.: time to clinical worsening, PH-related hospitalizations, PH-related death, all-cause death). Macitentan showed a modest effect in PVR and a trend to improvement in exercise capacity, while data on PH-worsening or mortality are very scarce and there was no benefit is expected in improvement of symptoms (i.e.: BDI) or quality of life in MERIT-1. In addition, patients with persistent CTEPH after surgery were excluded. Therefore, no efficacy data are available in this important subgroup, which contrasts with the data available for riociguat in the whole spectrum of CTEPH patients (i.e.: operable and inoperable). Furthermore, concomitant treatment with riociguat was not allowed in the MERIT-1 study. Therefore, in the absence of prospective comparison, either in head-to-head or add-on design versus or on top of riociguat, which is the only approved drug in CTEPH patients, the efficacy of macitentan in the new indication is difficult to be ascertained.

With respect to unfavourable effects, data available suggests a safety profile similar to the PAH indication. However, given the low number of patients with CTEPH studied and the lack of prospective comparison, either in head-to-head or add-on design with riociguat, the safety of macitentan in the new indication is also difficult to be ascertained.

### 5.7.2. Balance of benefits and risks

The results of the MERIT-1 are not robust enough to grant an indication in patients with inoperable CTEPH. According to the EMA guideline on applications based on one pivotal study (CPMP/EWP/2330/99), in cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling in terms of internal and external validity, clinical relevance and degree of statistical significance. In this respect, there should be no indications of potential bias, the estimated size of treatment benefit must be large enough to be clinically valuable and a degree of statistical significance considerably stronger than $p<0.05$ is usually required, accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. None of these features are entirely applicable to the MERIT-1 study.

Analyses of 6MWD in the per protocol population (not significant) and sensitivity analyses (significance obtained using non-conservative tests and some imputation methods, but not achieved when conservative tests, no imputation or imputation based on BOCF or LOCF were applied) shows that the results on exercise capacity are not robust. The point estimate for the effect in 6MWD favoured placebo in most countries, while the trend towards a benefit was only achieved in Russia, Ukraine and Thailand. Particularly in Ukraine, the difference in favour of macitentan was an impressive 122.5 m improvement versus placebo.

The high number of important protocol deviations in more than 50% of patients and the fact that these deviations were not at random (much higher in the placebo group) add uncertainties on whether study conduct and oversight was adequate and goes against the robustness of the results. The applicant is invited to discuss on the potential causes for these not at random protocol deviations.

In addition, the macitentan effect on symptoms (BDI), disease progression, change in WHO functional class were neither statistically nor clinically relevant. The additional responders' analyses submitted are also supportive of a lack of clinically meaningful effect (see 2nd RSI).

Despite some similarities, PAH and CTEPH are different diseases due to different causes (i.e.: primary or secondary vasoconstriction in PAH versus thromboembolism in CTEPH). Although safety can be extrapolated to some extent from PAH to CTEPH, dedicated pivotal study/ies using a morbidity/mortality or exercise capacity primary endpoint are needed to assess the efficacy of the compound in CTEPH.

Therefore, the Rapporteur is of the opinion that the results of the MERIT-1 study are not robust enough to be included in the SmPC, either as a new indication in section 4.1, or even only described in section 5.1.

### 5.7.3. Additional considerations on the benefit-risk balance

Despite across study comparisons are fraught with risk, the point estimates for the effects of macitentan on PVR and 6MWH are quite modest compared with those obtained with riociguat, the only approved drug in the CTEPH indication. Compared with previous applications (i.e.: riociguat, which is the only approved PH therapy in the indication of CTEPH), the absolute 120 dyn·s/cm$^5$ placebo-corrected decrease in PVR with macitentan is much lower than the - 246 dyn·s/cm$^5$ decrease in PVT achieved by riociguat in the CHEST-1 study [Ghofrani et al, *N Engl J Med.* 2013;369: 319–29]. The placebo-corrected improvement in 6MWD with macitentan (point estimate between 17 m to 36 m depending on the test/imputation method used) is also lower than the 46 m improvement achieved by riociguat in the CHEST-1 study [Ghofrani et al. *N Engl J Med.* 2013;369: 319–29]. In addition, the results with riociguat were highly statistically significant in the ITT analysis (Difference: 45.69 m; 95% CI: 24.74 m to 66.63 m; p<0.0001), in the Per Protocol analysis (52.24 m; 95% CI: 30.53 m to 73.95 m, p<0.0001) and in sensitivity analyses [Adempas EPAR. EMA/CHMP/734750/2013]. These results are much more robust than those achieved with macitentan in the MERIT-1 study.

## *5.8. Conclusions*

The overall B/R of Opsumit (macitentan) in the treatment of inoperable patients with CTEPH is still negative.

**Rapporteur's view:**
Despite some similarities, PAH and CTEPH are different diseases due to different causes (i.e.: primary or secondary vasoconstriction in PAH versus thromboembolism in CTEPH). Although safety can be extrapolated to some extent from PAH to CTEPH, dedicated pivotal study/ies using a morbidity/mortality or exercise capacity primary endpoint are needed to assess the efficacy of the compound in CTEPH. Different compounds have shown different degrees of effect in exercise capacity. In one RCT (BENEFIT) bosentan was shown to have significant effects on pulmonary haemodynamics, but not on 6MWT. In another study, sildenafil resulted in a non-significant increase in 6MWT. As such, CHEST-1 study with riociguat is the only study to show both statistically and clinically relevant improvements in 6MWT, pulmonary haemodynamics, pro-PNB, and FC WHO [Riociguat EPAR. January 2014; Available from: https://www.ema.europa.eu/documents/assessment-report/adempas-epar-public-assessment-report_en.pdf].
In the Rapporteur's view, the data provided for macitentan are not robust enough to grant an indication in patients with CTEPH.

**Co-Rapporteur's view:**

The overall B/R of Opsumit (macitentan) in the treatment of inoperable patients with CTEPH is still negative. The Rapporteurs' assessment of the responses and the raised MO concerning the robustness of the effect of macitentan on the 6MWD is supported. Given the discussions in the AR about the heterogeneity of the data presented and the large number of protocol violations reported the need for a GCP inspection of the pivotal study should be discussed.

# Annex 1: Rapporteur's proposed Request for Supplementary Information (first RSI)

## *Major objections*

### Non clinical aspects

None.

### Clinical pharmacology aspects

None.

### Clinical efficacy aspects

1. The benefit shown in the MERIT-1 study is currently insufficient to grant an indication in patients with inoperable CTEPH and needs further discussion and justification regarding:

- The effect of macitentan on PVR and 6MWD in the primary analyses and the sensitivity analyses based on different missing data imputation techniques shows that the effect estimates statistics are not robust and differences are difficult to interpret.

- The macitentan effect on clinical endpoints was neither statistically nor clinically relevant.

### Clinical safety aspects

None

### RMP

None

## *Other concerns*

### Non clinical aspects

2. The Applicant is requested to revise the $F_{pen}$ refinement with European disease prevalence data published by a reliable and independent source as recent as possible

### Clinical pharmacology aspects

None.

### Clinical efficacy aspects

3. The Applicant is requested to discuss the reasons for the important protocol deviations in MERIT-1 and the possible implications of these on the efficacy outcome (PVR and 6MWT),

especially since the percentage of patients with important protocol deviations was substantial and there is an imbalance between the macitentan and placebo group.

4. The Applicant is asked to discuss what estimand would be most suitable to describe the treatment effect in the population proposed (see ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials).

5. The study report states that administration of ERA, guanylate cyclase stimulators, L-arginine, intravenous or subcutaneous prostanoids, or any investigational drug (other than study drug) was not permitted from 1 month prior to baseline RHC and Randomization (excluding acute administration during a catheterization procedure to test vascular reactivity). Please, detail how many patients were withdrawn these medications 1 month before randomization just to fulfill with study inclusion criteria. If these data are known, please provide the efficacy results separately for patients who withdrew PAH-specific medications and for those who did not.

6. The Applicant is requested to justify that all patients received optimal standard of care, considering that according to the ESC/ERS guideline optimal medical treatment for CTEPH other than PAH medication consists of anticoagulants and diuretics and that not all patients received diuretics at baseline in MERIT-1 (72.5% and 80.5% of the subjects in the macitentan and placebo group, respectively).

7. Most of the 25 studies included in the list of the GCP statement are not included in the submission, while study AD-055E202 (MERIT-2, which is an open label extension of the "pivotal" phase II study MERIT-1), is included in the submission as supportive, but not included in the list of studies in the GCP statement. Please clarify.

8. According to European regulation, applications based on a single pivotal trial should be particularly compelling. In this case, the applicant's GCP statement provided is ambiguous on whether all studies, or only a part of them, are GCP compliant. This issue should be clarified. In addition, the results of any audits or inspections available for this clinical trial should be submitted.

9. The applicant is invited to discuss about the potential off-label use of the product in operable patients who refuse surgery, and to clarify if some of the patients recruited into the OPUS registry correspond to this patient’s subset.

10. The Applicant is requested to clarify why only few patients from West-Europe were included and why no patients from the USA have been recruited into the MERIT-1 study and whether this has to do with the approval and availability of Adempas for the treatment of CTEPH at the time of initiation of the MERIT-1 study.

11. With respect to internal consistency, from subgroup analyses it is apparent that most part of the effect on 6MWD is driven by results in Eastern Europe (36 subjects from Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine). In Western Europe the between-treatment difference is of only 6 metres (n=11 patients). However, given the low sample sizes, statistical heterogeneity between subgroups is not statistically significant. The applicant is requested to show the disaggregated data on 6MWD by country and center, in order to ascertain if there is an outlier center driving the positive trend on 6MWD

12. ERAs have a well defined AE profile, and it should be ruled out that patients with recognizable ERA-related AEs have no better performance in the 6MWD than those patients without these AEs due to unblinding (i.e.: ascertainment bias). The applicant is invited to provide sensitivity analyses in patients with and without ERA-related AEs.

13. In order to assess the clinical relevance of the effect of macitentan in the MERIT-1 study, the applicant is invited to provide exploratory analyses of the said study using different responder threshold criteria according to a previous analysis published with riociguat in the CTEPH indication [D'Armini, et al. Use of responder threshold criteria to evaluate the response to treatment in the phase III CHEST-1 study. J Heart Lung Transplant. 2015;34:348-55].

14. Subjects who received placebo in the MERIT-1 study showed a lower beneficial effect after 6 months of treatment in the OLE MERIT-2 study (19.8 m) compared with the macitentan group in MERIT-1 at Week 24 (34.0 m). A plausible explanation for this observation is that patients who received placebo during the blinded treatment period in the MERIT-1 study progressed to more irreversible disease, suggesting that patients can only benefit from treatment with macitentan when macitentan therapy is initiated as early as possible after the development of CTEPH. Notably, the time since diagnosis of CTEPH was 0.44 years in the macitentan group and 0.56 years in the placebo group of the MERIT-1 study. The Applicant is requested to discuss if this can have influenced the efficacy results.
    Furthermore, Table 14 of the Integrated Summary of Efficacy (Module 5.3.5.3) shows that the mean improvement from OL baseline in patients that were on placebo and are switched to macitentan is of only 2 metres (mean) or 5 metres (median) at 6 months after switching whwn baseline data for MERIT-2 are considered. Therefore, the analysis of MERIT-2 suggests no effect of macitentan in 6MWD after switching from placebo. The applicant is invited to comment.

15. The point estimate for BDI was far beyond the 0.9 units that are considered the minimal important difference in BDI in patients with PAH [Khair RM, et al. Ann Am Thorac Soc. 2016;13(6):842-9], which is against a meaningful effect in relief of symptoms. The company is invited to provide a post-hoc responder analysis showing the rate of patients with a >0.9 unit improvement vs. baseline (i.e.: above the minimal) per treatment group.

16. Quality of Life assessed by PAH-SYMPACT symptom and impact part scores and EQ-5D scores did not show differences in clinical significance between macitentan and placebo. Please comment.

17. It is unknown why a death due to hemorrhagic stroke in the placebo group of the MERIT-1 study was qualified as a PH-related disease progression. Please, discuss.

18. The applicant is requested to clarify, why the Kaplan-Meier curve of time to PH-related disease progression only included 5 events in the placebo group, whereas 7 placebo subjects were reported to have PH-related disease progression.

19. Regarding the MERIT-2 study the MAH is requested to explain the apparent lack of consistency between the change in 6MWD at Month 6 for the patients on placebo in MERIT-1 shown in Table 13 and Figure 8 of the JAR.

## Clinical safety aspects

20. The applicant is invited to provide information about planned studies to further assess the safety profile of macitentan in CTEPH standard practice (i.e.: in comparison with riociguat or on top of riociguat) upon an eventual approval of the new indication.

21. Analysis of AEs in subpopulations of MERIT-1 shows a higher proportion of subjects with PH advanced therapy at baseline in both treatment groups had edema/fluid retention AESIs (29.2% macitentan vs. 12.0% placebo) compared to subjects without PH advanced therapy (18.8% macitentan vs. 6.7% placebo). Patients on concomitant PH therapies represent a higher risk population with a more advanced disease. Increased risk of AESIs is not unexpected. Anyway, the applicant is invited to discuss whether this increase in AESIs could be due, at least to some extent, to drug-drug PK or PD interactions between macitentan and other drugs used in patients with CTEPH.

22. The Applicant is requested to clarify that, although considered as treatment-related, hematuria has not been proposed to be included as an ADR in section 4.8 of the SmPC.

## RMP

23. Taking into account the GVP V Rev2 the MAH is asked to further discuss and review whether changes to the list of safety concerns for macitentan are needed.

24. The MAH should include the FUQ for the safety concern "Teratogenicity" as routine pharmacovigilance activity in all the pertinent sections of RMP as appropriate.

25. The MAH should provide the specific follow up forms in full in annex 4- Specific adverse drug reaction follow-up forms.

26. The Annex 6 should be updated taking into account only the risks that need additional risk minimisations measures and the key messages of educational material.

27. The elements of the public summary of the RMP will require revision following the conclusion of the procedure.

# Annex 2: Rapporteur preliminary assessment report of the MAH responses to the Request for Supplementary Information

## *Major objections*

## Clinical efficacy aspects

***Question 1***

***The benefit shown in the MERIT-1 study is currently insufficient to grant an indication in patients with inoperable CTEPH and needs further discussion and justification regarding:***

- ***The effect of macitentan on PVR and 6MWD in the primary analyses and the sensitivity analyses based on different missing data imputation techniques shows that the effect estimates statistics are not robust and differences are difficult to interpret.***

- ***The macitentan effect on clinical endpoints was neither statistically nor clinically relevant.***

***Summary of MAH answer***

The development of macitentan for the treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) should be considered in view of the similarities between CTEPH and pulmonary arterial hypertension (PAH), as supported by literature [Pepke-Zaba 2011, Delcroix 2016, Sitbon 2016] and acknowledged in the riociguat European public assessment report (EPAR) [Adempas EPAR 2014]. In addition, the AC-055-E201/MERIT-1 study results should be evaluated in the context of the well-established efficacy and safety profile of macitentan in PAH, the rarity of CTEPH, and the unmet medical need for additional therapies for the treatment of CTEPH despite the availability of riociguat.

The applicant is of the opinion that, overall, the MERIT-1 study results provide evidence of the efficacy of macitentan on both pulmonary vascular resistance (PVR) and 6-minute walk distance (6MWD) in CTEPH patients with inoperable disease.

Results of the pre-specified primary and main secondary endpoints analyses show clinically and statistically significant beneficial effects of macitentan on hemodynamics at Week 16 (PVR: geometric mean ratio = 0.84, p = 0.041) and on 6MWD at Week 24 (34 m, p = 0.0326). The results on the Full analysis set (FAS) are confirmed by the per-protocol analyses on both PVR and 6MWD when correcting for 4 incorrect/non-plausible cardiac output (CO) and pulmonary artery wedge pressure (PAWP) values (geometric mean ratio of PVR = 0.84, p = 0.0388), and when considering an eligible population with relevant definition of intercurrent events for the 6MWD (41.66 m, p = 0.0118). Details are presented below and in the response to Question 4. Also, macitentan showed a clinically relevant and consistent treatment effect on both the PVR (0.84) and the 6MWD (32.4 m) in the FAS in the pre-specified subgroup of patients on background PAH-specific therapy at baseline, which was similar to that observed in the naïve patient population.

In the applicant's opinion, the MERIT-1 study has internal validity, as evidenced by the clinically relevant results on both PVR and 6MWD, which remain robust across sensitivity analyses and estimands applied.

For PVR, results of all sensitivity analyses of the main estimator for all estimands are clinically meaningful and statistically significant when accounting for corrected PVR values, with the macitentan effect size ranging between 0.80 and 0.84 compared to placebo at 16 weeks (corresponding to a 16–

20% decrease in PVR). This treatment effect was observed despite the unexpected, and to the applicant's knowledge, unprecedented decrease in PVR seen in the placebo group.

For 6MWD, all sensitivity analyses confirm the results of the main estimators: the sensitivity analyses on the FAS population using multiple imputations / analysis of variance [ANOVA] / extended analysis of covariance [ANCOVA] / repeated measures, all show clinically relevant effect ranging from 23 to 36 m (Estimand 1 – FAS) increase in 6MWD vs placebo at 24 weeks. In the new Per-protocol set (PPS) for 6MWD, macitentan shows a statistically significant and clinically relevant improvement ranging from 23 to 45 m compared to placebo (Estimand 3 – New PPS/6MWD PPS [Table 23]) in the main estimator as well as in all sensitivity analyses. It is acknowledged that confidence limits (CL) in some sensitivity analyses using a single imputation method under strong and very conservative assumptions include 0. Nonetheless, these analyses are consistent with the more relevant primary analysis, with similar treatment effect estimates, thus supporting the primary analysis conclusions.

In addition to the statistical significance noted consistently across the different sensitivity analyses as summarized above and detailed below, the magnitude of these improvements in both PVR and 6MWD are definitely clinically relevant and meaningful.

The assessment of the macitentan treatment effect on clinical endpoints is hampered by the fact that too few events occurred in 24 weeks to allow for a sound statistical estimation of the treatment effect on such events. During the 24-week study period, 3 patients in the placebo group had WHO functional class (FC) worsening compared to no patients in the macitentan group. This translates to an odds ratio (OR) of 0.21 (p = 0.0962). A clinically significant effect on disease progression was observed in the macitentan group (2 events) vs the placebo group (7 events), with respective Kaplan-Meier (KM) event-free rates of 95.0% and 87.5% at 24 weeks. This translates into a hazard ratio (HR) of 0.28 (p = 0.0847) [Table 47]. It is particularly important that the effect is driven by a reduction in hospitalization from 10% on placebo to 5% on macitentan. This is consistent with the effect of macitentan on hospitalization observed in patients with PAH. These findings are supported by the safety analyses showing a lower incidence of adverse events (AEs) indicative of disease worsening in the macitentan group (7.5%) compared to the placebo
group (20%), p = 0.1927) [Table 48]. Overall, these findings provide reassurance regarding the long-term effect of macitentan in CTEPH, which shares pathophysiological and clinical features with PAH.

In the applicant's experience, the Borg dyspnea index (BDI) is not a clinically relevant endpoint in the evaluation of pulmonary hypertension (PH) symptoms. In the published literature as well as in large studies with macitentan or selexipag in PAH (AC-055-302/SERAPHIN and AC-065A302/GRIPHON), no effect on BDI was observed, despite a clinically relevant effect on disease progression.

Although not explicitly requested in the Major Objection (MO), the following additional evaluations were performed:

1) To support the use of macitentan in the treatment of CTEPH, an evaluation of clinical outcomes and safety in the real-world setting was performed. The number of patients included in these analyses was 3-fold higher compared to the population considered in the original submission (144 patients vs 45 patients). The additional real-world data further support the original observation of clinical stability of CTEPH patients on macitentan treatment in this progressive disease [Module 5.3.5.4 D-18.430].

2) External validity of the study and its relevance to the EU population was also assessed. This assessment showed that the MERIT population, with approximately 60% of patients on concomitant PAH advanced therapy, reflects the treatment patterns in the EU based on registry data. These data show that the use of riociguat is less prevalent (approximately 40%) compared to unapproved drugs, such as endothelin receptor antagonists (ERAs) and phosphodiesterase-5 (PDE-5) inhibitors (approximately 60%).

In addition, the baseline characteristics of the MERIT patient population are representative of the characteristics of the wider EU CTEPH patient population. The strict eligibility criteria (including adjudication for operability) used in the MERIT-1 study make the MERIT population representative of the broader inoperable CTEPH population.

3) To address some concerns expressed in the assessment report regarding the comparative efficacy of macitentan and riociguat, an indirect comparison using established methodology (matching-adjusted indirect comparison [MAIC]) was performed. This assessment shows that when the MERIT-1 baseline disease characteristics are weighted for the CHEST-1 population characteristics, macitentan is as

effective as riociguat and may be better tolerated than riociguat [Appendix 2 D-19.020]. It is important, however, to note that the applicant's goal and the MERIT study design were not intended to make any statements regarding comparability of macitentan to riociguat, and any such comparisons are only made to address some of the questions and comments raised by the agency. The applicant believes that the data presented in this application should be assessed purely based on the robustness of the data in comparison to placebo, rather than indirect comparisons to riociguat.

In conclusion, the applicant is of the opinion that the data presented show that macitentan has been adequately studied in patients with inoperable CTEPH, and has good efficacy, safety, and tolerability profiles in this patient population. Macitentan offers a new mode of action and addresses an important unmet medical need for an alternative treatment in this indication. In addition, macitentan is expected to provide significant clinical benefit to a broad group of patients with inoperable CTEPH, including those treated with any background PH advanced therapy, such as PDE-5 inhibitors and soluble guanylate cyclase (sGC) stimulators. The applicant is of the opinion that the data provided support an extension of the indication for the treatment of inoperable CTEPH in adult patients with WHO FC II to III, to improve exercise capacity.

### 1.1.1 Background

Macitentan is developed for the treatment of CTEPH in adult patients of WHO FC II or III deemed inoperable (i.e., not candidates for pulmonary endarterectomy [PEA]). Although considered as separate conditions, similarities between CTEPH and PAH support the development of macitentan for use in patients with inoperable CTEPH [Pepke-Zaba 2011, Delcroix 2016, Sitbon 2016]. As no regulatory guidance for the development of medications in CTEPH exists, the CHMP concluded previously that as the relevant CHMP guideline [EMEA/CHMP/EWP/356954/2008] does not specifically address CTEPH, developing a clinical program in line with that recommended for PAH products is acceptable due to the disease similarities [Adempas EPAR 2014]. The same guideline states that the value of hemodynamic measurements, such as PVR, in the evaluation of the clinical outcome of the medicinal products is not clear. The first secondary endpoint of change from baseline to Week 24 in exercise capacity (6MWD) is considered by the guideline as an appropriate primary endpoint in pivotal studies for the registration of PAH drugs when the proposed indication is restricted to improvement in exercise capacity, and if no negative impact on survival is observed. This is exactly the case for macitentan with the MERIT-1 study.

The MERIT-1 study results should also be evaluated considering the well-established efficacy and safety profile of macitentan in patients with PAH. In the pivotal SERAPHIN study, treatment with macitentan 10 mg was associated with robust effects on the clinically relevant endpoint of morbidity/mortality, and on 6MWD.

The rarity of CTEPH and the unmet medical need for additional therapies should be considered. The treatment pattern of CTEPH patients shows that a minority are treated with riociguat, while the majority are treated with PDE-5 inhibitors and ERAs, despite the lack of controlled clinical data for these drug classes in this indication [Klose 2017, Gall 2016, Pepke-Zaba 2011, Delcroix 2016, Condliffe 2008]. As described in Section 1.1.5, only 43% of patients are on riociguat, while 37% are on PDE-5 inhibitors and 18% are on ERAs.

As mentioned in the assessment report, the relatively limited uptake of riociguat may be due to factors such as the three times daily dose regimen, need for up-titration, drug-drug interactions, and its safety profile. In this setting, macitentan may address a remaining medical need, based on convenience of use, reduced potential for drug-drug interactions, and a well-established safety profile.

### 1.1.2 PVR AND 6MWD

The applicant considers that the results of the MERIT study are robust and show a clinically meaningful and statistically significant effect.

For both 6MWD and PVR, multiple estimands (and sensitivity analyses for each estimand) were defined [see also response to Question 4]. Some of these estimands were pre-specified in the MERIT-1 CSR Statistical Analysis Plan (SAP) (finalized prior to MERIT-1 database lock), while others were defined after the database lock.

In the opinion of the applicant the relevant estimands to compare macitentan vs placebo under hypothesis testing are:

- PVR at Week 16 – Estimand 1 "PVR (FAS Corrected)" which corrects for errors in the calculation of the PVR for 4 subjects from China and Thailand [Question 4 Section 4.1.2]

and
• 6MWD at Week 24 – Estimand 1 "6MWD (FAS)" best tests the treatment effect of macitentan vs placebo on exercise capacity [Question 4 Section 4.1.3] The ANCOVA analysis is considered appropriate and robust to the small deviation from normal distribution of the data, as also acknowledged in the assessment report.

The FAS and PPS analyses as originally planned for 6MWD employed a very conservative approach in applying intercurrent events, which occurred in the placebo group. These events were relevant for PVR but not for 6MWD assessments. Also, the intercurrent event "administration of rescue medication" beyond Week 16 was not considered for 6MWD at Week 24.

Therefore, in the opinion of the applicant, the relevant estimands to quantify the treatment effect of macitentan vs placebo are as follows:
• PVR at Week 16 – Estimand 2 "PVR (PPS Corrected)" which corrects for errors in the calculation of the PVR for 4 subjects from China and Thailand [Question 4 Section 4.1.2] best describes the true effect of macitentan on pulmonary hemodynamics, including eligible population and appropriately handling intercurrent events, while preserving the randomization
and
• 6MWD at Week 24 – Estimand 3 "New PPS/6MWD (New PPS)" best quantifies the treatment effect of macitentan on exercise capacity in eligible inoperable CTEPH patients while on treatment and without intercurrent events (i.e., per protocol setting) [Question 4 Section 4.1.3].

The applicant considers the main estimator for each estimand as more appropriate than sensitivity estimators because of "established" imputation rules (no positive values imputed for subjects who died, similarly to CHEST-1) and statistical analysis (ANCOVA), as discussed in response to Question 4 and summarized below.

#### *1.1.2.1 PVR*

Three main estimands for the primary endpoint (PVR) were prospectively planned in the CSR SAP prior to database lock:
1. "FAS (Full Analysis Set), Not Corrected"
2. "PPS (Per-protocol Set), Not Corrected"
3. "FAS (Difference), Not Corrected"

All pre-planned analyses were performed including 4 PVR values from sites in China and Thailand which, as mentioned in the MERIT-1 CSR [Module 5.3.5.1 D-17.097 section 11.2.1.1], were calculated based on incorrect and clinically implausible values for CO (3 subjects on macitentan) and for PAWP (1 subject on placebo) [Table 16]. These errors impacted estimands for "PVR Not Corrected". Therefore, in this response (as in response to Question 4) the term "not corrected" is used for the pre-planned analyses that included these incorrect values.

Despite the impact of these data on the macitentan arm, the results of the main analysis ("FAS, not corrected") on the primary endpoint of PVR are clinically and statistically significant [Module 2.7.3 D-18.252 section 3.2.2.1] (geometric mean ratio 0.84, p = 0.041).

All sensitivity analyses performed to evaluate the robustness of this estimand confirm an effect size of 14–18% reduction in PVR vs placebo (geometric mean ratios ranging from 0.82–0.86) [Table 1].

The applicant agrees that the second estimand, the per-protocol one ("PPS, Not corrected") did not achieve statistical significance on the ratio of percent change from baseline, or when the analysis was performed, on absolute differences from baseline to Week 16.

**Table 1 Results for the primary endpoint of PVR (Not Corrected)**

| Estimands for Not Corrected PVR | *Geometric mean ratio (macitentan vs placebo, 95% CLs), p-value* |
|---|---|
| **Estimand 1 "FAS, Not Corrected"** | |
| Main Estimator (N = 80) | 0.84 (0.70, 0.99), p = 0.0410 |
| Multiple imputation (N = 80) | 0.84 (0.71, 1.00), p = 0.0456 |
| BOCF (N = 80) | 0.83 (0.70, 0.98), p = 0.0321 |
| Median (N = 80) | 0.85 (0.72, 1.00), p = 0.0557 |
| Extend ANCOVA (N = 80) | 0.86 (0.73, 1.02), p = 0.0883 |
| Hodges-Lehman (N = 80) | 0.82 (0.71, 0.94), p=0.0055 |
| Observed cases only (N = 76) | 0.85 (0.71, 1.02), p = 0.0749 |
| **Estimand 2 "PPS, Not Corrected"** | |
| PPS (N =74) | 0.87 (0.73, 1.04), p = 0.1302 |
| **Estimand 3 "FAS (Difference), Not Corrected"** | ***LS Mean Difference (macitentan – placebo, 95% CLs), p-value*** |
| Difference | -137.73 (-298.20, +22.75), p = 0.0915 |

ANCOVA = analysis of covariance; BOCF = baseline-observation-carried-forward; CL= confidence limit(s); FAS = Full analysis set; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.
Source: Module 5.3.5.1 D-17.097 table 15-33, table 15-35, table 15-36, table 15-39, table 15-41, table 15-42, table 15-44; D-18.062 table 10-27; Appendix 1 Table 45.

To quantifiy the true treatment effect, the corrected PVR values (as mentioned above) are used. These results are presented in Table 2.

**Table 2 Results for the primary endpoint of PVR (Corrected)**

| Estimands for Corrected PVR | *Geometric mean ratio (macitentan vs placebo, 95% CLs), p-value* |
|---|---|
| **Estimand 1 "FAS, Corrected"** | |
| Main Estimator (N = 80) | 0.81 (0.69, 0.95), p = 0.0084 |
| Multiple imputation (N = 80) | 0.81 (0.70, 0.95), p = 0.0090 |
| BOCF (N = 80) | 0.80 (0.68, 0.94), p = 0.0062 |
| Median (N = 80) | 0.82 (0.70, 0.96), p = 0.0121 |
| Extend ANCOVA (N = 80) | 0.83 (0.71, 0.97), p = 0.0225 |
| Hodges-Lehman (N = 80) | 0.80 (0.70, 0.93), p = 0.0038 |
| Observed cases only (N = 76) | 0.82 (0.70, 0.97), p = 0.0189 |
| **Estimand 2 "PPS, Corrected"** | |
| PPS (Corrected, N = 74) | 0.84 (0.71, 0.99), p =0.0388 |
| **Estimand 3 "FAS (Difference), Corrected"** | ***LS Mean Difference (macitentan – placebo, 95% CLs), p-value*** |
| Difference | -189.56 (-308.68, -70.44), p = 0.0022 |

ANCOVA = analysis of covariance; BOCF = baseline-observation-carried-forward; CL= confidence limit(s); FAS = Full analysis set; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.
Source: D-18.062 table 10-2, table 10-4, table 10-6, table 10-8, table 10-10, table 10-12, table 10-14, table 10-22; Appendix 1 Table 70.

The point estimates on the "FAS, corrected", "PPS, corrected" and "FAS (Difference) corrected" are not different from those based on non-corrected values and are between 0.80 and 0.84 [Table 2]. All analyses achieved statistical significance, probably due to exclusion of the PVR outliers, which were calculated using implausible CO or PAWP values as discussed in the CSR [Module 5.3.5.1 D-17.097 section 11.2.1.1]. These "corrected" analyses confirm the effect of macitentan and support the robustness of the results.

Furthermore, the effect on PVR was consistent across all subgroups analyzed and most notably in subjects with PH advanced therapy at baseline, mainly PDE-5 inhibitors (approximately 60%) [Table 3].

**Table 3 PVR analysis in the subgroup of subjects with or without PH advanced therapy at baseline, as reported in the CSR, with corrected hemodynamic values, FAS**

| Subgroup | Geometric mean ratio (macitentan vs placebo, 95% CLs) | |
|---|---|---|
| | As reported in the CSR | Corrected PVR values |
| **PH advanced therapy at status** | | |
| With PH advanced therapy at baseline (N = 49) | 0.84 (0.69, 1.03) | 0.81 (0.69, 0.95) |
| Without PH advanced therapy at baseline (N = 31) | 0.84 (0.62, 1.15) | 0.83 (0.60, 1.13) |
| **p-value (interaction test)** | p = 0.9636 | p = 0.8840 |

CL = confidence limit; CSR = clinical study report; FAS = Full analysis set; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.
Source: Module 5.3.5.1 D-17.097 figure 11-2; D-18.062 figure 10-6.

The effect on PVR is corroborated by consistent and clinically highly relevant effects on the other hemodynamic measurements indicative of improvement in global cardiac performance. Specifically, a significant improvement in CO likely reflects improved left ventricular mechanics (and filling), at least partly mediated through ventricular interdependence [Tonelli 2012]. The relevance of these findings is also supported by a favorable effect on mean right atrial pressure (mRAP), which in pre-capillary PH is reflective of right ventricle (RV) overload and is an established risk factor for mortality [Condliffe 2009, Saouti 2009]. The analysis on CO showed a clinically relevant and statistically significant effect of macitentan, which was further confirmed when using corrected values [Table 4].

The beneficial effect on hemodynamics observed in MERIT-1 was also corroborated by a 27% decrease in N-terminal pro B-type natriuretic peptide (NT-proBNP) favoring macitentan over placebo, a measure of inferred RV afterload. At Week 24, the geometric mean NT-proBNP concentration decreased to 72.6% of the baseline value (mean decrease from baseline of 651 pg/mL) in the macitentan group compared with 90.9% of the baseline value (mean decrease from baseline of 360 pg/mL) in the placebo group (ratio of geometric means 0.79, 95% CL 0.63–0.99, p = 0.040). This is reasonably attributed to the positive impact, based on its mode of action, that macitentan has on the RV. Furthermore, the favorable effect on PVR is incremental to that achieved with PH advanced therapy (mostly sildenafil), used at baseline by the majority of the population in MERIT-1. The use of PDE-5 inhibitors has been shown to be effective in improving some hemodynamic and functional variables in patients with CTEPH [Ghofrani 2003, Reichenberger 2007, Suntharalingam 2008] and as such, is recommended in the current PH guidelines
[Galiè 2015].

**Table 4 Cardiac output at Week 16, as reported in the CSR and with corrected hemodynamic values, FAS**

| Analyses | Number of subjects, treatment difference (macitentan - placebo, 95% CLs), p-value[#] | |
|---|---|---|
| | As reported in the CSR | Corrected values |
| FAS | N = 76<br>0.78 (0.35, 1.20)<br>p = 0.0005 | N = 76<br>0.83 (0.43, 1.23)<br>p <0.0001 |

[#]ANCOVA including cardiac output at baseline as a covariable and treatment as a factor in the model.
ANCOVA = analysis of covariance; CL = confidence limit; CSR = clinical study report; FAS = Full analysis set.
Source: Module 5.3.5.1 D-17.097 table 15-70; Appendix 1 Table 46.

**DISCUSSION – PVR**

MERIT-1 demonstrated a clinically relevant hemodynamic effect of macitentan in CTEPH as shown by all analyses when using the corrected PVR values.

In the assessment report, reference is made to the BENEFIT study in which a placebo-corrected effect on PVR similar to that in MERIT-1 was observed. However, this 'informal and direct' comparison is not deemed appropriate for two main reasons:

1) In MERIT-1, a placebo response on corrected PVR (i.e., a decrease of 83.8 dyn.sec/cm5 in PVR at Week 16 from a baseline of 982.3 dyn.sec/cm5) was observed, which was not the case in BENEFIT. Although the exact reason for this unexpected (and to our knowledge unprecedented) improvement in PVR in the placebo group cannot be fully explained, it is worth mentioning that the absolute effect vs baseline of macitentan in MERIT-1 was very similar to the improvement observed with riociguat in a similar population;

2) The main reason that the BENEFIT study could not provide a basis for an extension of indication for bosentan in CTEPH was that no effect on 6MWD was observed. This is in contrast to the MERIT-1 findings, which demonstrate a robust effect on 6MWD.

In conclusion, the results summarized above, pre-planned or *post-hoc* to account for the intercurrent events and incorrect values, consistently show a positive effect of macitentan vs placebo, with or without the presence of PDE-5 inhibitors at baseline.

***1.1.2.2 6MWD (at Week 24)***

There are 3 main estimands for the key secondary endpoint of 6MWD:
1. FAS (Full Analysis Set)
2. "PVR PPS" – based on the definition of the PPS for PVR
3. "New PPS/6MWD PPS" – based on the definition of PPS for 6MWD

In the original protocol and the CSR SAP, only the first 2 estimands were included. Furthermore, it should be noted that only one PPS (i.e., PVR PPS) was defined, and it was common to both the primary endpoint and the main secondary endpoint. The PPS was defined mainly to account only for eligibility and intercurrent events that would affect the evaluation of the primary endpoint (hemodynamics at Week 16) and did not consider eligibility and intercurrent events which would affect the evaluation of 6MWD at Week 24, i.e., including intercurrent events between Week 16 and Week 24. For example, 2 subjects
(China) were excluded from the PVR PPS because right heart catheterization (RHC) was not performed by the same operator, and 1 subject refused to undergo RHC assessment at Week 16. These deviations are important for the primary endpoint of PVR but not relevant to the secondary endpoint of 6MWD at Week 24.

Therefore, an additional estimand (Estimand 3) is defined for the 6MWD per-protocol analysis. This estimand, "New PPS/6MWD, PPS" includes subjects who were eligible for the study in terms of 6MWD baseline values. In this New PPS, 2 subjects (1 subject in each treatment group) with baseline 6MWD above 450 m were excluded. In addition, for 3 subjects who worsened and required rescue medication before their 6MWD assessment at Week 24, the last-observation-carried-forward (LOCF) rule was applied (i.e., 6MWD at Week 16 replaced the 6MWD values at Week 24).

Table 5 summarizes the main estimator and the sensitivity analyses on the 3 estimands.

**Table 5 Results for the key secondary endpoint of 6MWD at Week 24**

| **Estimands for 6MWD** | ***Between-treatment analysis Difference in LS Means (95% CLs) macitentan–placebo*** |
|---|---|
| **Estimand 1 "FAS, N = 80"** | |
| Main Estimator | 34.04 (2.90, 65.19), p = 0.0326 |
| MI1 | 35.19 (3.99, 66.38), p = 0.0270 |
| MI2 | 23.76 (1.51, 46.00), p = 0.0363 |
| BOCF | 20.21 (–0.92, 41.33), p = 0.0606 |
| LOCF | 16.85 (–4.39, 38.10), p = 0.1183 |
| Median | 19.21 (–1.86, 40.28), p=0.0733 |
| ANOVA | 33.96, (2.89, 65.03), p=0.0327 |
| Hodges-Lehmann | 17 (–1.00, 38.00), p = 0.0668 |
| Extended ANCOVA | 36.09 (4.32, 67.86), p = 0.0265 |
| Repeated Measures | 22.77 (2.44, 43.09), p = 0.0286 |
| Observed cases only (N = 76) | 18.31 (–3.9, 40.53), p = 0.1047 |
| **Estimand 2 "PVR PPS"** | |
| PVR PPS (N=74) | 27.5 (–1.5, 56.5), p = 0.0626 |
| **Estimand 3 "New PPS/6MWD PPS"** | |
| Main Estimator (N=78) | 41.66 (9.50, 73.82), p=0.0118 |
| MI1 (N = 78) | 43.20 (11.08, 75.33), p = 0.0084 |
| MI2 (N = 78) | 33.30 (9.16, 57.45), p = 0.0069 |
| BOCF (N = 78) | 27.49 (5.20, 49.77), p = 0.0163 |
| LOCF (N = 78) | 24.05 (1.53, 46.56), p = 0.0367 |
| Median (N = 78) | 26.77 (4.51, 49.03), p= 0.0191 |
| ANOVA (N = 78) | 41.47 (9.28, 73.67), p = 0.0124 |
| Hodges-Lehmann (N = 78) | 23 (2, 47), p = 0.0301 |
| Extended ANCOVA (N = 78) | 45.39 (12.71, 78.06), p = 0.0071 |
| Repeated Measures (N = 78) | 26.04 (5.10, 46.99), p = 0.0155 |
| Observed cases only (N = 74) | 26.25 (2.74, 49.76), p = 0.0292 |

6MWD = 6-minute walk distance; ANOVA = analysis of variance; ANCOVA = analysis of covariance; BOCF = baseline-observation-carried-forward; CL = confidence limit; FAS = Full analysis set; LOCF = last-observation-carried-forward; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.

Source: Module 2.7.3 D-18.252 figure 4 (for Estimand 1); Module 5.3.5.1 D-17.097 table 15-54 (Estimand 1 Observed), table 15-53 (Estimand 2, PVR PPS); Appendix 1 Table 66 (Estimand 3 Main estimator), Table 59 (Estimand 3 HL estimator), Table 64 (Estimand 3, MI1), Table 65 (Estimand 3, MI2), Table 61 (Estimand 3, BOCF), Table 62 (Estimand 3: LOCF), Table 63 (Estimand 3: Median), Table 68 (Estimand 3, ANOVA), Table 67 (Estimand 3, Extended ANCOVA), Table 60 (Estimand 3, Repeated Measures), Table 69 (Estimand 3: Observed).

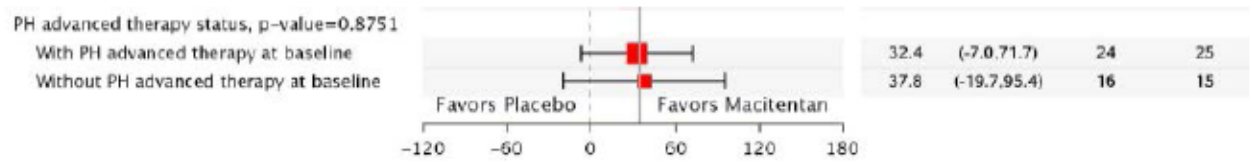
The FAS analysis on 6MWD (Estimand 1 – FAS) shows a treatment effect (macitentan – placebo) of 34 m [Module 5.3.5.1 D-17.097 table 11-5]. This effect is statistically significant and clinically relevant, especially considering that approximately 60% of subjects in MERIT-1 were on PDE-5 inhibitors.

All sensitivity analyses on Estimand 1 are consistent with the main analysis, showing macitentan efficacy on 6MWD [see also response to Question 4]. The sensitivity analyses using multiple imputations / ANOVA / Extended ANCOVA / repeated measures, show a statistically significant and

clinically relevant effect ranging from 23 to 36 m (Estimand 1, FAS). It is acknowledged that the CLs cross 0 in some of the sensitivity analyses using a single imputation method under strong and very conservative assumptions. As mentioned in the assessment report, these analyses are considered less important but go in the same
positive direction as the more relevant analyses.

The effect on 6MWD was consistent across all subgroups analyzed and most notably in subjects with PH advanced therapy at baseline, mainly PDE-5 inhibitors (approximately 60%). In this population the placebo-corrected effect of macitentan was 32.4 m, while in patients without background PH advanced therapy, it was 37.8 m [Figure 1].

**Figure 1** **Forest plot of change from baseline to Week 24 in 6MWD in subjects with or without PH advanced therapy at baseline, FAS**

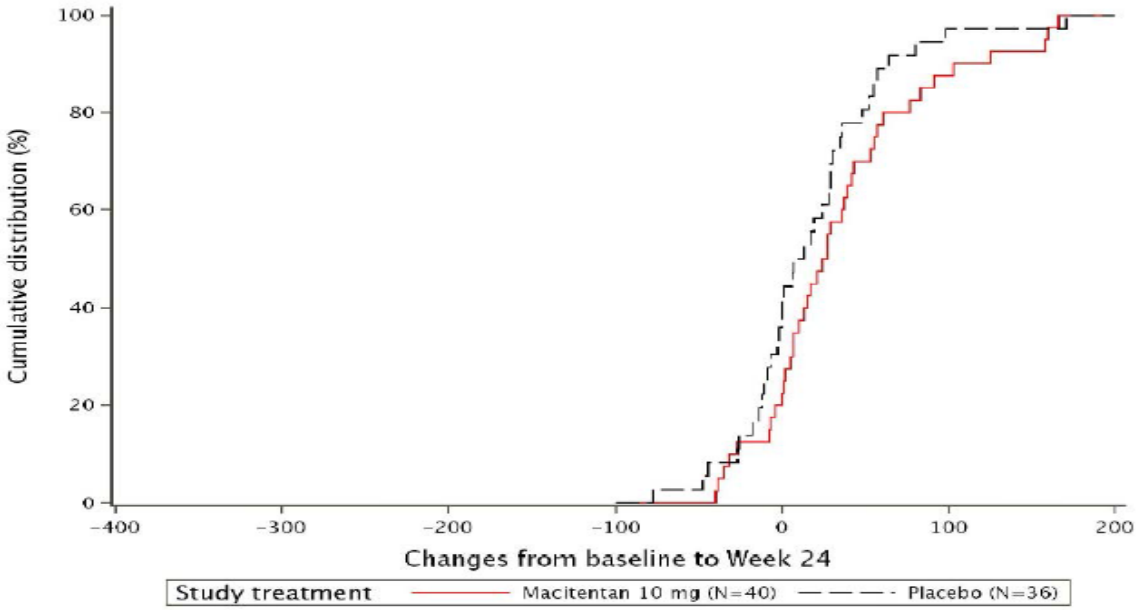



Source: Module 5.3.5.1 D-17.097 figure 11-5.

The originally planned per-protocol analysis did not achieve statistical significance. This analysis has limited clinical relevance, as eligibility criteria relevant for evaluating the 6MWD endpoint, as well as the relevant intercurrent events of worsening and addition of treatment should have been considered. This has now been done with the "New PPS/6MWD, PPS" estimand, which properly addresses the effect of macitentan in a relevant and eligible per-protocol population while on study treatment. The effect observed with macitentan is clinically and statistically significant, with a 42 m difference compared to placebo. For this estimand, all sensitivity analyses provide evidence of a clinically relevant and statistically significant effect ranging from 23 to 45 m.

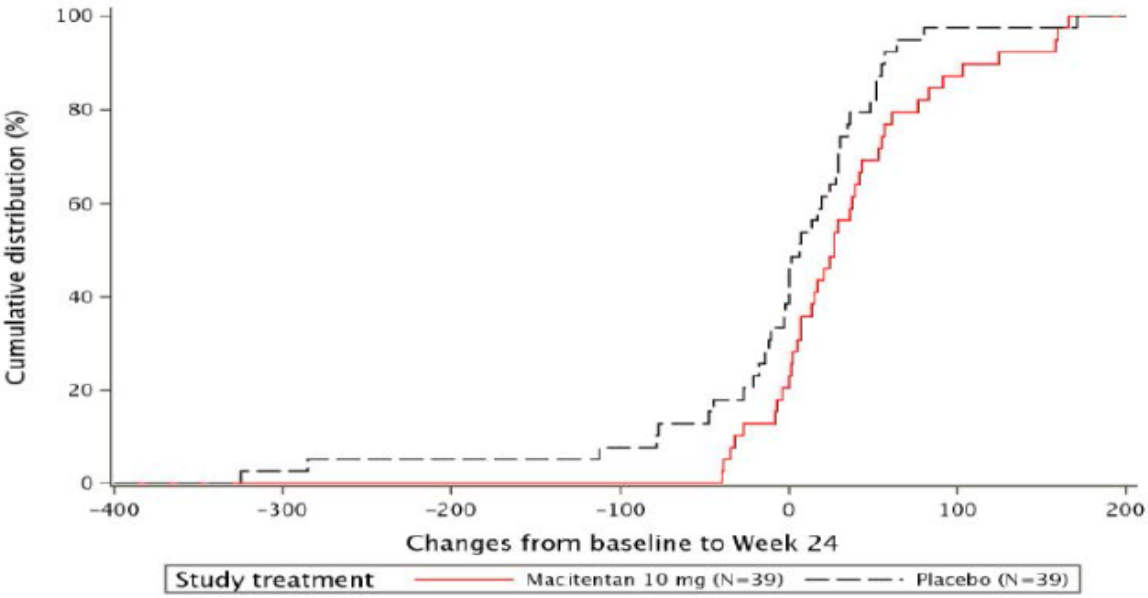
The cumulative distributions using observed data for Estimand 1 (FAS) and Estimand 3 ("New PPS/6MWD PPS") show a clear separation between the treatment groups for 6MWD at Week 24 [Figure 2 and Figure 3].

**Figure 2** **Cumulative distribution of change from baseline to Week 24 in 6MWD (as observed), Estimand 1: FAS**




*Output: F_O6MWDCDF2_EMA_FAS, Produced by biarnal1 on 17JAN2019 12:44 (CET), SDTM production date: 28MAY2018*
*Program: val_csr/program_output/f_6mwd_fd3_ema2.sas*

**Figure 3** **Cumulative distribution of change from baseline to Week 24 in 6MWD (as observed), Estimand 3: New PPS/6MWD PPS**




*For subjects without PAH therapy at baseline the 6MWD assesment performed after the initiation of PAH therapy during MERIT-1 is considered as missing and value is imputed with LOCF.*
*Output: F_I6MWDCDF2_EX_EMA_FAS, Produced by biarnal1 on 17JAN2019 12:44 (CET), SDTM production date: 28MAY2018*
*Program: val_csr/program_output/f_6mwd_fd3i_ema2.sas*

The clinical relevance of the result on 6MWD at 24 weeks is supported by all analyses performed. First and foremost, the pre-defined, main estimator FAS shows a clinically relevant effect on 6MWD of +34 m (p = 0.0326) and, importantly, a similar effect is observed between patients on PH-advanced therapies at baseline (+32.4 m) and those on macitentan monotherapy (+37.8 m). By defining a PPS population of eligible subjects while on treatment, that is clinically relevant for 6MWD, i.e., "New PPS/6MWD PPS", the

treatment effect on 6MWD was + 41.66 m (p = 0.0118).

The sensitivity analyses confirm the results of the main estimators: in the FAS population the sensitivity analyses using multiple imputations / ANOVA / Extended ANCOVA / repeated measures all show a statistically significant and clinically relevant effect ranging from 23 to 36 m (Estimand 1 – FAS). Also, in the new PPS for 6MWD, a statistically significant and clinically relevant improvement over placebo ranging from 23 to 45 m (Estimand 3 – "New PPS/6MWD PPS" [Table 23]) is observed in the main estimator as well as in all sensitivity analyses. It is acknowledged that the CLs cross 0 in some of the sensitivity analyses on the FAS population using a single imputation method under strong and very conservative assumptions. As mentioned in the assessment report, these analyses are considered less important but go in the same positive direction as the more relevant analyses.

The robustness of the finding is also seen in the cumulative distributions of change from baseline to Week 24, which shows a clear separation between macitentan and placebo.

### 1.1.3 Other clinical endpoints at 24 weeks

The assessment of effect on clinical events is hampered by the relatively small sample size and low incidence of events. As mentioned in the assessment report, determining the appropriate level of statistical power for hard endpoints such as mortality or even disease progression is not always feasible. In such cases, the consistency of the finding and the treatment effect estimates are more important than the statistical significance.

#### *1.1.3.1 WHO FC*

WHO FC worsened in 3 subjects in the placebo group, while no subject worsened in the macitentan group. The OR for the proportion of subjects with WHO FC worsening at Week 24 (macitentan vs placebo: 0.212, 95% CL: < 0.001, 1.464, p = 0.0962, exact logistic regression) favored macitentan [Module 5.3.5.1 D-17.097 table 15-63]. As mentioned above, this result needs to be interpreted with caution due to the small number of subjects with worsening in WHO FC.

#### *1.1.3.2 Disease progression*

Although the epidemiology of CTEPH is similar to that of PAH [Lang 2015], the feasibility of a properly powered CTEPH disease progression study, especially in a population on PH advanced therapy, is very limited, considering the small pool of CTEPH patients who are eligible for medical treatment (~ 24–37% of CTEPH patients are deemed technically inoperable) [Condliffe 2008, Bonderman 2009, Pepke-Zaba 2011, Hurdman 2012].

MERIT-1 provides interesting insights into the effect of macitentan on disease progression. Two events of disease progression were observed on macitentan as compared to 7 on placebo over 24 weeks. The disease progression-free survival rate showed a numerical difference favoring macitentan treatment (95.0% for macitentan vs 87.5% for placebo at Week 24). This translated into an HR of 0.28 (p = 0.0847), [Table 47]. Although not statistically significant, the difference favoring macitentan is noteworthy given the clinical and pathological similarities between PAH and CTEPH. This result is also consistent with the long-term outcome data from the Phase 3 SERAPHIN study with macitentan in PAH patients. The difference between the two treatment groups was driven by a hard component of the disease progression endpoint, namely hospitalization, with 2 events in the macitentan group (5%) vs 4 in the placebo group (10%) [Module 5.3.5.1 D-17.097 table 15-73]. These results are consistent with the results from the SERAPHIN study, in which a 50% reduction in hospitalization due to PAH was observed with macitentan compared to placebo. Results of the MERIT-1 study suggest that the effect of macitentan on reducing hospitalization may also be attained in CTEPH.

The relevance of these findings is further supported by the overall low long-term mortality in the macitentan 10 mg cohort across MERIT-1 and MERIT-2 (the KM estimates for survival in the macitentan 10 mg MERIT double-blind [DB] / open label [OL] cohort across MERIT-1 and MERIT-2 were 100% and 87.9% at 1 and 2 years, respectively) [Module 5.3.5.3 ISS Appendix 1 table 20 and figure 1]. This compares favorably with historical data in a similar population with a reported survival of 88% and 79% at 1 and 2 years, respectively [Delcroix 2016].

Furthermore, AEs reflecting manifestations of the underlying disease/disease progression were reported more frequently in the placebo group (acute RV failure, cardiac failure, RV failure, ascites, and PH). The incidence in the macitentan group was lower (7.5%) compared to placebo group (20.0%), with a treatment difference of −12.5% (95% CI: −34.6%, 10.6%; p= 0.1927) [Table 48].

It is also important to consider the occurrence of syncope, an uncommon symptom of PAH. Syncope often indicates severe limitations in flow reserve and is thus an independent predictor of a poor prognosis that is incremental to the risk attributable to other recognized prognostic factors. As such, syncope is particularly highlighted as part of the ongoing risk assessment of these patients. In MERIT-1, no AEs of syncope were reported in subjects on macitentan compared to 3 subjects on placebo (7.5%) [Module 5.3.5.1 D-17.097 table 12-4].

#### *1.1.3.3 Borg Dyspnea Index*

The lack of statistically or clinically significant improvement in BDI score despite an improvement in exercise capacity, as observed in MERIT-1, is in line with results from previous randomized-controlled studies performed in PH, including SERAPHIN and GRIPHON. For a thorough evaluation of this endpoint, please refer to the response to Question 15.

In conclusion, a neutral effect on BDI indicated that the respective 6-minute walk tests (6MWTs) were performed under similar conditions and with same level of effort, and as such are consistent with the standardization principles applicable to this exercise-related test.

**Conclusion on other clinical endpoints**

The assessment of the effect of macitentan on clinical endpoints is hampered by the fact that too few events occurred during the 24-week period to allow sound statistical estimation. During the study (24 weeks), 3 patients in the placebo group had worsening in WHO FC, while no patient in the macitentan group had worsening in WHO FC.

A clinically significant effect on disease progression was observed in MERIT-1 in the macitentan group (2 events) vs the placebo group (7 events). This finding is supported by the safety analyses showing a lower incidence of AEs indicative of disease worsening in the macitentan group (7.5%) compared to the placebo group (20%). Overall, these findings are reassuring regarding the long-term effect of macitentan in this indication, which shares pathophysiological and clinical features with PAH.

### 1.1.4 Real-world data

In the application submitted to the EMA on 28 August 2018, results (up to the data cut-off date of 17 April 2018) from the OPUS Registry, a multicenter, prospective, long-term, observational drug registry of new macitentan (Opsumit®) users in the US, were included [Module 5.3.5.4 D-18.259]. To fulfill the ongoing post-approval safety commitment in the US, OrPHeUS (a multicenter, retrospective, medical chart review) was conducted as a complementary data source to OPUS. In the combined OPUS-OrPHeUS dataset analysis, the sample size of the CTEPH population increased to 144 patients (data provided
previously included 45 patients from the OPUS registry alone as of 17 April 2018 [Module 5.3.5.4 D-18.259]).

In summary, based on a 3-fold larger sample size than submitted previously, the descriptive analysis suggests that CTEPH patients treated with Opsumit did not experience worsening in clinical outcomes analyzed (WHO FC and 6MWD). For WHO FC, 78.9% of patients did not worsen from baseline up to the last available follow-up assessment; and 78.8% did not experience a decrease in 6MWD of ≥ 15%. In addition, longitudinal analysis methods, which account for sparse data and variable times of measurement and duration of observation similarly showed that 6MWD values were stable over time, with an estimated change of 1.1 m (95% CLs: −5.0 to 7.2) 6 months after Opsumit initiation. The rate of hospitalizations observed in this cohort of CTEPH patients was similar to that of PAH patients treated with Opsumit (40.3% vs 36.9%). The combined OPUS-OrPHeUS dataset analysis also suggests a similar rate of safety events (AEs and all-cause death) with Opsumit use in CTEPH and PAH. The proportion of patients with at least 1 AE was 74.3% vs 66.1% for PAH and CTEPH respectively, and all-cause death was 10.1% vs 6.3% for PAH and CTEPH, respectively. Supportive data from the OPUS Registry and OrPHeUS
study confirm the extent of use, outcomes, tolerability, and safety profile of Opsumit in CTEPH, in a real-world setting [see Module 5.3.5.4 D-18.430].

### 1.1.5 External validity of the study: representativeness of the MERIT population for the EU population

The MERIT-1 study has external validity as its study population includes a large cohort of patients on PAH-advanced therapies at baseline, which although not approved for CTEPH, are widely used in clinical practice. According to the International CTEPH Association (ICA) registry, 54% of inoperable patients are treated with a PAH-advanced therapy. The data from the EU registry COMPERA show that

approximately 18% of all CTEPH patients are on ERAs, 37% are on PDE-5 inhibitors, and another 43% are on riociguat [data on file].

Thus, MERIT-1, with approximately 60% of patients on PDE-5 inhibitors could be considered as representative of the European treatment pattern for CTEPH patients. Although only a few patients from Western Europe and no patients from the USA were recruited into the MERIT-1 study, the data obtained from MERIT-1 have broad applicability to all regions in the world. The rationale for this is based on the following:

1. Confirmation of CTEPH diagnosis and assessment of operability: There is consistency across global expert recommendations relating to the clinical classification, diagnostic evaluation and determination of operability, as well as the approach to the treatment of CTEPH. The MERIT-1 study was designed in accordance with international recommendations for the diagnosis and operability assessment of CTEPH [Galiè 2015, Kim 2013, Jenkins 2017]. Similar to the CHEST-1 study with riociguat [Ghofrani 2013a, Ghofrani 2013b], MERIT-1 employed rigorous measures to ensure that only technically inoperable subjects were enrolled. This was achieved via an adjudication procedure prior to randomization, which served to harmonize the inclusion of eligible, inoperable subjects with confirmed CTEPH across sites.

2. The MERIT-1 study population is representative of the broader inoperable CTEPH population: Based on their baseline demographic, clinical and hemodynamic characteristics, the MERIT-1 study participants were generally similar in important aspects to the wider CTEPH population when considering ICA (international subgroup of technically inoperable CTEPH patients) data [Table 6] and other epidemiological studies [Pepke-Zaba 2011, Rådegran 2016, Saouti 2009, Delcroix 2016, Kim 2013,
Schweikert 2014]. To highlight some of the features, the study population consisted predominantly of subjects of more advanced age than PAH patients (median age 59 years). The majority of subjects were in WHO FC III (76.3%), which is consistent with epidemiological studies, indicating that most subjects with CTEPH are in a high FC at the time of diagnosis [Gall 2017]. Multiple comorbidities were prominent,
consistent with the high proportion of older subjects (35% were ≥ 65 years), medical conditions conferring an increased risk for developing CTEPH, and medical conditions associated with CTEPH complications. Such conditions included but were not limited to: pulmonary embolism (81.3%), RV failure (56.3%), systemic hypertension (41.3%), deep vein thrombosis (31.3%), and peripheral edema (22.5%) [Module 5.3.5.1 D-17.097 table 15-21]. The majority of subjects (61.3%) were on concomitant PH-specific therapy (primarily PDE-5 inhibitors). At baseline, all subjects had been on anticoagulant therapy for at least 3 months, as required by the protocol and as required to establish the diagnosis of CTEPH [Jenkins 2017].

**Table 6 ICA and MERIT-1 baseline characteristics**

| Characteristic | ICA technically inoperable* (N=235) | MERIT-1** (N = 80) |
|---|---|---|
| **Age, years: mean ± SD** | 62.9 ± 15.1 | 57.5 ± 13.9 |
| **Range** | 7–96 | 20–80 |
| | ⩾ 70 y: 93 (39.7%) | ⩾ 65 y: 28 (35%) |
| **Countries** | 19 (8 in common) | 20 |
| **Time from diagnosis, months – mean ± SD** | ⩽ 6 months | 18 ± 25.92 |
| **FC – n (%)** | NYHA | WHO |
| I | 3 (1.3) | 0 |
| II | 49 (20.9) | 18 (22.5) |
| III | 162 (68.9) | 61 (76.2) |
| IV | 21 (8.9) | 1 (1.3) |
| **6MWD, m – mean ± SD** | Not available | 352.1 ± 80.64 |
| **PVR, dyn.s/cm5 – mean ± SD** | 738.0 ± 382.1 | 957 ± 434.8 |
| **Use of PAH medications – n (%)** | | |
| No PAH medication | 109 (46.4) | 31 (38.8) |
| PAH medication | 126 (53.6) | 49 (61.2) |

* Data on file, results sent by the ICA registry (data-cut 31 October 2017)
** Ghofrani 2017. 6MWD = 6-minute walk distance; FC = functional class; ICA = International CTEPH Association; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

### 1.1.6 Comparison of macitentan vs riociguat

A benefit-risk evaluation for macitentan in comparison to riociguat has been performed by indirectly comparing MERIT-1 and CHEST-1.

The two studies differ in terms of sample size and patient populations, and therefore an anchored indirect comparison which accounts for these differences and for the imbalances in baseline characteristics and demographics has been implemented. The methodology used is that of Signorovitch et al. [Signorovitch 2010], which allows the comparison to be conducted on comparable populations based on a re-weighting method (MAIC).

The MAIC methodology is used in comparative effectiveness research when there are population imbalances across studies, and patient level data are not available for all sources of data but rather summary data (i.e., CHEST-1) [Bucher 1997, NICE DSU TECHNICAL SUPPORT DOCUMENT 2016, Signorovitch 2010, Signorovitch 2012, IQWiG 2017].

This methodology accounts for specific baseline characteristics that are known prognostic factors which, in the case of CTEPH, are age, gender, body mass index, WHO FC II, 6MWD and PVR.

An analysis of covariance with treatment as main fixed effect and baseline variables, using the weighted MERIT-1 data to match the CHEST-1 population characteristics, was performed. For safety, all MERIT-1 patients (FAS) and all CHEST-1 patients (intention to-treat) were compared. For efficacy, MERIT-1 patients without background PH advanced therapy were compared with all inoperable CHEST-1 patients. More details on the methodology are provided in Appendix 2 D-19.020.

**Efficacy**
To improve comparability of the efficacy analyses, a subset of patients in both MERIT-1 and CHEST-1 was selected: MERIT-1 patients without background PH therapy (N = 31) were selected, as CHEST-1 patients were not on background PH therapy. Similarly, in CHEST-1, the sub-population of reference is the subset of inoperable CTEPH patients.

Table 7 below summarizes the comparative effectiveness results for the primary and secondary endpoints. The effect of macitentan and riociguat on 6MWD as compared to placebo is virtually identical in this analysis, with an increase over placebo of approximately 54 m.

It should be noted that the analysis on PVR in MERIT-1, as mentioned in the response above, suffers from an unexpected and unprecedented (to our knowledge) decrease in PVR in the placebo group. The CLs crosses 0, i.e., results are not statistically significant. Additional analyses in different populations and on other secondary exploratory endpoints are provided in the MAIC report [Appendix 2 D-19.020]. In conclusion, in a comparable population of patients, macitentan appears as effective as riociguat.

**Table 7 Results of MAIC comparison between MERIT-1 no PH background (N = 31) versus CHEST-1 inoperable patients (N = 189) in change from baseline in 6MWD and PVR**

| Endpoint | MERIT-1: macitentan vs placebo LS-mean difference (95% CLs) | CHEST-1: riociguat vs placebo LS-mean difference (95% CLs) | ITC: macitentan vs riociguat difference of LS means (95% CLs) |
|---|---|---|---|
| 6MWD change from baseline (m) at 24 weeks | 53.9 [−25, 133] | 54.0 [29, 78] | −0.1 [-82, 82] |
| PVR change from baseline (dyn·s/cm$^{5}$) at 16 weeks | −164.7 [−355, 25] | −285 [−357, -213] | 120.3 [−83, 323] |

The time point considered for the 6MWD is the End of Study for both studies.
6MWD = 6-minute walk distance; CL = confidence limit; ITC =Indirect Treatment Comparison; LS = Least Squares; MAIC = matched-adjusted indirect comparison; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.
Source: Appendix 2 D-19.020 table 15; Ghofrani 2013a ; Simonneau 2016 ; Ghofrani 2017; Kim 2017.

**Safety**

For the safety analysis, the entire population, rather than the subgroups defined above for efficacy, is considered the relevant population. Table 8 summarizes the MAIC comparison on the key safety endpoints which include AEs, serious AEs (SAEs) and AEs leading to discontinuation. The AE PTs included in the table are events of special interest.

The MAIC results are expressed in terms of odds ratio, with an OR < 1 indicating results in favor of macitentan and an OR > 1 indicating a result in favor of riociguat. For most events indicated as 'NA' in the MAIC columns, the estimates could not be calculated as there were no events in the macitentan group (i.e., discontinuations due to AEs, hypotension, syncope, dyspepsia, nausea and vomiting). For headache, the MERIT-1 OR could not be calculated as there were no such events in the placebo arm, nor for
hemoptysis in CHEST-1.

**Table 8 Results of MAIC comparison between MERIT-1 overall population (N = 80) vs CHEST-1 overall population (N = 261) in the occurrence of events**

| Event | Odds Ratio (95% CL) | | |
|---|---|---|---|
| | MERIT-1 overall (weighted): Macitentan vs Placebo | CHEST-1 overall: Riociguat vs Placebo | MAIC Macitentan vs Riociguat |
| Any AE >=1 | 1.39 [0.45,4.36] | 1.79[0.79,4.06] | 0.78 [0.19,3.16] |
| Serious AE | 0.68 [0.14,3.25] | 1.29 [0.65,2.56] | 0.53 [0.10,2.90] |
| Discontinuation due to AE | NA | 1.28 [0.24,6.73] | NA |
| Peripheral Oedema | 2.91 [0.74,11.43] | 0.72 [0.37,1.39] | 4.04 [0.88,18.49] |
| Anaemia | 6.94 [0.42,115.95] | 3.13 [0.37,26.38] | 2.22 [0.06,75.95] |
| Hypotension | NA | 2.89 [0.82,10.19] | NA |
| Bleeding Event | 0.94 [0.23,3.81] | 1.20 [0.54,2.64] | 0.79 [0.16,3.92] |
| Dizziness | 0.71 [0.06,8.70] | 2.04 [0.99,4.21] | 0.35 [0.03,4.73] |
| Diarrhoea | 4.55 [0.39,53.49] | 2.29 [0.75,7.02] | 1.99 [0.13, 29.80] |
| Right ventricular failure | 0.22 [0.02,2.27] | 1.02 [0.25,4.17] | 0.21 [0.01,3.30] |
| Haemoptysis | 0.53 [0.03,8.87] | NA | NA |
| Nasopharyngitis | 0.25 [0.03,2.41] | 1.77 [0.77,4.09] | 0.14 [0.01,1.58] |
| Syncope | NA | 0.67 [0.15,3.06] | NA |
| Headache | NA | 2.09[1.04,4.22] | NA |
| Dyspepsia | NA | 2.53[1.06,6.00] | NA |
| Nausea | NA | 1.43[0.58,3.54] | NA |
| Vomiting | NA | 3.09[0.88,10.84] | NA |

AE ≥ 1: subjects with at least 1 treatment-emergent AE.
AE = adverse event; CL = confidence limit; MAIC = matched-adjusted indirect comparison; NA = not applicable.
Source: Appendix 2 D-19.020 table 22, Ghofrani 2013a, Simonneau 2016, Ghofrani 2017, Kim 2017.

The MAIC analysis of the safety endpoints suggests that macitentan has a similar or potentially more favorable safety profile when indirectly compared to riociguat. When interpreting the MAIC results on safety endpoints, it should be considered that patients in MERIT-1 were exposed to study medication for a longer period than in CHEST-1 (24 weeks vs 16 weeks), and therefore, MERIT-1 patients had a higher chance of having an AE.

As expected, peripheral edema and anemia occurred more frequently with macitentan, while bleeding events and dizziness occurred more frequently with riociguat. Unlike riociguat, no events of dyspepsia, nausea, hypotension, syncope, and vomiting occurred with macitentan.

Comparison of the overall safety profile of the two compounds based on the estimated MAIC ORs suggests a decrease in the risk of having any AE and most notably, a decrease in the risk of having an SAE for macitentan vs riociguat. It should be noted, however, that the CLs include 1. An additional analysis has been conducted using exposure-adjusted rate ratios per 100 patient-years (available for riociguat in Simonneau 2016) as shown in Table 9. This analysis confirms the results from the non-exposure adjusted ORs.

**Table 9 Results of MAIC exposure-adjusted comparison between MERIT-1 overall population (N = 80) vs CHEST-1 overall population (N = 261) in the occurrence of events**

| Event | MERIT-1 (weighted): Rate per 100-patient years | | MERIT-1 (weighted): RR (macitentan vs placebo) | CHEST-1: RR (riociguat vs placebo) | MAIC: RR (macitentan vs riociguat) |
|---|---|---|---|---|---|
| | Macitentan | Placebo | | | |
| Any AE | 452.02 | 584.82 | 0.77 (0.46, 1.30) | 1.14 (1.01, 1.28) | 0.68 (0.40, 1.16) |
| Nasopharyngitis | 4.66 | 18.04 | 0.26 (0.03, 2.33) | 1.50 (0.73, 3.08) | 0.17 (0.02, 1.74) |
| Peripheral Oedema | 58.49 | 19.23 | 3.04 (0.91, 10.19) | 0.78 (0.44, 1.37) | 3.90 (1.03, 14.82) |
| Dizziness | 4.20 | 5.94 | 0.71 (0.06, 8.09) | 2.27 (1.24, 4.14) | 0.31 (0.03, 3.84) |
| Diarrhoea | 18.16 | 4.35 | 4.17 (0.39, 44.26) | 3.48 (1.22, 9.96) | 1.20 (0.09, 15.89) |
| Syncope | 0.00 | 10.09 | NA | 0.52 (0.13, 2.07) | NA |
| Hypotension | 0.00 | 14.62 | NA | 2.76 (0.80, 9.48) | NA |
| Haemoptysis | 2.64 | 5.02 | 0.53 (0.03, 8.36) | NA | NA |

AE = adverse event; MAIC = matching-adjusted indirect comparison; NA = not applicable; RR = rate ratio.
Source: Appendix 2 D-19.020 table 23.

**In conclusion**, the indirect treatment comparison focusing on the subset of MERIT-1 patients without background PH therapy for efficacy and on all patients in MERIT-1 for safety was performed using the methodology of Signorovitch et al. [Signorovitch 2010]. Based on the results, macitentan is deemed as effective as riociguat and potentially better tolerated than riociguat.

### 1.1.7 Overall benefit–risk analysis

**Benefits**
The development of macitentan for the treatment of patients with CTEPH should be considered in view of the similarities between CTEPH and PAH, as supported by literature [Pepke-Zaba 2011, Delcroix 2016, Sitbon 2016] and acknowledged in the riociguat EPAR [Adempas EPAR 2014].

Overall, the MERIT-1 study included a severe CTEPH population. Of these subjects, a high proportion (61% overall) were on background PAH-advanced therapies. This study showed relevant hemodynamic and functional improvements in the population assessed. Macitentan demonstrated efficacy as monotherapy as well as in combination with PDE-5 inhibitors. MERIT-1 is the only randomized controlled trial in CTEPH providing data on combination therapy, highlighting an important benefit of macitentan, namely the possibility of using it in combination with drugs acting on the nitric oxide pathway
(PDE-5 inhibitors).

The applicant considers that the benefits of macitentan in CTEPH are established for the proposed population. On the basis of the pre-specified primary and main secondary endpoint analyses, there is a clinically and statistically significant effect on hemodynamics (PVR geometric mean ratio = 0.84, p = 0.041) and an equally clinically relevant and statistically significant effect on 6MWD at Week 24 (34 m, p = 0.0326). The per-protocol analyses on both PVR and 6MWD confirm the FAS when correcting for 4 incorrect/non-plausible CO and PAWP values in the PVR per-protocol analysis (geometric mean ratio = 0.84, p = 0.0388) and when considering an eligible population with relevant definition of intercurrent events for the 6MWD per-protocol analysis (41.66 m, p = 0.0118). Macitentan also shows clinically relevant and consistent effect on PVR (0.84) and the 6MWD (32.4 m) as add-on to PAH-specific treatment, i.e., similar to that observed in the treatment-naïve population.

The study has internal validity, as the results on both PVR and 6MWD are robust across sensitivity analyses and all estimands support a clinically significant effect of macitentan vs placebo. For PVR, all sensitivity analyses of the main estimator for all estimands are clinically and statistically significant once the corrected PVR values are considered. For 6MWD, the sensitivity analyses confirm the results

of the main estimators: the sensitivity analyses on the FAS population using multiple imputations / ANOVA /
Extended ANCOVA / repeated measures, all show a statistically significant and clinically relevant effect ranging from 23 to 36 m (Estimand 1– FAS). In the new PPS, an equally statistically significant and clinically relevant improvement over placebo of 23 to 45m (Estimand 3: New PPS/6MWD PPS [Table 23]) is observed. It is acknowledged that, in the FAS population and for some sensitivity analyses using a single imputation method under strong and very conservative assumptions, the CLs cross 0 (6MWD). Nonetheless, these analyses are consistent with the more relevant primary analysis, with similar treatment effect estimates, thus supporting the primary analysis conclusion.

In the applicant opinion, the results of the study are not difficult to interpret, as there is evidence of a clinically relevant effect in all analyses on PVR and on 6MWD. This effect ranges (for 6MWD) from 23 to 45 m depending on the estimand and the sensitivity analyses chosen, but in all cases, we observe an effect compared to placebo that is clinically relevant.

The assessment of macitentan effect on clinical endpoints is hampered by the fact that too few events occurred in 24 weeks to allow for a sound statistical estimation of the treatment effect on such events. During the 24-week study period, 3 patients in the placebo group had WHO FC worsening compared to no patients in the macitentan group. This translates into an OR of 0.21 (p = 0.0962). A clinically significant effect on disease progression was observed in the macitentan group (2 events) vs the placebo group (7 events), with the respective KM event free rates of 95.0% and 87.5% at 24 weeks. This translates into an
HR of 0.28 (p = 0.0847). It is particularly important that the effect is driven by a reduction in hospitalization from 10% on placebo to 5% on macitentan. These findings are supported by the safety analyses showing a lower incidence of AEs indicative of disease worsening in the macitentan group (7.5%) compared to the placebo group (20%). Overall, these findings provide reassurance regarding the long-term effect of macitentan in CTEPH, which shares pathophysiologic and clinical features with PAH.

In the applicant's experience, the BDI is not a clinically relevant endpoint in the evaluation of PH symptoms. In the literature as well as in large studies such as SERAPHIN or GRIPHON, no effect on BDI was observed, despite a clinically relevant effect on disease progression.

The magnitude of the observed improvements in both PVR (16–20% improvement in geometric mean ratio) and 6MWD (2345 m) are definitely clinically relevant and meaningful. Off-loading the RV, by decreasing the PVR in 16 weeks by 16–20% on average, has the potential to improve long-term clinical outcomes. CTEPH, like PAH, is a progressive disease. The pathophysiology of the progression is due to worsening vascular disease that manifests clinically as worsening in PVR, thereafter leading to right heart failure and death. This explains the severely limited life expectancy of a CTEPH patient of less than 23 years, if untreated. Therefore, a 16–20% improvement in PVR with the use of macitentan over only a 16-week period is clinically relevant and meaningful.

The 6MWD change of 23–45 m is also clinically relevant. Similar to the PVR worsening that is the hallmark of this progressive disease and the key catalyst of mortality (via induction of right heart failure), worsening of the 6MWD is a primary reflection of the CTEPH patient's functional status. A worsening in the 6MWD reflects disease progression and is part of the natural history of this patient population. An improvement of this magnitude in 6MWD in PAH, which as noted above has very similar pathophysiologic basis as CTEPH, has been established in PAH to be clinically meaningful and associated with other clinically important improvements. The improvements in these 2 important variables (PVR and 6MWD) are consistently associated in MERIT-1 with changes in other relevant hemodynamic variables including CO (the primary determinant of survival in this patient population) and other secondary outcomes, further supporting their clinical relevance.

Finally, the efficacy profile of macitentan shown in MERIT-1 compares well with that of riociguat, when adjusting the comparison to the different characteristics of the populations between MERIT-1 and CHEST-1 and the results show that macitentan is no less effective than riociguat in this population.

**Risks**
The safety profile of macitentan has been well-characterized and includes data from long-term studies in PAH [Opsumit® SmPC]; vast post-marketing experience (more than 50,000 patients as of the cut-off date of 17 October 2018); and large registries (over 3000 patients, including approximately 150 patients with CTEPH). No new safety concerns have been identified among the various sources of additional safety data reviewed, and the macitentan safety profile in CTEPH patients is very similar to

the safety profile observed in PAH patients. These data provide reassurance regarding the long-term safety profile of macitentan. This is relevant given the similarities in pathophysiology and treatment response between CTEPH and PAH.

The macitentan safety and tolerability profile compares well with that of riociguat in the CTEPH population. Unlike riociguat, macitentan is not associated with serious hemoptysis and pulmonary hemorrhage which can be fatal. Co-administration of PDE-5 inhibitors with macitentan has not raised any safety concerns.

Riociguat lacks controlled data in combination with other PH-advanced therapies and combination therapy with a PDE-5 inhibitor is contra-indicated due to the risk of hypotension, limiting its utility in a broader CTEPH population [Adempas® SmPC].

Another important limitation to the use of riociguat is that it cannot be used concurrently with nitrous oxide donors, such as nitroglycerine, due to the increased proclivity to develop hypotension with syncope. Hence, riociguat may not be a viable option for CTEPH patients with co-existing coronary artery disease, who represent a significant portion of the CTEPH population [Pepke-Zaba 2011, Roik 2016, Delcroix 2016].

**Overall benefit-risk conclusion**
Macitentan has been adequately studied in inoperable CTEPH patients, and has demonstrated a good efficacy, safety and tolerability profile in this patient population. It offers a new mode of action and addresses an important unmet medical need for an alternative treatment in this indication. Macitentan is expected to provide significant clinical benefit to a broader group of inoperable CTEPH patients, including those treated with any background PH advanced therapy, such as PDE-5 inhibitors and sGC stimulators.
The applicant is of the opinion that the data provided support an extension of indication for the treatment of inoperable CTEPH in adult patients of WHO FC II to III, to improve exercise capacity.

***Rapporteur Assessment***

The applicant has provided a discussion about data already presented in the initial submission.

As discussed in the answer to Q4, the main analysis of change in 6MWD using ANCOVA is biased by high variability (SD in mean change in 6MWD from baseline is more than two-fold higher than the mean value) probably due to the presence of extreme values. Therefore, an analysis focused on median would have been more appropriate. The applicant is invited to comment about the difference in standard deviations in change in 6MWD between the FAS and PP populations, despite no patient was excluded for the PP population in the macitentan group (see LoI). This issue is also related to assessment of Q11, with respect to internal consistency and the presence of an outlier center for 6MWD. The data on 6MWD by country and center show that, in most countries, placebo tended to be better than macitentan. The results on 6MWD only favoured macitentan in Russia, Ukraine and Thailand. Particularly in Ukraine, the difference in favour of macitentan was an impressive 122.5 m improvement versus placebo (Q11).

In this respect: a) Please, provide the interaction p-value by country for the effect on 6MWD and analyse the results of 6MWD including country as covariate.

b) The applicant is requested to provide a narrative for patient treated with macitentan in a centre in Ukraine, who improved 160 metres in 6MWD from baseline to week 24. Please, also discuss about the chance for a patient with inoperable CTEPH to improve 160 metres from baseline to week 24.

c) As sensitivity analysis, the applicant is requested to show MERIT-1 study results: c1) By excluding that patient and c2) by excluding a centre in Ukraine.

In addition, the MAH states that the efficacy shown with macitentan in PAH could be extrapolated to

CTEPH due to similarities between both diseases. However, despite some similarities, they have different etiologies (i.e.: thromboembolism vs. vasoconstriction) and they are considered as separate conditions in the classification of Pulmonary Hypertension (i.e.: PAH corresponds to Group 1 while CTEPH corresponds to Group 4).

Only riociguat has shown to be effective in both indications in appropriate phase III confirmatory trials, while bosentan only achieved a 2.2 m improvement in 6MWD compared with placebo in the other available clinical trial with an ERA in CTEPH (BENEFiT study; n=157) [Jais et al, J Am Coll Cardiol. 2008;52:2127–34]. Therefore, the efficacy of these products cannot be extrapolated from PAH to CTEPH.

In addition, a benefit-risk evaluation for macitentan in comparison to riociguat has been performed by the applicant by indirectly comparing CHEST-1 and MERIT-1. The data presented show that both studies are not comparable in study design (i.e.: phase III vs phase II; primary endpoint 6MWD vs PVR), study populations (mean age 63 years vs 57 yrs; PVR at baseline 738 dyn.s/cm5 vs 957 dyn.s/cm5), and robustness of the effect on PVR (decrease in PVR: 285 dyn.s/cm5 vs 165 dyn.s/cm5) and 6MWD (confidence intervals in the increase in 6MWD: +29 to +78 metres in CHEST-1 vs. -25 to +133 metres in MERIT 1). In the absence of direct comparisons (or on the comparison of macitentan on top of riociguat vs. riociguat alone) no meaningful conclusions can be drawn.

***Conclusion***

**Issue not solved.**

The benefit shown in the MERIT-1 study is currently insufficient to grant an indication in patients with inoperable CTEPH:

a. The effect of macitentan on 6MWD in the primary analyses and the sensitivity analyses based on different missing data imputation techniques shows that the effect estimates statistics are not robust and differences are difficult to interpret (see also assessment of Q3, Q4): a1) The main analysis of change in 6MWD using ANCOVA is biased by high variability (SD in mean change in 6MWD from baseline is more than two-fold higher than the mean value) probably due to the presence of extreme values. Therefore, an analysis focused on median would have been more appropriate. Please, discuss; a2) On the other hand, the applicant is invited to comment about the difference in standard deviations in change in 6MWD between the FAS and PP populations, despite no patient was excluded for the PP population in the macitentan group.

b. The point estimate for the effect in 6MWD favoured placebo in most countries, while the trend towards a benefit was only achieved in Russia, Ukraine and Thailand (see assessment of Q11). Particularly in Ukraine, the difference in favour of macitentan was an impressive 122.5 m improvement versus placebo. In this respect: b1) Please, provide the interaction p-value by country for the effect on 6MWD and analyse the results of 6MWD including country as covariate; b2) The applicant is requested to provide a narrative for patient treated with macitentan in one centre in Ukraine, who improved 160 metres in 6MWD from baseline to week 24. Please, also discuss about the chance for a patient with inoperable CTEPH to improve 160 metres from baseline to week 24; b3) As sensitivity analysis, the applicant is requested to show MERIT-1 study results: by excluding that patient; and by excluding one centre in Ukraine.

c. The high number of important protocol deviations in more than 50% of patients and the fact that these deviations were not at random (much higher in the placebo group) add uncertainties on

whether study conduct and oversight was adequate and goes against the robustness of the results. The applicant is invited to discuss on the potential causes for these not at random protocol deviations.

## *Other concerns*

# Non clinical aspects

***Question 2***

***The Applicant is requested to revise the $F_{pen}$ refinement with European disease prevalence data published by a reliable and independent source as recent as possible.***

***Summary of MAH answer***

The applicant has revised the fpen refinement and updated the environmental risk assessment [Module 1.6]. To re-calculate the fpen, the prevalence of PAH in Sweden, which has the highest PAH prevalence (49/1,000,000) in a European country publicly available [Rådegran 2016], and the prevalence of CTEPH in Great Britain (35/1,000,000), which has the highest CTEPH prevalence in a European country publicly available [NHS 2018, ONS 2017], were used. The applicant also used an updated population estimate in the EU as of 1 January 2017 (518,330,149 inhabitants) [Eurostat 2018]. The report concludes that the calculated Phase I $PEC_{surfacewater}$ of 0.00042 µg/L for macitentan is below the EMA action limit of 0.01 µg/L and according to EMA guideline [EMA/CHMP/SWP/4447/00]; an environmental risk assessment based on PEC/PNEC calculation for macitentan is therefore not required.

***Rapporteur Assessment***

The Applicant stated that $F_{pen}$ value is based on PAH and CTEPH prevalence data in Sweeden and Great Britain, respectevely, which are the countries with the highest PAH and CTEPH prevalences. Submitted references show the PAH prevalences vary largely among different member states (i.e. from 4.6 per million in Spain to 25 per million in Sweden) and thus the prevalence data of PAH from Sweden are acceptable for the refinement of $F_{pen}$. However, the Applicant should clarify how prevalence of CTEPH in Great Britain was calculated or use prevalence data from a reliable source as Orphanet. In both cases , PAH and CTEPH, prevalence data should be also updated with the most recent published data of European population (1st January of 2018) and $PEC_{surfacewater}$ value should be recalculated with the the new $F_{pen}$ values (OC).

# Clinical pharmacology aspects

None

## Clinical efficacy aspects

### *Question 3*

***The Applicant is requested to discuss the reasons for the important protocol deviations in MERIT-1 and the possible implications of these on the efficacy outcome (PVR and 6MWT), especially since the percentage of patients with important protocol deviations was substantial and there is an imbalance between the macitentan and placebo group***

***Summary of MAH answer***

During the MERIT-1 study, 19 (47.5%) subjects in the macitentan group and 26 (65.0%) of subjects in the placebo group had at least one protocol deviation that was defined as 'important' according to the following criteria.

- Those violating any eligibility criterion.
- Those affecting the assessment of the primary efficacy endpoint (PVR at rest at Week 16), or the key secondary efficacy endpoint (change from baseline to Week 24 in 6MWD)
- Those that may have put the subject's safety or the validity of the trial at risk [Module 5.3.5.1 D-17.097 section 10.3].

The applicant has performed a comprehensive review of the important deviations in the MERIT-1 study and assessed their impact on the PVR and 6MWD endpoints [Table 10].

The most frequently reported deviations were changes in diuretic therapy and assessments performed outside the protocol-defined window. A small number of important protocol deviations were associated with the assessment of PVR or 6MWT [Table 10]. No apparent systematic trend was observed regarding the occurrence of any specific deviation.

**Table 10 Important protocol deviations and their relevance for PVR and 6MWD endpoints, MERIT-1, FAS**

| Protocol deviation | Timepoint | Macitentan | | Placebo | | Pot impact on PVR | Pot impact on 6MWD | Comments |
|---|---|---|---|---|---|---|---|---|
| | | N | % | n | % | | | |
| 6MWT corridor deviations not approved by Actelion and documented on the site 6MWT corridor card before performing any study-specific 6MWT | Prior to screening | 0 | 0.0% | 1 | 2.5% | No | Yes | This subject had > 450 m 6MWD at MERIT-1 baseline [Module 5.3.5.1 D-17.097 appendix 16.2.6.2]. The subject was excluded in Estimand 3, New PPS/6MWD PPS [Table 23] |
| Second screening 6MWD differs from the first 6MWD by > 10% and no third 6MWD obtained | At screening | 1 | 2.5% | 0 | 0.0% | No | No | Value not used for any efficacy assessment; unlikely to affect eligibility of a patient in FC II |
| Subject on diuretic and/or calcium channel blocker treatment for whom the dose has not been stable for at least 1 week prior to baseline RHC up to randomization | At screening | 1 | 2.5% | 4 | 10.0% | No | No | Criteria of disease stability. Diuretics: no impact on efficacy assessment with chronic dosing of CCB's for vasoreactivity testing (by definition low/no response) |
| Symptomatic acute pulmonary embolism in the 6-month period prior to randomization | At screening | 1 | 2.5% | 0 | 0.0% | Unlikely | Unlikely | Safety-relevant eligibility criterion without direct impact on efficacy |
| The baseline RHC was not performed as per the study-specific RHC guidelines | At screening | 1 | 2.5% | 1 | 2.5% | No | No | The deviations do not affect the primary endpoint: "A blood sample was not drawn for mixed venous oxygen saturation ($SvO_2$)" |
| Female of childbearing potential not using 2 reliable methods of contraception from screening AND not truly abstinent (as per protocol definition) | At screening | 0 | 0.0% | 1 | 2.5% | No | No | Safety-relevant eligibility criterion without impact on efficacy |
| No baseline V/Q scan available | At screening | 0 | 0.0% | 2 | 5.0% | No | No | Perfusion scintigraphy available for adjudication only; presence of acceptable diagnostic evidence confirmed by adjudication committee |
| Subject did not personally sign & date the informed consent prior to initiation of a study-mandated procedure | At screening | 0 | 0.0% | 1 | 2.5% | No | No | GCP relevant (IC signed by son as patient was illiterate); no impact on efficacy data |
| Three 6MWTs were performed on the same day | At screening | 0 | 0.0% | 1 | 2.5% | No | Potential | Minor impact expected, given the potential training effect which could be offset by exhaustion |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Diuretics did not remain unchanged from randomization up to EOT (i.e., prescribed dose changed and/or new diuretic initiated, and/or diuretic stopped) | After randomization | 13 | 32.5% | 10 | 25.0% | No | No | Chronic diuretic therapy is not expected to have an impact on PVR in the studied population. |
| Laboratory re-test due to decrease in Hb from baseline of >20 g/L not performed | After randomization | 5 | 12.5% | 2 | 5.0% | No | No | Safety-relevant criterion without direct impact on efficacy |
| The RHC at Visit 4 or Visit 5a was not performed within the allowed time window | After randomization | 3 | 7.5% | 5 | 12.5% | No | No | RHC performed a few days after the pre-specified time window is not considered to impact the assessments (deviation between 2 days and 1 week) |
| Visit 4 not performed within allowed time window (Day 113 +/−7d) | After randomization | 3 | 7.5% | 1 | 2.5% | No | No | Performing a visit a few days after the pre-specified time window is not expected to impact efficacy data (deviations between 1 and 3 days) |
| Dose of calcium channel blocker did not remain unchanged from randomization up to EOT | After randomization | 1 | 2.5% | 2 | 5.0% | Minor | No | All study subjects with negative vasoreactivity testing, hence change in CCB dose is expected to be without relevant impact on hemodynamics |
| PK sample collected more than 48 hours after last dose of study drug | After randomization | 1 | 2.5% | 0 | 0.0% | No | No | PK analysis-relevant eligibility criterion without direct impact on efficacy |
| Subjects with WHO FC III or IV at baseline for whom the dose of PDE-5 inhibitor, or oral / inhaled prostanoid did not remain unchanged from randomization up to Week 16/Visit 4 | After randomization | 1 | 2.5% | 0 | 0.0% | No | No | Deviation: sildenafil tablet strength changed from 20 to 25 mg, however, daily dose remained unchanged |
| The RHC at Visit 4 or Visit 5a was not performed as per the study-specific RHC guidelines | After randomization | 1 | 2.5% | 1 | 2.5% | No | No | Not relevant for primary or secondary efficacy endpoint: "A blood sample was not drawn for mixed venous oxygen saturation ($SvO_2$)" |
| No post-baseline RHC available (Visit 4 and/or Visit 5a present but no RHC reported at Visit 4 and 5a reported) | After randomization | 0 | 0.0% | 3 | 7.5% | Yes | No | Values imputed for the PPS analysis |
| Patient has not performed safety follow-up visit and laboratory assessment not performed or not evaluable | After randomization | 0 | 0.0% | 1 | 2.5% | No | No | Safety relevant finding, no impact on efficacy readings |
| Subject received a PH therapy (i.e., ERA, i.v. or subcutaneous prostanoid, guanylate cyclase stimulator, or Larginine) from Week 16/Visit 4 up to EOT | After randomization | 0 | 0.0% | 1 | 2.5% | Potential | Yes | During MERIT-1, subjects with initiation of PAH therapies (i.e, rescue medications) after Week 16 were imputed with LOCF at Week 24 [Table 23, Table 66] |
| Subject with WHO FC II at baseline received a PDE-5 inhibitor, or an oral or inhaled prostanoid prior to Week 16/Visit 4 | After randomization | 0 | 0.0% | 1 | 2.5% | Potential | Yes | This subject received (initiated) PAH therapies prior to Week 16. The subject had 2 intercurrent events, death at Day 129 and use of sildenafil prior to Week 16. The intercurrent event death was used for Estimand 3 [Table 23] |
| Subjects with WHO FC III or IV at baseline for whom the dose of PDE-5 inhibitor, or oral / inhaled prostanoid did not remain unchanged from Week 16/Visit 4 up to EOT | After randomization | 0 | 0.0% | 1 | 2.5% | Potential | Yes | Durin MERIT-1, subjects with initiation of PAH therapies after Week 16 were imputed with LOCF at Week 24 [Table 23, Table 66] |
| The RHC at Visit 4 or Visit 5a was not performed at the same location and in the same condition as the baseline RHC | After randomization | 0 | 0.0% | 2 | 5.0% | Potential | No | RHC performance at different locations is unlikely to impact readings |
| Visit not performed | After randomization | 0 | 0.0% | 1 | 2.5% | No | Yes | Subject was lost to follow-up after Week 16; 6MWD value was imputed for the PPS analysis |
| Week 24 visit performed but 6MWD missing | After randomization | 0 | 0.0% | 2 | 5.0% | No | Yes | Values imputed for the PPS analysis |

No important protocol deviation was reported in the MERIT-1 CSR for 1 macitentan subject with > 450 m 6MWD at MERIT-1 baseline [Module 5.3.5.1 D-17.097 appendix 16.2.2 and appendix 16.2.6.2]. This subject was excluded in Estimand 3 New PPS/6MWD PPS [Table 23].
No important protocol deviation was reported in the MERIT-1 CSR for 1 placebo subject who received PH advanced therapy beyond Week 16 [Module 5.3.5.1 D-17.097 appendix 16.2.2 and appendix 16.2.4.4]. This subject was included in Estimand 3, with LOCF rule applied at Week 24 [Table 23].
Source: Module 5.3.5.1 D-17.097 table 15-11 (per-protocol analysis set)
6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CCB = calcium channel blocker; EOT = End-of-Treatment;ERA = endothelin receptor antagonist; FC = functional class; GCP = Good Clinical Practice; Hb = hemoglobin; IC = Informed Consent; i.v. = intravenous; LOCF = last-observation-carried-forward; PDE-5 = phosphodiesterase-5; PH = pulmonary hypertension; PK = pharmacokinetic(s); PPS = Per-protocol set; PVR = pulmonary vascular resistance; RHC = right heart catheterization; $SvO_2$ = mixed venous oxygen saturation; WHO = World Health Organization.

As described in the MERIT-1 CSR, in the PPS for PVR, no subject in the macitentan group and 6 (15.0%) subjects in the placebo group were excluded [Module 5.3.5.1 D-17.097 table 15-10]. The qualifying deviations were: WHO FC II at baseline and use of PH advanced therapy before Week 16, AE/SAEs that prevented RHC assessment, refusal by the subject to perform the RHC assessment at Week 16 or change in RHC Operator [see also Question 4].

In the updated PPS for 6MWD (New PPS/6MWD PPS) [see Question 1 and Question 4], 2 subjects (1 subject in each treatment group) with a baseline 6MWD > 450 m were excluded as ineligible [Table 10, Table 23], and for 3 placebo subjects in MERIT-1 who received sildenafil or riociguat beyond Week 16, the Week 24 6MWD values were replaced by the Week 16 values (LOCF) [Table 10, Table 23 and Question 4].

***Rapporteur Assessment***

The applicant has provided a description of number and causes of protocol deviations without giving any clear explanation for the high number of important protocol deviations reported in most patients. In addition, these protocol deviations were not at random. There were imbalances between treatment groups in the number of important protocol deviations [19 (47.5%) on macitentan vs 26 (65%) on placebo] and reasons of protocol deviations (more changes in diuretic use in the macitentan group vs placebo: 13 vs. 10 patients, without specifying the direction of the change; more visits not performed and more missing values at study time points for PVR or 6MWD in the placebo group without a clear explanation), as well as in the number of patients that were excluded in the per protocol analysis (0 patients on macitentan vs. 6 patients on placebo).

Given the small sample size and the relatively wide number of reasons that led to the qualifying per protocol deviations, no clear conclusions can be drawn. All these imbalances in protocol deviations could be due to different causes including some imbalances in baseline characteristics, systematic bias during study conduct, or not optimal study oversight and/or patients' follow-up. In addition, when analyzing the results per protocol, the differences in PVR and 6MWD become not statistically significant. All these findings go in favor of concluding that the study results are not robust.

***Conclusion:***

***Issue not solved. Data provided are supportive of the major objection.***

The high number of important protocol deviations in more than 50% of patients and the fact that these deviations were not at random (much higher in the placebo group) add uncertainties on whether study conduct and oversight was adequate and goes against the robustness of the results. The applicant is invited to discuss on the potential causes for these not at random protocol deviations. (see joint conclusion in the conclusion of the assessment of Q1).

***Question 4***

***The Applicant is asked to discuss what estimand would be most suitable to describe the treatment effect in the population proposed (see ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials).***

***Summary of MAH answer***
The relevant estimands for the treatment effect of macitentan vs placebo under hypothesis testing are:
• PVR at Week 16 – Estimand 1 "PVR (FAS, Corrected)" which corrects for errors in the calculation of the PVR for 4 subjects from China and Thailand and describes the treatment effect based on hypotheses testing [Table 17]

and

• 6MWD at Week 24 – Estimand 1 "6MWD (FAS)" best tests the treatment effect of macitentan versus placebo on exercise capacity [Table 21]. Same as for Estimand 3 for 6MWD, the pre-specified statistical analysis ANCOVA is considered appropriate and robust to the small deviation from the normal distribution of the 6MWD data.

Intercurrent events, i.e., death, AEs, and study discontinuation, are included for PVR (FAS, Corrected) and 6MWD (FAS). Administration of rescue medication beyond Week 16 was not considered as an intercurrent event for the 6MWD (FAS), a limitation for this estimand. The relevant estimands to quantify the treatment effect of macitentan vs placebo in eligible patients with inoperable CTEPH while on treatment without intercurrent events are as follows:

• PVR at Week 16 – Estimand 2 "PVR (PPS, Corrected)" which corrects for errors in the calculation of the PVR for 4 subjects from China and Thailand [Table 18] and best quantifies the true effect of macitentan on pulmonary hemodynamics, including correct population (PPS) and appropriately handling intercurrent events, while preserving the randomization
and

• 6MWD at Week 24 – Estimand 3 "New PPS/6MWD (New PPS)" best quantifies the true treatment effect of macitentan on exercise capacity, including correct population (eligible patients only) and accounting for all relevant intercurrent events for 6MWD [Table 23]. The ANCOVA analysis is considered appropriate and robust to the small deviation from normal distribution of the data, as also acknowledged in the assessment report.

For each estimand, we consider the main estimator to be the appropriate one. This is because of "logical" imputation rules (no positive values imputed for placebo subjects who died); and use of appropriate statistical analyses method (ANCOVA).

The applicant considers the main estimator for each estimand as more appropriate than sensitivity estimators because of "established" imputation rules (no positive values imputed for subjects who died, as in CHEST-1) and statistical analysis (ANCOVA), as discussed in response to Question 4 and summarized below.

**Table 11 Main estimators for PVR and 6MWD for the chosen estimands**

| Main estimators for PVR and 6MWD | *Geometric mean ratio (macitentan vs placebo, 95% CLs), p-value* |
|---|---|
| **PVR at Week 16** | |
| **Estimand 1 "FAS, Corrected"** | |
| Main Estimator (N = 80) | 0.81 (0.69, 0.95), p = 0.0084 |
| **Estimand 2 "PPS, Corrected"** | |
| PPS (Corrected, N = 74) | 0.84 (0.71, 0.99), p = 0.0388 |
| **6MWD at Week 24** | *Difference in LS Means (macitentan – placebo, 95% CLs), p-value* |
| **Estimand 1 "FAS"** | |
| Main Estimator (N = 80) | 34.04 (2.90, 65.19), p = 0.0326 |
| **Estimand 3 "New PPS/6MWD PPS"** | |
| Main Estimator (N = 78) | 41.66 (9.50, 73.82), p= 0.0118 |

Source: Table 20 and Table 24.
6MWD = 6-minute walk distance; CL= confidence limit(s); FAS = Full analysis set; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.

### 4.1 Detailed considerations

In Table 12–Table 14, 3 estimands for PVR are presented, with the detailed description of the main estimator and several sensitivity estimators. Table 15 provides the results of all analyses for each estimator of PVR (Not Corrected). As PVR was wrongly calculated for 4 subjects in the MERIT-1 CSR [Table 16], 3 additional estimands which mirror the previous ones were defined but with corrected values [Table 17–Table 19]. The results of these analyses are presented in Table 20 and Figure 4.

In Table 21–Table 23, 3 estimands for 6MWD are presented and the results from these analyses are presented in Table 24 and Figure 5. The new estimand for 6MWD [Table 23] is introduced based on the PPS for 6MWD.

Overall conclusions are provided in Section 4.1.4.

#### 4.1.1 PVR (Not Corrected): Estimand 1 (FAS), Estimand 2 (PPS), Estimand 3 (FAS [Difference])

There were 3 main estimands for the primary endpoint of PVR that were prospectively planned in the MERIT-1 CSR SAP prior to database lock:

i) "FAS, Not Corrected" with population-level summary measure: ratio of geometric means of PVR including all randomized subjects in MERIT-1 (N = 80) [Table 12].
ii) "PPS, Not Corrected" with population-level summary measure: ratio of geometric means of PVR for MERIT-1 randomized subjects without protocol deviations that could have impacted PVR assessment at Week 16 (N = 74) [Table 13]
iii) "FAS, Not Corrected – (Difference)" with population-level summary measure: difference from baseline to Week 16 in PVR for all randomized subjects in MERIT-1 (N = 80) [Table 14]

**Table 12 Estimand 1 (FAS, Not Corrected) for the primary endpoint of PVR**

| | |
|---|---|
| **A) Population:** All randomized subjects with inoperable CTEPH, defined through protocol inclusion/exclusion criteria (Full Analyses Set [FAS])<br>**B) Variable:** PVR at Week 16, expressed as percent of the baseline value, i.e., (PVR at Week 16/PVR at Baseline)*100<br>**C) Intercurrent events and strategies**: See below description for main estimator and sensitivity estimators<br>**D) Population-level summary measure:** Ratio of geometric means of PVR (Geometric mean ratio= Geometric mean macitentan/Geometric mean placebo) where endpoint is defined as above. | |
| **Estimand 1 "FAS Not Corrected"** | |
| **Estimators** | **Details of planned analyses and handling of intercurrent events** |
| **Main estimator** | **Handling of intercurrent events:**<br>**Death***: for 1 placebo subject [redacted] PVR value at Week 16 was imputed by the largest percent deterioration in the placebo group (worst observation), i.e., 55%.<br>**AE/SAE events that prevent RHC assessment at Week 16***: for 2 placebo subjects ([redacted]), PVR at Week 16 was imputed as 12% improvement based on the median PVR at Week 16 in the placebo group [D-17.097 table 11-1], expressed as percent of baseline.<br>**Subject refusal to perform RHC assessment at Week 16***: 1 placebo subject ([redacted]) PVR at Week 16 was imputed as 12% improvement.<br><br>**Analysis:** Change from baseline to Week 16 in log PVR was analyzed using an ANCOVA model with treatment as factor and baseline log PVR as covariable. Ratio of geometric means (macitentan over placebo) was obtained by exponentiation.<br>**Strengths**: initial randomization was fully preserved and a conservative approach for missing values was applied; 12% improvement was imputed for 3 subjects in the placebo group (not deterioration). Assigning a meaningful value for the outcome variable for subjects who died is not straightforward, however the imputation of 55% deterioration (worst case scenario) was considered to be appropriate. Missing values occurred only in placebo treatment arm, i.e., subjects who received placebo deteriorated and could not perform the Week 16 PVR assessment.<br>**Limitations**: The imputations assume missing at random for subjects alive, which was an assumption that was hard to test. Because of this, different sensitivity estimators are proposed below. |

| Estimators | Details of planned analyses and handling of intercurrent events |
|---|---|
| Sensitivity estimator#1 **Multiple imputation** | **Handling of intercurrent events:**<br>**Death**: Multiple imputation with categorization "Worsening" for 1 subject who died (Subject [redacted].<br>**SAE event that prevent RHC assessment:** Multiple imputation with categorization "Worsening" for 1 subject. (Subject [redacted])<br>**AE and Subject refusal to perform RHC assessment at Week 16**: Multiple imputation with categorization "No change" for 2 subjects ([redacted])<br><br>**Analysis:** Multiple imputation was applied that included reasons for missing values ("Worsening", "No Change" or "Improvement"), The randomly imputed value was generated from a normal distribution with a mean value that depended on the reason for missingness and variance estimated from the complete cases within the placebo group.<br>**Limitations**. All missing values were for subjects who received placebo, no imputation was applied for the macitentan group. Reason for missingness might be not the "perfect fit/categorization" that one would expect for few subjects, i.e., "Worsening" for 2 subjects, subject who died and subject with an SAE (supraventricular tachycardia) and "No Change" for 2 subjects, one who had a procedural hemorrhage (but no SAE and no worsening in WHO FC) and one who refused to perform RHC assessment at Week 16. |
| Sensitivity estimator#2 **BOCF for subjects who are alive and with an intercurrent event** | **Handling of intercurrent events**:<br>**Death**: same as for main estimator.<br>**AE/SAE events that prevent RHC assessment/Subject refusal to perform RHC assessment at Week 16:** baseline observation carried forward.<br><br>**Analysis**: Same as for main estimator.<br>**Limitations:** Same as for main estimator. |
| Sensitivity estimator#3 **Extended ANCOVA model** | **Handling of intercurrent events:** Same as for main estimator.<br><br>**Analysis:** Same as for main estimator but WHO FC was added in the ANCOVA model together with the baseline and treatment.<br>Strength: Same as for main estimator. Adding WHO FC as a covariate, but not as a stratification factor, increases the precision/accuracy of the estimator.<br>**Limitations**: Same as for main estimator. |
| Sensitivity estimator#4 **Hodges-Lehman estimator** | **Handling of intercurrent events:** Same as for main estimator.<br><br>**Analysis**: Hodges-Lehmann estimate from the non-parametric procedure and p-value based on Wilcoxon rank sum test on residuals<br>**Limitations:** Treatment effect estimated without adjustment for 6MWD baseline value. |
| Sensitivity estimator#5 **Observed (without imputations)** | **Handling of intercurrent events:**<br>**Death**: excluded<br>**AE/Study discontinuation**: excluded<br>**AE/SAE events that prevent RHC assessment at Week 16*:** excluded<br>**Subject refusal to perform RHC assessment at Week 16**: excluded<br><br>**Analysis**: same as for main estimator<br>**Limitations**: Subjects with missing values were not included resulting in bias and imbalance between the treatment groups, and reasons (e.g., disease progression, AEs/SAEs) for missing values were not considered. In addition, further imbalance was introduced against active treatment (macitentan) not including these "worse placebo cases". |

* MERIT-1 CSR [Module 5.3.5.1 D-17.097 table 11-3].

6MWD = 6-minute walk distance; AE = adverse event; ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; FAS = Full analyses set; FC = functional class; LOCF = last observation carried forward; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

## Table 13 Estimand 2 (PPS, Not Corrected) for the primary endpoint of PVR

| | |
|---|---|
| **A) Population:** Randomized subjects with inoperable CTEPH, defined through protocol inclusion/exclusion criteria and excluding randomized subjects with protocol deviations that could impact assessment of PVR (Per Protocol Set [PPS]). Protocol Deviations were: WHO FC II at baseline and use of PH advanced therapy before Week 16: Subject [redacted] was excluded, AE/ SAE events that prevent RHC assessment at Week 16: Subjects [redacted] were excluded, Subject refusal to perform RHC assessment at Week 16: Subject [redacted] was excluded and Change in RHC Operator: Subjects [redacted] were excluded [Module 5.3.5.1 D 17.097 table 10-2].<br>**B) Variable:** as for main estimator: PVR at Week 16, expressed as percent of the baseline value, i.e., (PVR at Week 16/PVR at Baseline)*100<br>**C) Intercurrent events and strategies**: See below description<br>**D) Population-level summary measure: as for main estimator:** Ratio of geometric means of PVR (Geometric mean ratio= Geometric mean macitentan/Geometric mean placebo) where endpoint is defined as above. | |
| **Estimand 2 "PPS Not Corrected"** | |
| Estimator #1<br>**PPS (PVR)** | **Handling of intercurrent events: Same as for main estimator**<br>• Subjects [redacted] were excluded<br>**Analysis:** same as for main estimator<br>**Limitations:** 6 placebo subjects (no macitentan subject) with protocol deviations that could impact assessment of PVR were excluded resulting in bias and imbalance in number of subjects between treatment groups. |

AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; FC = functional class; PPS = Per protocol set; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

## Table 14 Estimand 3 (Difference in PVR from baseline to Week 16, Not Corrected) for the primary endpoint of PVR

| | |
|---|---|
| **A) Population:** Same as for main estimand above (Table 12), i.e., all randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria (Full Analyses Set [FAS])<br>**B) Variable:** PVR at Week 16, expressed as change from baseline to Week 16 (absolute values)<br>**C) Intercurrent events and strategies**: Same as for main estimator.<br>**D) Population-level summary measure:** Difference in means of change from baseline PVR to Week 16 between macitentan and placebo. | |
| **Estimand 3 "FAS Difference, Not Corrected"** | |
| Sensitivity Estimator<br>**Absolute difference in PVR from baseline to Week16** | **Handling of intercurrent events:** Same as for main estimator<br>**Analyses:** Same statistical method, ANCOVA, as for main estimator, but ANCOVA on absolute values that includes treatment as a factor and baseline PVR as a covariable.<br>**Limitations:** same as for main estimator. |

ANCOVA = analysis of covariance; FAS = Full Analyses Set; PVR = pulmonary vascular resistance.

**Table 15 Results for the primary endpoint of PVR (Not Corrected)**

| Estimands for Not Corrected PVR | *Geometric mean ratio (macitentan vs placebo, 95% CLs), p-value* |
|---|---|
| **Estimand 1 "FAS, Not Corrected"** | |
| Main Estimator (N = 80) | 0.84 (0.70, 0.99), p = 0.0410 |
| Multiple imputation (N = 80) | 0.84 (0.71, 1.00), p = 0.0456 |
| BOCF (N = 80) | 0.83 (0.70, 0.98), p = 0.0321 |
| Median (N = 80) | 0.85 (0.72, 1.00), p = 0.0557 |
| Extend ANCOVA (N = 80) | 0.86 (0.73, 1.02), p = 0.0883 |
| Hodges-Lehman (N = 80) | 0.82 (0.71, 0.94), p=0.0055 |
| Observed cases only (N = 76) | 0.85 (0.71, 1.02), p = 0.0749 |
| **Estimand 2 "PPS,Not Corrected"** | |
| PPS (N =74) | 0.87 (0.73, 1.04), p = 0.1302 |
| **Estimand 3 "FAS (Difference), Not Corrected"** | |
| | *LS Mean Difference (macitentan – placebo, 95% CLs), p-value* |
| Difference | -137.73 (-298.20, +22.75), p = 0.0915 |

Source: Appendix 1 Table 45; Module 5.3.5.1 D-17.097 table 15-33, table 15-35, table 15-36, table 15-39, table 15-41, table 15-42, table 15-44)]; D-18.062 table 10-27.
ANCOVA = analysis of covariance; BOCF = baseline-observation-carried-forward; CL= confidence limit(s); FAS = Full analysis set; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance

### 4.1.2 PVR (Corrected): Estimand 1 (FAS), Estimand 2 (PPS), Estimand 3 (FAS [Difference])

As mentioned in the MERIT-1 CSR addendum [D-18.062 section 4.1], following database closure of AC-055E201/MERIT-1 on 25 October 2016, and after the discovery of a computer error at one site in China that affected some of the hemodynamic variables, a comprehensive assessment of all local RHC values was conducted and corrections were reported in the addendum along with the results of sensitivity analyses.

The changes (corrections) that affected the PVR calculation of 4 subjects are summarized in Table 16.

**Table 16 Changes affecting PVR that were reported after AC-055E201 clinical database closure**

| Treatment group | Subject number (country) | Visit | RHC parameter | Changes | | | |
|---|---|---|---|---|---|---|---|
| | | | | Values as reported in the CSR | Corrected values | PVR reported in CSR | Corrected PVR |
| Macitentan | [redacted] | Week 16 | CO (L/min) | 1.06 L/min* | 2.63 L/min | 2868 dyn·s/cm$^5$ | 1155.9 dyn·s/cm$^5$ |
| | | Week 16 | CO (L/min) | 4.7 L/min | 4.92 L/min | 1311 dyn·s/cm$^5$ | 1252 dyn·s/cm$^5$ |
| | | Screening (baseline) | CO (L/min) | 2.5 L/min | 1.97 L/min | 1216 dyn·s/cm$^5$ | 1543.1 dyn·s/cm$^5$ |
| Placebo | | Screening (baseline) | PAWP (mmHg) | 4 mmHg | 10 mmHg | 488 dyn·s/cm$^5$ | 406.8 dyn·s/cm$^5$ |

CO = cardiac output; CSR = clinical study report; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance, RHC = right heart catheterization
* A value that is hardly compatible with life
Source: D-18.062 section 4.1.

Three additional estimands for PVR Corrected which mirror the previous ones (PVR Not Corrected) were defined:
i) "FAS, Corrected" with population-level summary measure: ratio of geometric means of PVR for all randomized subjects in MERIT-1 (N = 80), including corrected PVR values for 4 subjects [Table 16, Table 17].
ii) "PPS, Corrected" with population-level summary measure: ratio of geometric means of PVR for MERIT-1 randomized subjects without protocol deviations that could have impacted PVR assessment at Week 16, including corrected PVR values for 4 subjects (N = 74) [Table 18].
iii) "FAS, Corrected – (Difference)" with population-level summary measure: difference from baseline to Week 16 in PVR for all randomized subjects in MERIT- 1 including corrected PVR values (N = 80) [Table 19].

**Table 17 Estimand 1 (FAS, Corrected) for the primary endpoint of PVR**

| | |
|---|---|
| **A) Population:** All randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria (Full Analyses Set [FAS])<br>**B) Variable:** PVR at Week 16, expressed as percent of the baseline value, i.e., (PVR at Week 16/PVR at Baseline)*100<br>**C) Intercurrent events and strategies**: See below description for main estimator and sensitivity estimators<br>**D) Population-level summary measure:** Ratio of geometric means of PVR (Geometric mean ratio= Geometric mean macitentan/Geometric mean placebo) where endpoint is defined as above. | |
| **Estimand 1 "FAS Corrected"** | |
| **Main Estimator (Corrected)** | **Handling of intercurrent events (same as for Not Corrected Estimand 1):**<br>**Death*:** for 1 placebo subject ([redacted]) PVR value at Week 16 was imputed (due to death) by the largest percent deterioration in the placebo group (worst observation), i.e., 55%.<br>**AE/SAE events that prevent RHC assessment at Week 16*:** for 2 placebo subjects ([redacted]), PVR at Week 16 was imputed as 12% improvement based on the median PVR at Week 16 in the placebo group, expressed as percent of baseline.<br>**Subject refusal to perform RHC assessment at Week 16*:** 1 placebo subject ([redacted]) PVR at Week 16 was imputed as 12% improvement.<br>**Analysis:** Change from baseline to Week 16 in log PVR was analyzed using an ANCOVA model with treatment as factor and baseline log PVR as covariable. Ratio of geometric means (macitentan over placebo) was obtained by exponentiation.<br>**Strengths**: initial randomization is fully preserved and a conservative approach for missing values was applied (please see also below), 12% improvement was imputed for 3 subjects in the placebo group. Assigning a meaningful value of the outcome variable for subjects who died is not straightforward, however the imputation of 55% deterioration (worst case scenario) was considered appropriate. Missing values occurred only in the placebo group, i.e. subjects who received placebo deteriorated and could not perform the Week 16 PVR assessment.<br>**Limitations**: It was performed after the database lock. The Sponsor agrees with Co-Rapporteur that these imputations assume missing at random for living subjects, which is an assumption that is hard to test. Because of this, different sensitivity estimators are proposed below. |
| Sensitivity estimator#1 **Multiple imputation (Corrected)** | Same as for Not-Corrected |
| Sensitivity estimator#2 **BOCF for subjects who are alive and with an intercurrent event (Corrected)** | Same as for Not-Corrected |
| Sensitivity estimator#3 **Extended ANCOVA model (Corrected)** | Same as for Not-Corrected |
| Sensitivity estimator#4 **Hodges-Lehman estimator (Corrected)** | Same as for Not-Corrected |
| Sensitivity estimator#5 **Observed (without imputations) (Corrected)** | Same as for Not- Corrected |

* MERIT-1 CSR [Module 5.3.5.1 D-17.097 table 11-3].
AE = adverse event; ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; FAS = Full Analyses Set; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SAE = serious adverse event.

## Table 18 Estimand 2 (PPS, Corrected) for the primary endpoint of PVR

| | |
|---|---|
| **A) Population:** Randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria and excluding randomized subjects with protocol deviations that could impact assessment of PVR (Per Protocol Set [PPS]). Protocol deviationswere : WHO FC II at baseline and use of PH advanced therapy before Week 16: Subject [redacted] was excluded; AE/ SAE events that prevent RHC assessment at Week 16: Subjects [redacted] and [redacted] were excluded; Subject refusal to perform RHC assessment at Week 16: Subject [redacted] was excluded and Change in RHC Operator: Subjects [redacted] and [redacted] were excluded [Module 5.3.5.1 D 17.097 table 10-2].<br>**B) Variable:** as for main estimator: PVR at Week 16, expressed as percent of the baseline value, i.e., (PVR at Week 16/PVR at Baseline)*100<br>**C) Intercurrent events and strategies**: See below description<br>**D) Population-level summary measure: as for main estimator:** Ratio of geometric means of PVR (Geometric mean ratio= Geometric mean macitentan/Geometric mean placebo) where endpoint is defined as above. | |
| **Estimand 2 "PPS, Corrected"** | |
| Estimator #1<br>**PPS (PVR) (Corrected)** | **Handling of intercurrent events: Same as for main estimator**<br><br>**Analysis:** same as for main estimator<br>**Possible limitations:** 6 placebo subjects (no macitentan subject) with protocol deviations that could impact assessment of PVR were excluded resulting in bias and imbalance in number of subjects between treatment groups. |

AE = adverse event; FC = functional class; RHC = right heart catheterization; PPS = Per Protocol Set; PVR = pulmonary vascular resistance; SAE = serious adverse event; WHO = World Health Organization.

## Table 19 Estimand 3 (Difference in PVR (Corrected) from baseline to Week 16) for the primary endpoint of PVR

| | |
|---|---|
| **A) Population:** Same as for main estimand above (Table 12)], i.e., all randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria (Full Analyses Set [FAS])<br>**B) Variable:** PVR at Week 16, expressed as change from baseline to Week 16 (absolute values)<br>**C) Intercurrent events and strategies**: Same as for main estimator.<br>**D) Population-level summary measure:** Difference in means of change from baseline PVR to Week 16 between macitentan and placebo. | |
| **Estimand 3 "FAS Difference in PVR, Corrected"** | |
| Sensitivity Estimator<br>**Difference in PVR (Corrected) from baseline to Week 16** | **Handling of intercurrent events:** Same as for main estimator<br><br>**Analyses:** Same statistical method, ANCOVA, as for main estimator, but ANCOVA on absolute values that includes treatment as a factor and baseline PVR as a covariable.<br>**Possible limitations:** same as for main estimator. |

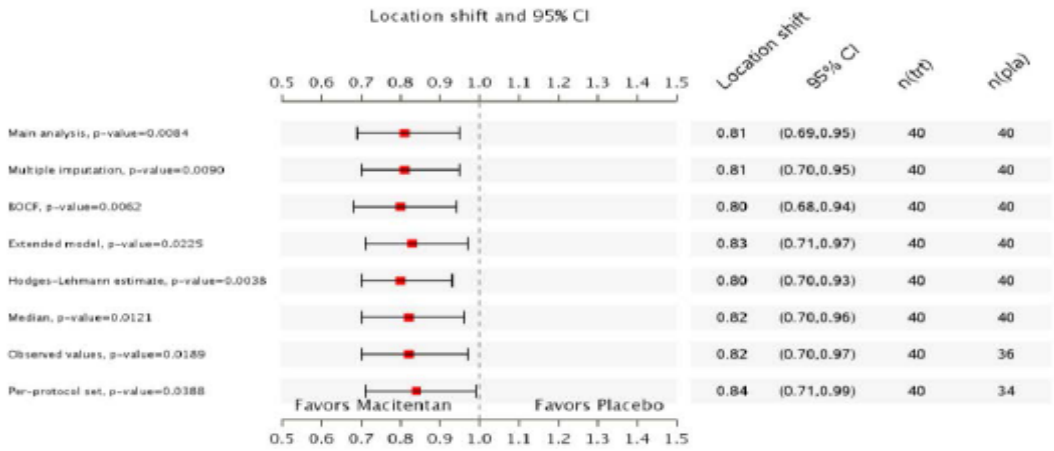
ANCOVA = analysis of covariance; FAS = Full Analyses Set; PVR = pulmonary vascular resistance.

**Table 20 Results for the primary endpoint of PVR (Corrected)**

| Estimands for Corrected PVR | *Geometric mean ratio (macitentan vs placebo, 95% CLs), p-value* |
|---|---|
| **Estimand 1 "FAS, Corrected"** | |
| Main Estimator (N = 80) | 0.81 (0.69, 0.95), p = 0.0084 |
| Multiple imputation (N = 80) | 0.81 (0.70, 0.95), p = 0.0090 |
| BOCF (N = 80) | 0.80 (0.68, 0.94), p = 0.0062 |
| Median (N = 80) | 0.82 (0.70, 0.96), p = 0.0121 |
| Extend ANCOVA (N = 80) | 0.83 (0.71, 0.97), p = 0.0225 |
| Hodges-Lehman (N = 80) | 0.80 (0.70, 0.93), p = 0.0038 |
| Observed cases only (N = 76) | 0.82 (0.70, 0.97), p = 0.0189 |
| **Estimand 2 "PPS, Corrected"** | |
| PPS (Corrected, N = 74) | 0.84 (0.71, 0.99), p =0.0388 |
| **Estimand 3 "FAS (Difference), Corrected"** | |
| | *LS Mean Difference (macitentan – placebo, 95% CLs), p-value* |
| Difference | −189.56 (−308.68, −70.44), p = 0.0022 |

Source: Appendix 1 Table 70; D-18.062, table 10-2, table 10-4, table 10-6, table 10-8, table 10-10, table 10-12, table 10-14, table 10-22.
ANCOVA = analysis of covariance; BOCF = baseline-observation-carried-forward; CL= confidence limit(s); FAS = Full analysis set; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.

**Figure 4 Results for Estimand 1 "FAS Corrected" and Estimand 2 "PPS Corrected"**




n(trt) = No. of Subjects in Macitentan. n(pla) = Number of Subjects in Placebo
Main analysis: Statistical model is Analysis of Covariance including log(PVR at baseline) as a covariate, with Treatment as factor in the model;
BOCF: Baseline observation carried forward (for subjects with missing data the baseline carried forward is imputed, except for the subjects who died imputed with the worst case observed within the treatment arm they were randomized);
Extended model: Analysis of Covariance with log(PVR at baseline) and WHO functional class at baseline as covariates with Treatment as a factor in the model;
Multiple imputation: Multiple imputation method is applied under the assumption of missing at random (MAR), with a slight modification based on the reason for missingness;
Median: For subjects with missing data, imputed with median of the percent of baseline PVR from all subjects in the same treatment group and analysis set.
Output: F_PVR_FP_EMA_FAS, Produced by biarnal1 on 19DEC2018 15:39 (CET), SDTM production date: 28MAY2018
Program: val_csr/program_output/f_pvr_fp_ema.sas

**4.1.3 6MWD: Estimand 1 (FAS), Estimand 2 (PVR PPS), Estimand 3 (New PPS/6MWD PPS)**
A short summary of the limitations of different statistical methods used for analyzing 6MWD is provided in the statistical methodology section in the Summary of Clinical Efficacy (SCE) [D-18.252 section 2.1.3, sensitivity analysis for 6MWD]. Table 21 and Table 22 below summarize different estimands for the 6MWD analyses.

There were 3 main estimands for the key secondary endpoint of 6MWD:
i) FAS (includes all 80 randomized subjects in MERIT-1 [Table 21]

ii) "PVR PPS"– based on the definition of the PPS for PVR includes randomized subjects in MERIT-1 without protocol deviations that could have impacted the PVR assessment at Week 16 (N = 74) [Table 22]
iii) New estimand "New PPS/6MWD PPS": This estimand was not included in the SCE or Clinical Overview submitted in August 2018. This estimand includes subjects who were eligible for 6MWD post-baseline assessments. In addition, the adjustment for the new intercurrent event, rescue medication during MERIT-1 study, is also applied (N = 78) [Table 23].

**Table 21 Estimand 1 (FAS) for the key secondary endpoint of 6MWD**

| | |
|---|---|
| **A) Population:** All randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria (Full Analyses Set [FAS])<br>**B) Variable:** 6MWD at Week 24, expressed as change from baseline value to Week 24<br>**C) Intercurrent events and strategies**: See below description for main estimator and sensitivity estimators<br>**D) Population-level summary measure:** difference in means of change from baseline 6MWD to Week 24 between macitentan and placebo | |
| **Estimand 1 "FAS"** | |
| **Main estimator FAS** | **Handling of intercurrent events:**<br>**Death***: For 2 placebo subjects ([redacted] who died, 0 m were imputed (the worst possible outcome)<br>**AE/SAE events that prevent 6MWD assessment at Week 24**: 1 placebo subject ([redacted]) experienced AE Arthralgia, LOCF was imputed<br>**Discontinuation from the study (Lost to Follow up)**: 1 placebo subject ([redacted], LOCF was imputed<br>Administration of rescue medications occurred only in placebo, was not handled. There were 3 subjects in the placebo group in MERIT-1 ([redacted] riociguat, [redacted] sildenafil, [redacted] riociguat) who initiated PH therapy after Week 16. Their 6MWD data were included without modification for use of rescue medications.<br><br>**Analysis:** Change from baseline to Week 24 in 6MWD was analyzed using an ANCOVA model with treatment as a factor and baseline 6MWD as a covariable.<br>**Strength**: initial randomization is fully preserved; quite conservative approach for missing values was applied (please see also below), 0 meters for 2 subjects who died and LOCF for a subject who was lost to follow up (488 m for 6MWD at Week 24, 52 meters more than on baseline) and one subject who experienced an AE of Arthralgia (283 m was imputed for 6MWD at Week 24 that was the same as 6MWD at baseline), hence quite sensible imputations.<br>A similar statistical analysis (ANCOVA) was used in riociguat Main publication [Ghofrani 2013a] and CHMP Assessment Report [Adempas EPAR 2014] and statistical methods were considered acceptable. The deviation from the normal distribution of the 6MWD data was not large, and the ANCOVA test was valid as it is robust to some deviation from normality [Blance 2017].<br>**Limitations**: Administration of rescue medications, intercurrent event that occurred only in placebo, was not handled. All missing values were reported only for placebo, hence no imputation for macitentan. The imputations assume missing at random for subjects alive, which was an assumption that was hard to test. |
| Sensitivity estimator#1 **Multiple Imputation 1** | **Handling of intercurrent events:**<br>**Death**: same as for main estimator (0 m for subjects who died)<br>**AE/Study discontinuation**: the estimated change in 6MWD from the regression model was imputed for subjects with missing values who were alive (multiple imputations is applied under the assumption of missing at random (MAR) for intercurrent events).<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis:** Pattern-mixture model approach for multiple imputation - determination of tipping point, then ANCOVA same as for main estimator of 6MWD.<br>**Strength**: similar to main estimator but, for subjects who are alive and with missing values in 6MWD, missing values were imputed from the model.<br>**Limitations**: Administration of rescue medications, occurred only in placebo, was not handled. All missing values were reported in the placebo group and no imputations were applied for macitentan. |

| Estimand 1 "FAS" | |
|---|---|
| Sensitivity estimator#2 **Multiple Imputation 2** | **Handling of intercurrent events:**<br>**Death**: imputed by worst change from baseline to Week 24 in 6MWD within the treatment in placebo, i.e. -78 meters.<br>**AE/Study discontinuation**: Same as Sensitivity Estimator 1, i.e., the estimated change in 6MWD from the regression model was imputed for subjects with missing values who were alive (multiple imputations is applied under the assumption of missing at random (MAR) for intercurrent events).<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis:** Same as Sensitivity Estimator 1, i.e. Pattern-mixture model approach for multiple imputation, then ANCOVA<br>**Strength:** As for the main estimator.<br>**Limitations:** As above, administration of rescue medications, occurred only in placebo, was not handled; all missing values were reported in the placebo group and no imputations were applied for macitentan. In this sensitivity estimator, a positive 6MWD value was imputed for subjects who died. |
| Sensitivity estimator#3 **BOCF** | **Handling of intercurrent events:**<br>**Death**: BOCF<br>**AE/Study discontinuation**: BOCF<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis**: Same as for main estimator<br>**Limitations**: Administration of rescue medications, occurred only in placebo, was not handled. All missing values were reported in the placebo group, hence imputations performed only for these subjects. Positive 6MWD imputed for subjects who died. Subjects were deteriorated from baseline due to intercurrent events defined above but BOCF imputation did not reflect it. |
| Sensitivity estimator#4 **LOCF** | **Handling of intercurrent events:**<br>**Death**: LOCF<br>**AE/Study discontinuation**: LOCF<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis:** Same as for main estimator<br>**Limitations:** Same as for BOCF sensitivity estimator. |
| Sensitivity estimator#5 **Median** | **Handling of intercurrent events:**<br>**Death:** Median of change from baseline to Week 24 in placebo group.<br>**AE/Study discontinuation**: Median of change from baseline to Week 24 in the placebo group.<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis**: Same as for main estimator of 6MWD<br>**Limitations**: Same as BOCF sensitivity estimator. |
| Sensitivity estimator#6 **ANOVA model** | **Handling of intercurrent events:** Same as for main estimator.<br><br>**Analysis:** Same as for main estimator but only treatment was included in ANOVA model (no adjustment for baseline).<br>**Limitations:** Treatment effect estimated without adjustment for 6MWD baseline value. |
| Sensitivity estimator#7 **Hodges-Lehman estimator** | **Handling of intercurrent events:** Same as for main estimator.<br><br>**Analysis:** Hodges-Lehmann estimate from the non-parametric procedure and p-value based on Wilcoxon rank sum test on residuals<br>**Limitations:** Treatment effect estimated without adjustment for 6MWD baseline value. . |

| Estimand 1 "FAS" | |
|---|---|
| Sensitivity estimator#8 **Extended ANCOVA model** | **Handling of intercurrent events:** Same as for main estimator.<br><br>**Analysis:** Same as for main estimator but WHO FC is added in the ANCOVA model together with the baseline and treatment.<br>**Limitations**: Same as for main estimator; also, WHO FC was included in the model, but WHO FC was not a stratification factor. |
| Sensitivity estimator#9 **Repeated measures** | **Handling of intercurrent events:**<br>**Death**: as for main estimator.<br>**AE/Study discontinuation**: the estimated change in 6MWD from the regression model was imputed for subjects who were alive and with missing values.<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis:** This model considered that 6MWD was measured as a continuous variable at Week 8, Week 16, and Week 24. This model assumed that data were missing at random for subjects with missing values who were alive and imputed to 0 m for subjects who died<br>**Limitations: Repeated measure model is based on assumption "missing at random (MAR)".** |
| Sensitivity estimator#10 **Observed (without imputations)** | **Handling of intercurrent events:**<br>**Death:** excluded<br>**AE/Study discontinuation:** excluded<br>**Administration of rescue medications, occurred only in placebo, was not handled.**<br><br>**Analysis**: same as for main estimator<br>**Limitations: Administration of rescue medications, occurred only in placebo, was not handled, all missing values were only in placebo group, no missing values for macitentan, hence** subjects with missing values were not included in placebo group resulting in bias and imbalance between the treatment groups. Also, reasons (e.g., disease progression, AEs/SAEs) for missing values were not considered. |

* MERIT-1 CSR [Module 5.3.5.1 D-17.097 table 11-6].

6MWD = 6-minute walk distance; AE = adverse event; ANCOVA = analysis of covariance; ANOVA = analysis of variance; BOCF = baseline observation carried forward; CHMP = Committee for Medicinal Products for Human Use; FAS = Full analyses set; FC = functional class; LOCF = last observation carried forward; MAR = missing at random; PH = pulmonary hypertension; SAE = serious adverse event; WHO = World Health Organization.

## Table 22 Estimand 2 (PVR, PPS) for the key secondary endpoint of 6MWD

| | |
|---|---|
| **A) Population:** Randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria and excluding randomized subjects with protocol deviations that could impact assessments of PVR (Per Protocol Set [PPS]). Protocol Deviations were: WHO FC II at baseline and use of PH advanced therapy before Week 16: Subject [redacted] was excluded; AE/ SAE events that prevent RHC assessment at Week 16: Subjects [redacted] and [redacted] were excluded; Subject refusal to perform RHC assessment at Week 16: Subject [redacted] was excluded and Change in RHC Operator: Subjects [redacted] were excluded [Module 5.3.5.1 D 17.097 table 10-2]<br>**B) Variable:** 6MWD at Week 24, expressed as change from baseline value to Week 24<br>**C) Intercurrent events and strategies:** See below description for main estimator and sensitivity estimators<br>**D) Population-level summary measure:** difference in means of change from baseline 6MWD to Week 24 between macitentan and placebo | |
| **Estimand 2 "PVR PPS"** | |
| Estimator **PVR PPS (as in SCE section 3.2.1.2 and based on PVR)** | **Handling of intercurrent events: Same as main estimator.**<br><br>**Analysis:** same as for main estimator<br>**Limitations**: Majority of intercurrents events /deviations for PVR were not intercurrent events/deviations for 6MWD, e.g., AE/SAE events that prevent RHC assessment, or subject refusal to perform RHC assessment at Week 16 or Change in RHC Operator. Initial randomization is not preserved, and slight imbalance introduced, because there were only subjects in placebo who were excluded, no macitentan subjects had protocol deviations. There were 2 subjects who did not fulfil inclusion criteria 4 (Protocol Version 2, March 2015) and had 6MWD at baseline above 450 meters but they were still included in this estimand. The intercurrent event "Administration of Rescue Medication" was not handled, there were 3 subjects in placebo treatment group who took sildenafil and riociguat. Details are provided in Table 23. |

6MWD = 6-minute walk distance; AE = adverse event; FC = functional class; PH = pulmonary hypertension; PPS = Per protocol set; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SAE = serious adverse event; SCE = Summary of Clinical Efficacy; WHO = World Health Organization

## Table 23 Estimand 3 (New PPS/6MWD PPS) for the key secondary endpoint of 6MWD

| | |
|---|---|
| **A) Population**: Randomized subjects with inoperable chronic thromboembolic pulmonary hypertension, defined through protocol inclusion/exclusion criteria and excluding ineligible randomized subjects or subjects with protocol deviations that could impact assessments of 6MWD. For Inclusion Criterion 4* there were 2 subjects, [redacted](placebo) who had 467 m in 6MWD at baseline and [redacted](macitentan) who had 455 m at baseline<br>**B) Variable**: 6MWD at Week 24, expressed as change from baseline value to Week 24<br>**C) Intercurrent events and strategies**: as for main estimator, and considering the administration of rescue medications<br>**D) Population-level summary measure**: difference in means of change from baseline 6MWD to Week 24 between macitentan and placebo | |
| **Estimand 3: New PPS/6MWD PPS** | |
| **New PPS/6MWD PPS Estimator** | **Handling of intercurrent events:**<br>**Administration of Rescue Medication**: There were 3 subjects in placebo group during MERIT-1 ([redacted]riociguat, [redacted]sildenafil, [redacted]riociguat), initiated PH therapy after Week 16. All 6MWD data are included for 3 subjects until Week 16 (i.e. before administration of rescue medication), then LOCF is applied (i.e. 6MWD at Week 24 is replaced by 6MWD at Week 16).<br>**Death/AE/SAE/Discontinuation of study**, similar to the main estimator (FAS):<br>**Death***: For placebo 2 subjects ([redacted] who died 0 m were imputed (the worst possible outcome)<br>**AE/SAE events that prevent 6MWD assessment at Week 24**: 1 placebo subject ([redacted] experienced AE Arthralgia, LOCF was imputed<br>**Discontinuation from the study (Lost to Follow up)**: 1 placebo subject ([redacted], LOCF was imputed<br><br>**Analysis**: A similar statistical analysis (ANCOVA) was used as for the main estimator "FAS" [Table 21].<br>**Strength**; same as for main estimator [Table 21] but the new intercurrent event is added: Administration of rescue medication. The estimator best describes the net treatment effect of macitentan while patients on treatment without intercurrent event that may interfere with the evaluation of such effect.<br>**Limitations**: For intercurrent events such as Death/AE/Discontinuation of study the same limitations as for main estimator. To be noted that subject 5301002 had 2 intercurrent events (death at Day 129 and use of rescue medication). This subject discontinued study treatment on Day 108, died on Day 129, i.e., after EOT, due to the SAE right ventricular failure with embolism reported as a secondary cause of death [MERIT-1 CSR; Module 5.3.5.1 D-17.097]. The intercurrent event - death was taken as the main intercurrent event for this estimand, and 0 m was imputed for 6MWD at Week 24. |
| Sensitivity estimator#1<br>**Multiple Imputation 1** | Same as 6MWD PPS estimator. |
| Sensitivity estimator#2<br>**Multiple Imputation 2** | Same as above. |
| Sensitivity estimator#3<br>**BOCF** | Same as above. |
| Sensitivity estimator#4<br>**LOCF** | |
| Sensitivity estimator#5<br>**Median** | Same as above. |
| Sensitivity estimator#6<br>**ANOVA model** | Same as above. |
| Sensitivity estimator#7<br>**Hodges-Lehman estimator** | Same as above. |
| Sensitivity estimator#8<br>**Extended ANCOVA model** | Same as above. |
| Sensitivity estimator#9<br>**Repeated measures** | Same as above. |
| Sensitivity estimator#10<br>**Observed (without imputations)** | Same as above. |

*Inclusion Criterion 4: Subject able to perform the 6MWT with a minimum distance of 150 m and a maximum distance of 450 m, documented by 2 tests performed during the Screening period, at least 2 hours apart. The second Screening 6MWD must not differ from the first by more than 10% or a third test is required. The third Screening 6MWD must not differ from the highest by more than 10%.

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; AE = adverse event; ANCOVA = analysis of covariance; ANOVA = analysis of variance; BOCF = baseline observation carried forward; CSR = clinical study report; EOT = End-of-Treatment; FAS = Full analyses set; LOCF = last observation carried forward; PPS = Per-protocol set; SAE = serious adverse event.

**Table 24 Results for the key secondary endpoint of 6MWD**

| Estimands for 6MWD | *Between-treatment analysis Difference in LS Means (95% CLs) macitentan–placebo* |
|---|---|
| **Estimand 1 "FAS, N=80"** | |
| Main Estimator | 34.04 (2.90, 65.19), p = 0.0326 |
| MI1 | 35.19 (3.99, 66.38), p = 0.0270 |
| MI2 | 23.76 (1.51, 46.00), p = 0.0363 |
| BOCF | 20.21 (−0.92, 41.33), p = 0.0606 |
| LOCF | 16.85 (−4.39, 38.10), p = 0.1183 |
| Median | 19.21 (−1.86, 40.28), p=0.0733 |
| ANOVA | 33.96, (2.89, 65.03), p = 0.0327 |
| Hodges-Lehmann | 17 (−1.00, 38.00), p = 0.0668 |
| Extended ANCOVA | 36.09 (4.32, 67.86), p = 0.0265 |
| Repeated Measures | 22.77 (2.44, 43.09), p = 0.0286 |
| Observed cases only (N = 76) | 18.31 (−3.9, 40.53), p = 0.1047 |
| **Estimand 2 "PVR PPS"** | |
| PVR PPS (N=74) | 27.5 (−1.5, 56.5), p = 0.0626 |
| **Estimand 3 "New PPS/6MWD PPS"** | |
| Main Estimator (N=78) | 41.66 (9.50, 73.82), p = 0.0118 |
| MI1 (N = 78) | 43.20 (11.08, 75.33), p = 0.0084 |
| MI2 (N = 78) | 33.30 (9.16, 57.45), p = 0.0069 |
| BOCF (N = 78) | 27.49 (5.20, 49.77), p = 0.0163 |
| LOCF (N = 78) | 24.05 (1.53, 46.56), p = 0.0367 |
| Median (N = 78) | 26.77 (4.51, 49.03), p= 0.0191 |
| ANOVA (N = 78) | 41.47 (9.28, 73.67), p = 0.0124 |
| Hodges-Lehmann (N = 78) | 23 (2, 47), p = 0.0301 |
| Extended ANCOVA (N = 78) | 45.39 (12.71, 78.06), p = 0.0071 |
| Repeated Measures (N = 78) | 26.04 (5.10, 46.99), p = 0.0155 |
| Observed cases only (N = 74) | 26.25 (2.74, 49.76), p = 0.0292 |

Source: Module 2.7.3 D-18.252 figure 4 (for Estimand 1); Module 5.3.5.1 D-17.097 table 15-54 (Estimand 1 Observed), table 15-53 (Estimand 2, PVR PPS); Appendix 1 Table 66 (Estimand 3 Main estimator), Table 59 (Estimand 3 HL estimator), Table 64 (Estimand 3, MI1), Table 65 (Estimand 3, MI2), Table 61 (Estimand 3, BOCF), Table 62 (Estimand 3: LOCF), Table 63 (Estimand 3: Median), Table 68 (Estimand 3, ANOVA), Table 67 (Estimand 3, Extended ANCOVA), Table 60 (Estimand 3, Repeated Measures), Table 69 (Estimand 3: Observed).

6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; ANOVA = analysis of variance; BOCF = baseline observation carried forward; CL= confidence limit(s); FAS = Full analyses set; LOCF = last observation carried forward; LS = Least Squares; PPS = Per-protocol set; PVR = pulmonary vascular resistance.

### 4.1.4 Conclusions

The applicant considers that Estimand 1 "PVR (FAS, Corrected)" and Estimand 1 "6MWD (FAS)" are the most appropriate estimands to compare macitentan versus placebo on hemodynamics and exercise capacity, based on hypotheses testing. For these estimands, the initial randomization is preserved and adequate imputation rules for missing data are applied.

In addition, the applicant considers Estimand 2 "PVR (PPS, Corrected)" and Estimand 3 "New PPS/6MWD PPS for 6MWD" as the most appropriate estimands to quantify the true treatment effect of macitentan vs placebo in eligible patients with inoperable CTEPH while on treatment without intercurrent events.

Furthermore, within the estimands, the most suitable main estimators were chosen based on "established" imputation rules (i.e., no positive value imputed for subjects who died as in CHEST-1) and adequate statistical methods (ANCOVA) were used.

Using these estimands, the following geometric mean ratios (95% CLs) for macitentan/placebo were obtained:
• PVR:
– Estimand 1 (FAS, Corrected) = 0.81 (0.69, 0.95)
– Estimand 2 (PPS, Corrected) = 0.84 (0.71, 0.99)
• 6MWD, LS mean treatment difference (95% CLs):
– Estimand 1 (FAS) = 34.04 m (2.90, 65.19)
– Estimand 3 (New PPS/6MWD PPS) = 41.66 m (9.50, 73.82)

***Rapporteur Assessment***
The applicant has provided a discussion about estimands used for PVR and 6MWD in MERIT-1. Looking at potential estimands and sensitivity analyses the sponsor's choice cannot be qualified as inappropriate but it was close to the best-case scenario favoring the demonstration of the effect, particularly for 6MWD. It is worth mentioning that the "estimand definition" also covers not only the variable, population and timepoint for analysis but also the type of measure (mean, median, etc.) and statistical test to be applied. An appropriate analysis would provide a point estimate that is unlikely to be biased in favour of experimental treatment to an important degree (under reasonable assumptions) and a confidence interval that does not underestimate the variability of the point estimate to an important extent (EMA/CPMP/EWP/1776/99 Rev. 1). In this respect:

- For the analysis of PVR, the estimands chosen (mean change in PVR from baseline to week 16, FAS population, corrected values, ANCOVA) are acceptable. The ANCOVA test for the analysis of mean change in PVR is considered appropriate, as standard deviation of the PVR values and change from baseline was relatively low. In addition, it is not questioned that macitentan, as vasodilator, decreases PVR to a greater extent than placebo. The main concern about PVR as the primary endpoint is that it is a haemodinamic endpoint suitable for phase II exploratory trials but it is not sufficient to support a new indication. The additional concern about PVR is that the absolute decrease in PVR versus placebo was much lower than the one achieved by riociguat, the only approved drug in this indication, in the phase III CHEST-1 pivotal study in CTEPH, despite MERIT-1 included a sicker population than CHEST-1 in which relevant differences with placebo are theoretically easier to obtain.

- For the analysis of 6MWD, the sponsor considers the ANCOVA test appropriate and robust due to the small deviation from the normal distribution of the 6MWD data and makes some assertions about the assessment report regarding the (small) deviation of the data of 6MWD that are not entirely correct. It is true that deviation of baseline 6MWD is small (mean 352 ± 87.90 metres on macitentan and 351.23 ± 73.79 m on placebo). However, deviation in the change in 6MWD from baseline to week 24 was high in the FAS population chosen for the primary analysis of exercise (mean 35 metres ± SD **52.52** metres on macitentan and mean 1 meter ± SD **83.24** metres, main analysis, statistically significant), and low in the per protocol population (mean 35.18 ± **7.59** and 17.14 ± **8.62** on placebo, not statistically significant), which indicates that the main FAS analysis is biased in favour of the experimental treatment by the use of ANCOVA when SD of change in 6MWD was more than two-fold the mean value. An appropriate analysis would provide a point estimate that is unlikely to be biased in favour of experimental treatment to an important degree (under reasonable assumptions) and a confidence interval that does not underestimate the variability of the point estimate to an important extent (EMA/CPMP/EWP/1776/99 Rev. 1). Therefore, an analysis based on median values would have been more appropriate.

**Conclusion**

**Issue partly solved (solved for PVR but not for 6MWD) (see joint conclusion in the assessment of Q1).**

a) The main analysis of change in 6MWD using ANCOVA is biased by a high variability (SD in mean change in 6MWD from baseline is more than two-fold higher than the mean value) probably due to the presence of extreme values. Therefore, an analysis focused on median values would have been more appropriate. Please comment. This issue is related to assessment of Q11 related to internal consistency and the presence of an outlier center for 6MWD (4100 Ukraine).

b) The applicant is invited to comment about the difference in standard deviations in change in 6MWD between the FAS and PP populations, despite no patients were excluded for the PP population in the macitentan group.

***Question 5***

***The study report states that administration of ERA, guanylate cyclase stimulators, L-arginine, intravenous or subcutaneous prostanoids, or any investigational drug (other than study drug) was not permitted from 1 month prior to baseline RHC and Randomization (excluding acute administration during a catheterization procedure to test vascular reactivity). Please, detail how many patients were withdrawn these medications 1 month before randomization just to fulfill with study inclusion criteria. If these data are known, please provide the efficacy results separately for patients who withdrew PAH-specific medications and for those who did not.***

***Summary of MAH answer***
No subject was withdrawn from any PAH-specific therapy less than 1 month prior to randomization into MERIT-1 [Module 5.3.5.3 ISS appendix 1 listing 4]. The AC-055E201/MERIT-1 protocol [D-15.160 section 4.3 exclusion criteria #24] contained clear guidance that it was neither recommended, nor in the scope of the MERIT-1 study to withdraw subjects from ongoing PAH therapy in order to enter the study. However, the study did allow the inclusion of subjects previously treated with PAH therapy, who were not adequately controlled on such medication, who had failed such treatment, or may have encountered safety issues due to such treatment.

Overall, pre-existing PAH-specific therapy was stopped for a total of 2 subjects prior to the start of study treatment in MERIT-1. Both subjects were temporarily treated with inhaled iloprost for acute vasoreactivity testing at time of the RHC. [Module 5.3.5.1 D-17.097 appendix 16.2.4.4].

**Conclusion:** In MERIT-1, no subject was withdrawn from any PAH-specific therapies for the purpose of entering the study. No PAH-specific medical therapy was changed for any subject to meet the study eligibility criteria, as this was prohibited by the protocol and is considered unethical.

***Rapporteur Assessment***
The applicant has clarified that in MERIT-1 no subject was withdrawn from any PAH-specific therapies for the purpose of entering the study.

**Conclusion**

**Issue solved.**

***Question 6***

***The Applicant is requested to justify that all patients received optimal standard of care, considering that according to the ESC/ERS guideline optimal medical treatment for CTEPH other than PAH medication consists of anticoagulants and diuretics and that not all patients received diuretics at baseline in MERIT-1 (72.5% and 80.5% of the subjects in the macitentan and placebo group, respectively).***

***Summary of MAH answer***
In MERIT-1, all subjects were required to have received anticoagulants for ≥ 3 months prior to randomization, and indeed all 80 randomized subjects were on anticoagulant therapy at baseline as required per protocol [D-17.097 table 15-30]. This timeframe is consistent with the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH [Galiè 2015], which state: "The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation in order to discriminate this condition from 'subacute' PE." This cut-off was also used in the BENEFIT study with bosentan and in the CHEST-1 study with riociguat. Regardless of CTEPH subtype, operable or inoperable, the mainstay of treatment is lifelong anticoagulation with a target international normalized ratio of 2.0 to 3.0. Thus, anticoagulation is a primary therapy in CTEPH directed at the underlying cause of PH,

specifically to prevent *in situ* pulmonary artery thrombosis and recurrent thromboembolic events rather than reversal of the underlying pulmonary artery obstructions [Hoeper 2006].

In MERIT-1, diuretics were used in 72.5% and 80.5% of the subjects in the macitentan and placebo group, respectively [Module 5.3.5.1 D-17.097 table 15-30]. In general, diuretics in CTEPH are considered supportive treatments and are used to treat fluid retention due to PH and to reduce hepatic congestion and peripheral edema [Cannon 2013]. Moreover, diuresis can prevent a distended RV from impeding left ventricular filling. However, this therapy is considered supportive as there are no randomized controlled trials of diuretics in CTEPH and, in general, pre-capillary PH [Hoeper 2015, Hansen 2018]. As in PAH,
diuretics are usually reserved to provide symptomatic benefit to patients who have decompensated right heart failure. In MERIT-1, 60.0% and 52.5% of the subjects in the macitentan and placebo groups, respectively, had RV failure in their medical history [Module 5.3.5.1 D-17.097 table 15-21]. Other relevant conditions included cor pulmonale (7.5% subjects in each the macitentan and placebo group) and chronic cardiac failure (7.5% and 5% of subjects in the macitentan and placebo groups, respectively). Diuretics could also have been administered for the treatment of other comorbidities such as hypertension (45.0% and 37.5% of subjects in the macitentan and placebo groups, respectively).
Moreover, use of diuretics may have been limited by other factors, such as associated comorbidities, particularly the presence of renal dysfunction (in MERIT-1, chronic kidney disease was present in 10.0% and 12.5% of subjects in the macitentan and placebo groups, respectively).

**Conclusion:** Overall, in MERIT-1, all study participants were on optimal medical treatment for CTEPH other than PAH medication, consistent with ESC/ERS guideline recommendations, which recommend life-long anticoagulation and diuretics in cases of decompensated right heart failure.

***Rapporteur Assessment***

The applicant has provided information about concomitant medications recommended in CTEPH. All patients were anticoagulated per protocol and most of them were treated with diuretics.

**Conclusion**

Issue solved.

***Question 7***

***Most of the 25 studies included in the list of the GCP statement are not included in the submission, while study AD-055E202 (MERIT-2, which is an open label extension of the "pivotal" phase II study MERIT-1), is included in the submission as supportive, but not included in the list of studies in the GCP statement. Please clarify.***

***Summary of MAH answer***

The applicant would like to clarify that all clinical studies listed in the cumulative Module 1.9 [D-18.261] were submitted to EMA either in the initial Marketing Authorization Application or after Marketing Authorization of Opsumit on 20 December 2013. In addition, MERIT-1, AC-55-122 and AC-055-123 studies submitted with this extension of indication application have been added to this list.

The MERIT-2 (AC-055E202) and SERAPHIN-OL (AC-055-303) studies were not listed in the initial Module1.9 as they are still ongoing. Both studies are conducted within and outside of the European Union according to the ethical requirements of Directive 2001/20/EC.

The applicant is submitting an updated Module 1.9 [D-19.019] to specify that "all listed studies" were conducted "within and outside of the EU":
*The applicant confirms that all the above studies conducted within and outside of the European Union meet the ethical requirements of Directive 2001/20/EC.*

***Rapporteur Assessment***

The applicant has clarified that MERIT-1, AC-55-122 and AC-055-123 studies submitted with this extension of indication application have been added to the list of GCP statement in Module 1.9 [D-18.261]. In addition, the MERIT-2 (AC-055E202) and SERAPHIN-OL (AC-055-303) studies were not

listed in the initial Module1.9 as they are still ongoing. Both studies are conducted within and outside of the European Union according to the ethical requirements of Directive 2001/20/EC.

**Conclusion**

**Issue solved.**

***Question 8***

***According to European regulation, applications based on a single pivotal trial should be particularly compelling. In this case, the applicant's GCP statement provided is ambiguous on whether all studies, or only a part of them, are GCP compliant. This issue should be clarified. In addition, the results of any audits or inspections available for this clinical trial should be submitted.***

***Summary of MAH answer***
As mentioned in the response to Question 7, the applicant confirms that all studies listed in the GCP statement in Module 1.9 have been *conducted within and outside of the European Union and meet the ethical requirements of Directive 2001/20/EC.*

As stated in section 9.7.3 of the MERIT-1 CSR [Module 5.3.5.1 D-17.097], independent auditing was conducted by the Actelion GQM department according to Actelion SOPs. The audit certificates are provided in appendix 16.1.8. of the CSR.

***Rapporteur Assessment***
The applicant has provided the requested information. As stated in section 9.7.3 of the MERIT-1 CSR [Module 5.3.5.1 D-17.097], independent auditing was conducted by the Actelion GQM department according to Actelion SOPs. No GCP inspections are available for MERIT-1.

**Conclusion**

**Issue solved.**

***Question 9***

***The applicant is invited to discuss about the potential off-label use of the product in operable patients who refuse surgery, and to clarify if some of the patients recruited into the OPUS registry correspond to this patient's subset.***

***Summary of MAH answer***
The intended target population proposed in the Opsumit Summary of Product Characteristics (SmPC) section 4.1 is limited to inoperable adult CTEPH patients, which is in line with the population studied in MERIT-1, thus limiting the possibility for off-label use in operable CTEPH patients opting out of surgery. In fact, recent data (described below) suggest that this population of operable CTEPH patients who refuse surgery has markedly declined. The field of CTEPH is rapidly evolving with major advances in diagnostic/imaging modalities, improvements in balloon pulmonary angioplasty (BPA) procedure and surgical (PEA) outcomes. All these factors are likely contributing to a decrease in the proportion of CTEPH patients who refuse surgery, as observed in the new ICA registry and the Royal Papworth hospital database (described below). The OPUS registry is a new user cohort of patients treated with macitentan, and therefore by design CTEPH patients who have undergone surgery are generally not well represented.
Another limitation of the OPUS registry is that the corresponding case report form (CRF) does not have a dedicated question eliciting reasons for not having surgery. In free text, only 4 patients indicated surgery refusal. In summary, due to the factors described, the potential for off-label use of macitentan in this group of patients is very limited.

Further background information is provided below:
In the Request for Supplementary Information assessment report received on 14 December 2018, the assessor commented on real-world data from the OPUS Registry that were included in the submission

dossier. The Rapporteur highlighted that about 30% of patients refuse PEA [Quadery 2018] and instead receive pharmacological treatment. However, as discussed below, contemporary data suggest that the population of operable CTEPH patients at risk for off-label use of PH-advanced therapies has markedly declined.

The article by Quadery [Quadery 2018] presents data from a historical cohort of 550 treatment-naïve (newly diagnosed) CTEPH patients at the Pulmonary Vascular Disease unit of the Royal Hallamshire Hospital in Sheffield. During the 14-year observation period (2001–2014), 32% (n = 176) of patients were assessed as having 'technically operable disease but did not undergo surgery'. Only 13% (n = 72) refused to have surgery; no details are provided in the article regarding factors that might have influenced their decision. The data presented in this report pre-date the availability of catheter-directed BPA and riociguat therapy in the UK (available in 2013), making it difficult to assess the current proportion of operable patients that refuse surgery.

Two more contemporaneous CTEPH databases provide reliable recent epidemiology estimates beyond the UK registry described by Quadery: the Royal Papworth hospital database, UK (220 CTEPH patients included in 2016 and 2017, data on file courtesy of Dr Joanna Pepke-Zaba) and the current ICA registry (launched in 2015, with extensive data on over 1000 CTEPH patients globally). Both sources reported a lower rate of CTEPH patients assessed as technically operable but not having undergone surgery (13% and 11%, respectively). Surgery was rejected on the basis of underlying comorbidities and patient
choice. Dr Pepke-Zaba indicated that "the proportion of patients who refuse surgery is negligible" in her UK cohort and 4.4% (n = 44) refused surgery in the ICA registry [data on file], i.e., substantially lower than what is described by Quadery (13%).

All patients included in the OPUS Registry (N = 56) were treated with macitentan; therefore, the registry does not provide accurate estimates of patients who refuse surgery in the general CTEPH population, as most CTEPH patients medically treated are those that are non-operated. In the updated OPUS Registry dataset, 42 patients (76.4%) were not candidates for surgery for any reason [Module 5.3.5.4 D-18.430 table 9]. No dedicated question eliciting the reasons for not operating the patient is included in the OPUS Registry CRF. However, according to the comments made by the investigators (free text field in the OPUS Registry CRF only, not included in OrPHeUS study), 4 OPUS Registry CTEPH patients refused to undergo surgery. These 4 OPUS patients could be considered as operable patients who refused surgery and were treated off-label with macitentan.

***Rapporteur Assessment***

The target population for macitentan is the 36% of patients are considered ineligible for surgery [15]. Potential for off-label use is high for operable patients that refuse surgery (the applicant has clarified that this proportion has decreased up to 4% of the 64% of operable patients), but also in half of operable patients that undergo surgery (≈30% of all patients with CTEPH) that will have persistent or recurrent pulmonary hypertension after surgery [Pepke-Zaba J, et al. Eur Respir Rev 2017; 26: 160107].

The applicant has provided information indicating that only 4 OPUS registry CTEPH patients were operable and refused surgery, which is consistent with current trends. In the assessor's view, as more patients undergo surgery and half of them will have persistent or recurrent CTEPH (i.e.: about 30% of the overall CTEP population), the off-label use in persistent or recurrent CTEPH after surgery may be significant.

**Conclusion**

Issue solved (no further information pursued).

***Question 10***

***The Applicant is requested to clarify why only few patients from West-Europe were included and why no patients from the USA have been recruited into the MERIT-1 study and whether this has to do with the approval and availability of Adempas for the treatment of CTEPH at the time of initiation of the MERIT-1 study.***

***Summary of MAH answer***
The low number of subjects included in MERIT-1 from the US and Western Europe is attributable to several factors, all of which contributed to an already challenging recruitment in this rare indication. These were mainly driven by the staggered approval among participating countries of newly approved riociguat in this indication, as well as regional differences in the availability of other competing studies.

**The availability of newly approved riociguat (an sGC stimulator)**
Riociguat (FDA approval granted on October 2013 in the USA and by the European Commission on 27 March 2014) is the first pharmacological therapy approved for CTEPH, and its availability certainly contributed to the recruitment challenges faced in MERIT-1 in these regions. The MERIT-1 study protocol Version 1 was finalized on 22 October 2013 and approved by Independent Ethics Committees / Institutional Review Boards in the EU countries between 5 February 2014 and 9 July 2014. The first subject, first visit in MERIT-1 was on 20 August 2014. As the clinical development program of macitentan in CTEPH was initiated around or prior to the approval of riociguat, administration of guanylate cyclase stimulators as background therapy was not allowed in the MERIT-1 study. An amendment to the MERIT-1 protocol was also not considered at the time as there was little experience with riociguat, and its availability was limited due to the usual delays in reimbursement and access. In addition, experience of administering macitentan to patients receiving PDE-5 inhibitors and/or oral/inhaled prostanoids was well established in PAH, but no data were available on the use of riociguat in combination with macitentan (subsequently, it has been shown in two studies that there is no pharmacokinetic (PK) interaction of macitentan at steady state with the breast cancer resistance protein substrates, rosuvastatin and riociguat [Module 2.7.2 D-18.185 section 3]). As riociguat was not yet approved in Eastern Europe and Asia-Pacific regions, this made recruitment less challenging in these regions (approval date of riociguat in China received in September 2017 and in Russia January 2017). Consequently, the majority of subjects were enrolled at centers in Eastern Europe (42.5% macitentan, 47.5% placebo) and Asia (37.5% macitentan, 35.0% placebo) [Module 5.3.5.1 D-17.097 table 10-3].

**Competing studies**
Several studies enrolling a similar population were either ongoing or initiated in the US and/or Western Europe during the recruitment period, which significantly reduced the pool of eligible patients. Competing studies included the AMBER study with ambrisentan in CTEPH [NCT01884675], which started in September 2013 and was prematurely terminated in March 2015 due to low recruitment; the study of riociguat vs BPA in non-operable CTEPH [NCT02634203], which started in January 2016 and is actively
recruiting; and the CTEPH study with subcutaneously administered treprostinil in patients with severe (non-operable) CTEPH [NCT01416636], which started in March 2009 and completed recruitment in June 2016.

**Conclusion:** Although the rarity of CTEPH prevented enrollment of a large number of subjects and contributed to regional recruitment differences, the population randomized in MERIT-1 represents a homogeneous population of technically inoperable CTEPH subjects, with similar demographic and clinical characteristics that allow the MERIT-1 findings to be generalized to the wider inoperable CTEPH population [see Question 1 Section 1.1.5].

***Rapporteur Assessment***
The applicant has provided an explanation for the low number of subjects included in MERIT-1 from the US and Western Europe, which can be attributable to several factors, all of which contributed to an already challenging recruitment in this rare indication. These were mainly driven by the staggered approval among participating countries of newly approved riociguat in this indication, as well as regional differences in the availability of other competing studies (AMBER study with ambrisentan, terminated after 33 out of 160 planned patients were recruited; RACE study with riociguat, n=120; CTREPH study with SC treprostinil, n=105).

In the assessor's view, the company did not make any effort in providing data on top of riociguat, despite there was no indication of drug interactions between riociguat and ERAs at the time of approval of Adempas. Most of the data come from Eastern countries (i.e.: Russia and China) probably to the combination of availability of a higher number of inoperable patients available in that countries (unavailability of centers with adequate standard of care to conduct PEA or surgery; difficulties for access to new therapies unless under clinical trials; less regulatory barriers, etc) and the barrier of not allowing the administration of riociguat by protocol, which prevents from authorizing the study protocol in Western countries where riociguat was already approved.

The CTREPH study with treprostinil has been recently reported (Sadushi-Kolici R, et al. Lancet Respir Med. 2018), but have not been subject to regulatory review. According to the publication, a total of 105 inoperable patients in FC III-IV were enrolled with 53 (50%) patients randomly assigned to high-dose (30 ng/kg per min) and 52 (50%) patients to low-dose (3 ng/kg per min) subcutaneous treprostinil. At week 24, marginal mean 6-min walk distance improved by 44.98 m (95% CI 27.52 to 62.45) in the high-dose group, and by 4·29 m (95% CI -13.34 to 21.92) in the low-dose group (treatment effect 40.69 m; 95% CI 15.86 to 65.53; p=0.0016). 12 serious adverse events were reported in ten (19%) of 52 patients from the low-dose group and 16 serious adverse events were reported in nine (17%) of 53 patients from the high-dose group. The most common treatment-related adverse events in both groups were infusion site pain and other infusion site reactions.

In summary, the company did not make any effort in providing data on top of riociguat (already approved in Western countries before the first patient was recruited into the MERIT-1 study). This issue, coupled with the availability of a higher number of inoperable patients in Eastern Countries, led to the recruitment of only 15 patients in the EU and no patients in the US. In all EU countries recruiting at least 1 patient in each group, the point estimate favoured placebo (see assessment of Q11). Therefore, the MERIT-1 study is poorly representative of the Western population.

**Conclusion**

Issue solved (no further information pursued.

***Question 11***

***With respect to internal consistency, from subgroup analyses it is apparent that most part of the effect on 6MWD is driven by results in Eastern Europe (36 subjects from Czech Republic, Hungary, Lithuania, Poland, Russia and Ukraine). In Western Europe the between-treatment difference is of only 6 metres (n=11 patients). However, given the low sample sizes, statistical heterogeneity between subgroups is not statistically significant. The applicant is requested to show the disaggregated data on 6MWD by country and center, in order to ascertain if there is an outlier center driving the positive trend on 6MWD.***

***Summary of MAH answer***
As described in the Clinical Overview [D-18.251], the clustering of countries in Eastern and Western Europe suffers from the comparatively small sample size in some countries [Module 2.5 D-18.251 figure 4; Table 25 below], hence all countries in Europe were grouped together as one geographical region 'Europe' [D-18.251 figure 5]. This approach is similar to the one used in the riociguat application [Adempas FDA review 2013, Adempas EPAR 2014]. Irrespective of how Europe was defined, no indication of heterogeneity of treatment effects for 6MWD was observed across regions, with p-values of 0.6965 for heterogeneity in protocol-defined regions (Asia, Eastern Europe, Western Europe and Latin America) and 0.8752 for the sensitivity analysis combining Western and Eastern Europe as Europe [Module 2.5 D-18.251 figure 4 and figure 5]. The revised geographical region Europe is deemed appropriate given the similarities in physiological and genetic characteristics between subjects in different countries.

Acknowledging the impact of imputed values on the 6MWD at Week 24, Table 25 also displays the counts of observed 6MWD data, defined as all randomized subjects without missing 6MWD values at

Week 24. There were 4 subjects in the placebo group who had missing 6MWD values at Week 24; 1 subject in Germany (due to an AE of arthralgia), 1 subject in Russia (death), 1 subject in South Korea (death), and 1 subject in Switzerland (lost to follow-up) [Module 5.3.5.1 D-17.097 table 11-6]. No subjects in the macitentan group had missing 6MWD values at Week 24.

**Disaggregated 6MWD data by country**

In MERIT-1, the highest number of subjects were randomized in China (n = 24) and Russia (n = 21) [Table 25]. For China, the unadjusted mean treatment difference of change from baseline to Week 24 (macitentan vs placebo) in 6MWD was −5.8 m (95% CI: −49.0, 37.4) for imputed as well as the observed data [Table 26; Appendix 1 Table 49]. For Russia, the unadjusted mean treatment differences of change from baseline to Week 24 (macitentan vs placebo) in 6MWD were 72.2 m (95% CI: −3.9, 148.2) and 35.2 m (95% CI: −4.3, 74.6) for imputed and observed data, respectively [Table 26; Appendix 1 Table 49]. Overall, the analysis of change from baseline to Week 24 in 6MWD did not identify any outlier country driving the overall results with expected variability due to relatively low number of
subjects. Changes from baseline to Week 24 in 6MWD (observed) by country are summarized in Table 26.

**Table 26 Summary of change from baseline to Week 24 in 6MWD (observed) by country, FAS**

| (unadjusted) | Macitentan 10 mg n | Mean | SD | Placebo n | Mean | SD | Treatment difference Mean (95%CLs) |
|---|---|---|---|---|---|---|---|
| BELGIUM | 0 | | | 1 | -9.0 | | |
| CHINA | 12 | 20.2 | 41.05 | 12 | 26.0 | 59.32 | -5.8 (-49.0, 37.4) |
| CZECH REPUBLIC | 2 | 82.5 | 109.60 | 0 | | | |
| FRANCE | 2 | -17.0 | 25.46 | 1 | 24.0 | | -41.0 (-437.1, 355.1) |
| GERMANY | 1 | 91.0 | | 1 | -7.0 | | |
| HUNGARY | 2 | -20.0 | 16.97 | 2 | -7.0 | 7.07 | -13.0 (-68.9, 42.9) |
| LITHUANIA | 0 | | | 2 | 0.0 | 0.00 | |
| MEXICO | 1 | 7.0 | | 1 | -14.0 | | |
| POLAND | 0 | | | 3 | 25.7 | 63.09 | |
| RUSSIAN FEDERATION | 12 | 43.2 | 38.84 | 8 | 8.0 | 44.56 | 35.2 (-4.3, 74.6) |
| THAILAND | 3 | 67.3 | 81.03 | 1 | 54.5 | | 12.8 (-389.7, 415.4) |
| TURKEY | 2 | 32.5 | 31.82 | 0 | | | |
| UKRAINE | 1 | 166.0 | | 3 | 25.3 | 34.24 | 140.7 (-29.4, 310.8) |
| UNITED KINGDOM | 2 | 8.5 | 17.68 | 1 | 35.0 | | -26.5 (-301.6, 248.6) |

One subject from Switzerland (lost to follow up) and one subject from South Korea (died) are not displayed. Their values were imputed for Week 24 (i.e., not observed).
As there was only one subject in each treatment group in Germany as well as in Mexico, treatment difference, mean, and 95% CIs are not presented.
CL = confidence limit, SD = standard deviation.
Source: Modified from Appendix 1 Table 50 (T_6MWDO_COUN3_EMA_FAS).

**Disaggregated 6MWD data by site**
To allow for a meaningful interpretation of 6MWD data by site, the analysis described below (observed values) focuses on the centers with at least 2 randomized subjects [Table 27]. The change from baseline to Week 24 in 6MWD for all sites, irrespective of the number of subjects randomized, is summarized in Appendix 1 Table 51.

**Table 27 Change from baseline to Week 24 in 6MWD (observed), by site with at least 2 subjects, FAS**

| Site # country | Number of subjects macitentan / placebo (n/n) | Macitentan mean (median) [SD] change from baseline to Week 24 (m) | Placebo mean (median) [SD] change from baseline to Week 24 (m) |
|---|---|---|---|
| [redacted] | 2 / 0 | 82.5 (82.5)<br>[109.60] | – |
| | 1 / 2 | −8.0 / (-8.0)<br>[–] | −7.0 (−7.0)<br>[7.07] |
| | 0 / 2 | – | 0.0 (0.0)<br>[0.0] |
| | 0 / 2 | – | −10.5 (−10.5)<br>[10.61] |
| | 6 / 2 | 55.3 (49.0)<br>[51.33] | −35.5 (−35.5)<br>[60.10] |
| | 1 / 3 | 43.0 (43.0)<br>[–] | 37.3 (29.0)<br>[23.63] |
| | 1 / 1 | 36.0 (36.0)<br>[–] | 1.0 (1.0)<br>[–] |
| | 3 / 2 | 35.7 (27.0)<br>[15.01] | 11.0 (11.0)<br>[52.33] |
| | 1 / 2 | 166.0 (166.0)<br>[–] | 43.5 (43.5)<br>[19.09] |
| | 2 / 0 | 32.5 (32.5)<br>[31.82] | – |
| | 6 / 7 | 19.0 (20.5)<br>[47.26] | 48.1 (36.0)<br>[66.90] |
| | 1 / 2 | 7.0 (7.0)<br>– | −36.0 (−36.0)<br>[12.73] |
| | 2 / 1 | 58.0 (58.0)<br>[26.87] | 13.0 (13.0)<br>- |
| | 1 / 1 | 29.0 (29.0)<br>[–] | 28.0 (28.0)<br>– |
| | 2 / 0 | −12.0 (−12.0)<br>[38.18] | – |
| | 2 / 0 | 80.0 (80.0)<br>[110.31] | - |
| | 1 / 1 | 7.0 (7.0)<br>[–] | −14.0 (−14.0)<br>- |

Source: Modified from Appendix 1 Table 51 (T_6MWDO_SITE_EMA_FAS).
6MWD = 6-minute walk distance; FAS = Full analyses set; SD = standard deviation.

**MAH's Conclusion:** In MERIT-1, China (n = 24) and Russia (n = 21) accounted for the highest number of subjects enrolled in the study. One site in each country (one site in China, n = 13; one site in Russia, n = 9) enrolled most subjects. No individual country or center was identified to have driven the overall study results.

***Rapporteur Assessment***

The applicant has provided the results on 6MWD by country and center, given that in subgroup analyses there was a signal of some outlier center/country in Eastern Europe.

The data show (Table 26) that, in most countries, the point estimate favoured placebo over macitentan including France (24 m), UK (26 m), Hungary (13 m) and China (5.8 m), while the positive trend in favour of macitentan was found in Ukraine (140.7 m), Russian Federation (35.2 m) and Thailand (12.8 m).

Two centers drive the difference between macitentan and placebo:

- center 4100 in Ukraine, with a +122.5 m difference in favour of macitentan and

- center 3800 in Russia, with a +90.8 m difference in favour of macitentan

Therefore, the results in 6MWD by country and center are not considered robust, thus supporting the Rapporteur's conclusion: This is a exploratory phase II study and, accordingly, the results of the secondary outcome of 6MWD are considered exploratory and not robust enough to grant an indication.

**Conclusion**

**Issue not solved (joint to the MO; see assessment of Q1).**

The data on 6MWD by country and center show that, in many countries, placebo tended to be better than macitentan. The results on 6MWD only favored macitentan in Russia, Ukraine and Thailand. Particularly in Ukraine, the difference in favor of macitentan was an impressive 122.5 m improvement versus placebo. In this respect:

a) Please, provide the interaction p-value by country for the effect on 6MWD and analyze the results of 6MWD including country as covariate.

b) The applicant is requested to provide a narrative for patient treated with macitentan in the centre in Ukraine, who improved 160 meters in 6MWD from baseline to week 24. Please, also discuss about the chance for a patient with inoperable CTEPH to improve 160 meters from baseline to week 24.

c) As sensitivity analysis, the applicant is requested to show MERIT-1 study results: c1) By excluding that patient and c2) by excluding one centre in Ukraine.

***Question 12***

***ERAs have a well defined AE profile, and it should be ruled out that patients with recognizable ERA-related AEs have no better performance in the 6MWD than those patients without these AEs due to unblinding (i.e.: ascertainment bias). The applicant is invited to provide sensitivity analyses in patients with and without ERA-related AEs.***

***Summary of MAH answer***
A large number of placebo-controlled trials with different ERAs have been conducted, without creating any evidence of recognizable AEs that could lead to unintentional unblinding. Macitentan is devoid of distinct side-effects such as 'jaw and leg pain' associated with the use of prostanoids. In addition, unlike sGC stimulators, macitentan does not require any dose-titration or continual dose adjustments to reduce the risk of hypotension [Ghofrani 2013a, Ghofrani 2013b]. The potential for ascertainment bias with macitentan in MERIT-1 is considered to be negligible.

Common AEs related to the vasodilatory action of ERAs are not specific to this class of medication. These events are confounded by the pathophysiology of CTEPH (pre-capillary PH with RV dysfunction/failure), the advanced age and the many comorbidities associated with this chronic disease, as well as co-administration of advanced PH therapies, including other vasoactive medications (e.g., diuretics). Consequently, events such as edema/fluid retention do not always occur more frequently in the ERA treatment group, making potential unblinding unlikely. This was illustrated in the pivotal PAH study SERAPHIN, in which edema-related AEs occurred at a similar incidence across all treatment groups (18.8% in the macitentan 3 mg group, 20.7% in the macitentan 10 mg group, and 20.1% in the placebo group) [D-12.425 table 41].

In the MERIT-1 study, AEs of special interest for which a causal relationship to ERA use could not be excluded, namely AEs associated with edema/fluid retention and anemia/hemoglobin (Hb) decrease, were carefully monitored and reported [D-18.253 table 13 and table 14]. Similarly, laboratory abnormalities relating to hepatic function and anemia were also carefully monitored [D-18.253 table 15 and table 16].

To assess if the presence or absence of such ERA-related AEs had an impact on 6MWD performance (at Week 24), the following AEs and relevant laboratory abnormalities were used to create an 'ERA-related variable' to perform the analysis described below.

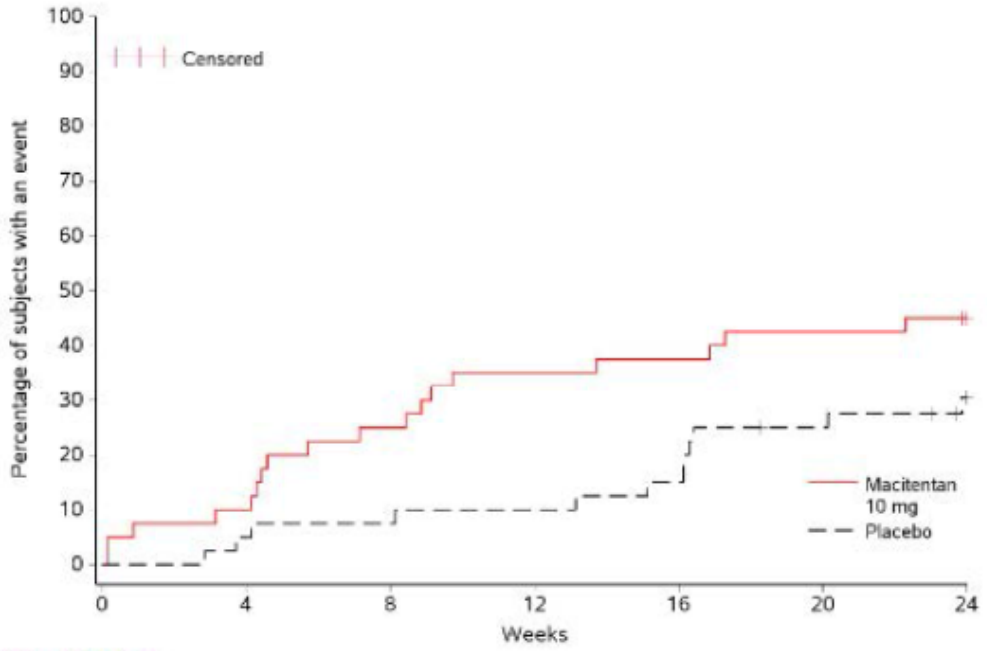
- AEs denoting:
  - Edema and/or fluid retention
  - Anemia and/or Hb decrease
- Laboratory abnormalities related to hepatic function and anemia
  - Hb ≤ 100g/L
  - Hb decrease > 20g/L from baseline
  - Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN)
  - Alanine aminotransferase (ALT) > 3 × ULN
  - Total bilirubin (TBIL) > 2 × ULN.

The analysis evaluated the potential unblinding due to AEs that were observed at least once during the first two months (up to Week 8) of treatment. This period was chosen as the potential for unblinding is greatest in this period, given:

a) The difference in the reported incidence of these events between macitentan and placebo is highest in this period and hence the bias potentially introduced by the investigator would have a greater effect. The proportions of subjects with ERA-related events in the macitentan and placebo groups were 27.5% and 10%, respectively, at Week 8 and 45% and 30%, respectively, at any time during the study, with the majority of "excess macitentan events" reported during the first 8 weeks of treatment [Table 28, Table 29, and Figure 6]. In addition, in the macitentan group, the estimated HR (event rate) of first occurrence of an ERA-related event (based on Life Table Method) between randomization and Month 1 was 0.0053 and between Months 1 and 2 was 0.0052, with the HR decreasing to 0.0030 beyond Month 2 [Appendix 1 Table 52]. In the placebo group, the respective rates were 0.0026, 0.0009, and 0.0028. It should be noted that, beyond Month 2, the HRs were similar for macitentan (0.0030) and placebo (0.0028) [Appendix 1 Table 52].

The observation of these events comes before the first post-baseline 6MWD assessment (at Week 8), which is also known to correlate with the subsequent assessments at 16 and 24 weeks.

**Figure 6** **Kaplan-Meier estimates of time to first occurrence of ERA-related event from start of treatment up to EOT in MERIT-1, FAS**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Macitentan 10 mg | | | | | | | |
| at risk \| | 40 | 36 | 30 | 26 | 25 | 23 | 19 |
| event(s) \| | 0 | 4 | 10 | 14 | 15 | 17 | 18 |
| :ensored \| | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Placebo | | | | | | | |
| at risk \| | 40 | 38 | 37 | 36 | 34 | 29 | 24 |
| event(s) \| | 0 | 2 | 3 | 4 | 6 | 10 | 12 |
| :ensored \| | 0 | 0 | 0 | 0 | 0 | 1 | 4 |

Curves are presented up to 24 weeks which corresponds to the time when more than 10% of the subjects are still at risk
Output: F_TIMERA_EMA_FAS, Produced by biarnal1 on 04DEC2018 8:47 (CET), SDTM production date: 28MAY2018
Program: val_csr_CTEPH/program_output/f_era_km.sas

**Table 28** **Occurrence of ERA-related events within 8 weeks of treatment start, FAS**

| | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) |
|---|---|---|
| Number (%) of subjects with Hb <= 100g/L | 0 | 0 |
| Number (%) of subjects with Hb decrease > 20g/L from baseline | 4 (10.0) | 3 (7.5) |
| Number (%) of subjects with edema and fluid retention events | 6 (15.0) | 1 (2.5) |
| Number (%) of subjects with anemia events | 3 (7.5) | 0 |
| Number (%) of subjects with AST > 3ULN | 0 | 0 |
| Number (%) of subjects with ALT > 3ULN | 0 | 0 |
| Number (%) of subjects with TBIL > 2ULN | 0 | 0 |
| Number (%) of subjects with at least one of the event above | 11 (27.5) | 4 (10.0) |

Output: T_REL_EVENT2M_EMA_FAS

**Table 29 Occurrence of ERA-related events anytime during MERIT-1, FAS**

| | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) |
|---|---|---|
| Number (%) of subjects with Hb <= 100g/L | 1 (2.5) | 1 (2.5) |
| Number (%) of subjects with Hb decrease > 20g/L from baseline | 11 (27.5) | 7 (17.5) |
| Number (%) of subjects with edema and fluid retention events | 10 (25.0) | 4 (10.0) |
| Number (%) of subjects with anemia events | 7 (17.5) | 1 (2.5) |
| Number (%) of subjects with AST > 3ULN | 0 | 0 |
| Number (%) of subjects with ALT > 3ULN | 0 | 0 |
| Number (%) of subjects with TBIL > 2ULN | 2 (5.0) | 2 (5.0) |
| Number (%) of subjects with at least one of the event above | 18 (45.0) | 12 (30.0) |

Output: T_REL_EVENTA_EMA_FAS

**6MWD data (imputed) by the occurrence of ERA-related events in the first 8 weeks after treatment initiation (yes/no)**

6MWD data at Week 24 were analyzed by the occurrence of ERA-related events (yes/no). Although the threshold for occurrence of ERA-related events used in the analysis described above is up to 8 weeks after baseline, it should be noted that post-baseline 6MWD was measured at Week 8, Week 16, and Week 24 in MERIT-1. Hence, any comparison of the treatment groups regarding 6MWD should not be affected by the occurrence of ERA-related events categorization (Yes/No) using the 8-week post-randomization threshold. The Least Squares (LS) mean changes from baseline to Week 24 in 6MWD in the macitentan and placebo groups for subjects with/without ERA-related AEs are presented in Table 30.

**Table 30 Change from baseline to Week 24 in 6MWD (imputed and observed) in subjects with ERA-related events within 8 weeks of study treatment start in MERIT-1 (yes/no), FAS**

| | N | Macitentan 10 mg MERIT DB LS Mean ± SE* | n | Placebo MERIT DB LS Mean ± SE* |
|---|---|---|---|---|
| **Imputed data** | | | | |
| ERA-AEs (Yes) | 11 | 30.54 ± 10.65 | 4 | −4.72 ± 17.91 |
| ERA-AEs (No) | 29 | 37.44 ± 14.14 | 36 | 1.02 ± 12.69 |
| **Observed data** | | | | |
| ERA-AEs (Yes) | 11 | 30.54 ± 10.65 | 4 | −4.72 ± 17.91 |
| ERA-AEs (No) | 29 | 37.21± 9.57 | 32 | 18.79 ± 9.11 |

*ANCOVA model including treatment as factor and baseline 6MWD as covariables.
Source: Appendix 1 Table 53 (T_6MWDACS2M_ERA_EMA_FAS), Table 54. (T_6MWDACS2MO_ERA_EMA_FAS).
6MWD = 6-minute walk distance; ANCOVA = analysis of covariance; AE = adverse event; DB = double-blind; ERA = endothelin receptor antagonist; FAS = Full analyses set; LS = Least Squares; SE = standard error.

In the presence of ERA-related events (based on the 8-week analysis), the change from baseline to Week 24 in 6MWD (imputed data) was 30.54 ± 10.65 m on macitentan, which was lower than that in the subgroup of subjects who did not have ERA-related events (37.44 ± 14.14 m). Observed data were in a similar range for both subsets [Table 30]. These changes are also consistent with the FAS

result presented in the MERIT-1 CSR, i.e., for the mean change from baseline to Week 24 in 6MWD on macitentan (35.0 ± 52.52 m) [Module 5.3.5.1 D-17.097 table 15-49].

The change from baseline to Week 24 in 6MWD for placebo subjects who had ERA-related events, was −4.72 ± 17.91 m (both imputed and observed data) as compared to 1.02 ± 12.69 m (imputed) in placebo subjects who did not have ERA-related events [Table 30]. This argues against any potential unblinding, as ERA-related events that could have presumably introduced an ascertainment bias would not have favored only the macitentan group, but also the placebo group. Similar gains would therefore be expected in both groups, which clearly is not the case. Also, opposing the theory of potential unblinding is the positive treatment trend noted in the observed data for placebo subjects who did not have ERA-related events (18.79 ± 9.11 m), as compared to the negative trend in subjects who did have ERA related events (−4.72 ± 17.91 m).

**Applicant's conclusion:** Overall, there is no recognizable ERA-related AE that could have contributed to ascertainment bias during the MERIT-1 study. Common AEs related to the vasodilatory action of ERAs are not unique to the macitentan group and are confounded by the pathophysiology and clinical presentation of CTEPH as well as co-administered vasoactive medications, including PH-advanced therapies. In addition, analysis of 6MWD for MERIT-1 by the occurrence of ERA-related AEs in the first 8 weeks after randomization showed no evidence that systematic unblinding affecting exercise capacity assessments occurred in the study afterwards. A further indication that no systematic unblinding affecting exercise capacity assessments occurred in the MERIT-1 study is evident from the observation that subjects in both treatment arms employed a comparable level of effort in each 6MWT. As described in the response to Question 15, the fact that BDI assessment did not show any change from baseline in the context of an improvement in 6MWD as observed in the macitentan treatment arm indicates that the assessment was performed in an unbiased and non-encouraged manner.

***Rapporteur Assessment***

Only 11 patients on macitentan and 4 on placebo had recognizable ERA-related AEs. Treatment effect on 6MWD was not significantly different in the subgroup of patients with or without ERA-related AEs.

**Conclusion**

**Issue solved.**

***Question 13***

***In order to assess the clinical relevance of the effect of macitentan in the MERIT-1 study, the applicant is invited to provide exploratory analyses of the said study using different responder threshold criteria according to a previous analysis published with riociguat in the CTEPH indication [D'Armini, et al. Use of responder threshold criteria to evaluate the response to treatment in the phase III CHEST-1 study. J Heart Lung Transplant. 2015;34:348-55].***

***Summary of MAH answer***

To assess the clinical relevance of the effect of macitentan in the MERIT-1 study, the applicant was invited to provide an exploratory analysis, applying responder thresholds of variables included in the stratification strategy proposed by the ESC/ERS 2015 PAH guidelines [Galiè 2015], similar to the one used in CHEST-1. However, it is important to consider an important limitation of this analysis: in contrast to PAH, there is no established risk assessment strategy to guide treatment decisions in inoperable CTEPH. The prognostic relevance of target responder thresholds, established in PAH has not been widely studied in CTEPH patients who are not candidates for surgery, and is thus not fully understood. In particular, it remains unclear whether short-term changes in these clinical variables and their thresholds adopted by the PH guidelines ultimately relate to long-term survival in inoperable CTEPH patients.

In line with the risk assessment proposed in the PH guidelines at the time, CHEST-1 response criteria included 6MWD ≥ 380 m, WHO FC I/II, cardiac index ≥ 2.5 L/min/m2, right atrial pressure < 8 mmHg, mixed venous oxygen saturation (SvO2) ≥ 65% and NT-proBNP < 1800 pg/mL. Since then, the low-risk threshold for 6MWD has increased from 380 to 440 m, as suggested during the 5th World Symposium on Pulmonary Hypertension, while the NT-proBNP low-risk threshold has been further defined and set to < 300 pg/mL [Galiè 2009, McLaughlin 2013, Galiè 2015]. In addition, the

exploratory responder analysis in CHEST-1 included a 6MWD threshold value of an improvement of > 40 m, based on publications that calculated the minimally clinically important difference for 6MWD in patients with PAH; as well as a responder threshold of < 500 dyn.sec.cm-5 for PVR, as values above this level are strongly correlated with increased risk of mortality in CTEPH patients [D'Armini 2015]. Therefore, the required analysis includes responder threshold criteria as described in D'Armini and the updated criteria.

To address the CHMP request, Actelion conducted the following 3 responder analyses to compare the macitentan and placebo groups in MERIT-1:

1. Proportion of responders (i.e., subjects who achieved the responder threshold at baseline and at Week 16/24) [Table 31, Figure 7]
2. Proportion of subjects who achieved ≥ 1, ≥ 2, ≥ 3, etc., threshold parameters up to all 8 threshold parameters [Table 32]
3. OR and corresponding 95% CLs were calculated to show which treatment group has higher odds of an event and by how much, where an event was defined as achieving ≥ 5 or ≥ 6 thresholds parameters. In addition, the relative risk (RR) and corresponding 95% CLs were calculated to investigate if there was a difference between OR and RR [Table 33, Table 34].
4. Statistical likelihood of observing ≥ 5 or ≥ 6 efficacy thresholds. The reason for limiting the analysis to 6 clinical parameters is driven by the sensitivity of the measure and limiting the number of criteria to those achieved by at least 10% of the study population.

Overall, as summarized in Table 31, the proportion of subjects in the macitentan group with 6MWD ≥ 440 m, WHO FC I/II, confidence interval (CI) ≥ 2.5 L/min/m2, NT-proBNP < 300 pg/mL, and mRAP < 8 mmHg, at Week 16 or Week 24, was higher compared to placebo at Weeks 16 and 24. Furthermore, in the macitentan group, the proportion of subjects who achieved the thresholds at Week 16/24 increased from baseline, whereas in the placebo group there was a decrease from baseline for the proportion of subjects with CI ≥ 2.5 L/min/m2 and SVO2 ≥ 65% at Week 16. The proportion of subjects with an increase in 6MWD of > 40 m in the macitentan and placebo groups at Week 24 is graphically presented in Figure 7. At Week 24, a higher proportion of subjects **(n=14; 35%)** in the macitentan group had achieved an increase in 6MWD of > 40 m compared to subjects in the placebo group **(n= 9; 22.5%).**

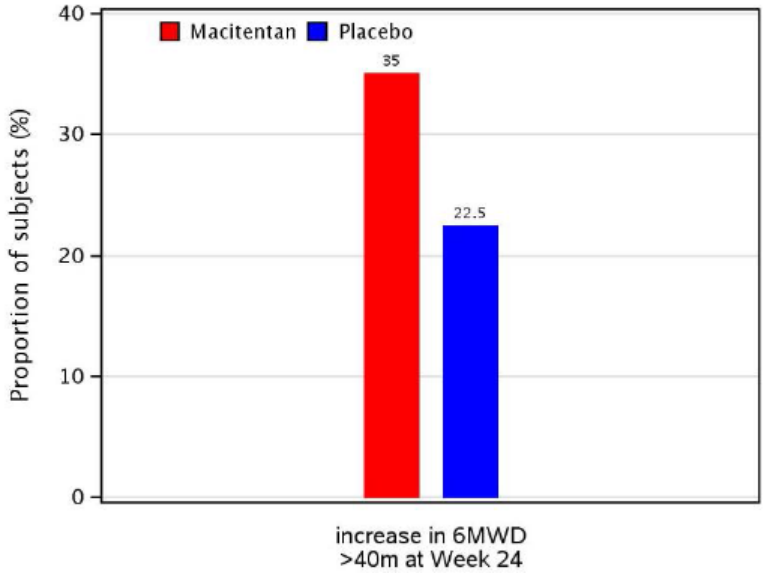
**Table 31 Number (%) of subjects who achieved the responder thresholds at baseline and at Week 16/24 (imputed) in analysis in MERIT-1**

| Responder thresholds for different variables | Macitentan N = 40 | | Placebo N = 40 | |
|---|---|---|---|---|
| | Baseline n (%) | Week 16/24 n (%) | Baseline n (%) | Week 16/24 n (%) |
| 6MWD ≥ 440 m [1] | 6 (15) | 11 (27.5) | 4 (10) | 10 (25) |
| WHO FC I/II [1] | 12 (30) | 18 (45) | 6 (15) | 11 (27.5) |
| Cardiac index ≥ 2.5 L/min/$m^2$ | 14 (35) | 20 (50) | 13 (32.5) | 11 (27.5) |
| $SvO_2$ ≥ 65%[2] | 17 (43.6) | 18 (46.2) | 22 (56.4) | 20 (51.3) |
| PVR < 500 dyn·s·$cm^{-5}$ | 6 (15) | 11 (27.5) | 7 (17.5) | 11 (27.5) |
| NT-proBNP < 300 pg/mL[1] [2] | 15 (37.5) | 18 (45) | 10 (26.3) | 12 (31.6) |
| mRAP < 8 mmHg | 16 (40) | 24 (60) | 17 (42.5) | 18 (45) |

[1] Assessed at baseline and Week 24, other parameters were assessed at baseline and at Week 16.
[2] Some subjects did not have values at baseline, hence the denominator was not 40 subjects.
Source: Appendix 1 Table 55 (T_EFF2 BASE_EMA_FAS), Table 56 (T_EFF2_WEEK_EMA_FAS).
6MWD = 6-minute walk distance; FC = functional class; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PVR = pulmonary vascular resistance; $SvO_2$ = mixed venous oxygen saturation; WHO = World Health Organization.

**Figure 7 Responder threshold criterion 8: Proportion of subjects with an increase in 6MWD > 40 m, at Week 24, FAS**

ACT-064992
Protocol: AC-055E201
Proportion of subjects with increase in 6MWD > 40m at Week 24
Analysis Set: Full analysis set




Output: F_EFF_6MWD_INC40_EMA_FAS, Produced by biarnal1 on 07DEC2018 15:27 (CET), SDTM production date: 28MAY2018
Program: val_csr_CTEPH/program_output/f_hist03.sas

The proportions of subjects who achieved at least 1, 2, 3, and up to 8 responder threshold criteria, as defined in Table 31 and Figure 7, are presented in Table 32. Compared to placebo, a higher proportion of subjects in the macitentan group achieved ≥ 1 (37 subjects [92.50%] and 34 [85%] in the macitentan and placebo groups, respectively) and up to ≥ 6 (8 subjects [20.0%] and 2 [5.0%] in the macitentan and placebo groups, respectively) combination response criteria at Week 16/24. The proportion of subjects who met at least 7 or all 8 combination response criteria is too small to draw any meaningful conclusions,
with only 1 subject difference between the two groups (1 subject on macitentan and 2 subjects on placebo).

## Table 32 Proportion of subjects who achieved at least 1, 2, 3 and up to 8 responder criteria at Week 16/24, FAS

| | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) |
|---|---|---|
| Number (%) of subjects with: | | |
| at least 1 efficacy parameters thresholds | 37 (92.5) | 34 (85.0) |
| at least 2 efficacy parameters thresholds | 29 (72.5) | 26 (65.0) |
| at least 3 efficacy parameters thresholds | 24 (60.0) | 19 (47.5) |
| at least 4 efficacy parameters thresholds | 19 (47.5) | 11 (27.5) |
| at least 5 efficacy parameters thresholds | 15 (37.5) | 6 (15.0) |
| at least 6 efficacy parameters thresholds | 8 (20.0) | 2 (5.0) |
| at least 7 efficacy parameters thresholds | 1 (2.5) | 2 (5.0) |
| all 8 efficacy parameters thresholds | 1 (2.5) | 2 (5.0) |

Efficacy parameter thresholds include 6MWD >=440m at Week 24, increase in 6MWD >40m at Week 24, WHO FC I-II at Week 24, CI>=2.5 L/min/m2 at Week 16, SVO2 >=65% at Week 16, PVR<500 dyn.sec/cm$^5$ at Week 16, NTproBNP<300 pg/mL at Week 24, mRAP < 8mm Hg at Week 16.
Output: T_EFF3_WEEK_EMA_FAS

**Responder analyses at Week 16/24:** Overall, subjects who received macitentan were 3.4-fold (95% CLs: 1.156, 9.996, p = 0.0261) and 4.75-fold (95% CLs: 0.941, 23.985, p = 0.0593) more likely to achieve thresholds for at least 5 or at least 6 efficacy parameters, respectively, as compared to placebo subjects [Table 33, Table 34]. Similarly, based on RR, subjects who received macitentan were 2.5-fold (95% CLs: 1.080, 5.786) and 4-fold (95% CLs: 0.905, 17.681) more likely to achieve thresholds for ≥ 5 or ≥ 6 efficacy parameters, respectively, as compared to placebo subjects.

## Table 33 Responder analysis at Week 16/24: Proportion of subjects who achieved ≥ 5 vs < 5 efficacy threshold parameters, FAS

| | Macitentan 10 mg N=40 | Placebo N=40 | Macitentan 10 mg versus placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Odds-Ratios (OR) | | | Relative Risk (RR) | |
| | n / N1 (%) | n / N1 (%) | OR | 95%CL | p-value | RR | 95%CL |
| at least 5 efficacy parameters thresholds | 15 / 40 (37.5) | 6 / 40 (15.0) | 3.40 | 1.156, 9.996 | 0.0261 | 2.50 | 1.080, 5.786 |
| less than 5 efficacy parameters thresholds | 25 / 40 (62.5) | 34 / 40 (85.0) | | | | | |

The odds ratio (OR) >1 indicates that responders were more likely in macitentan, while OR < 1 indicates that responders were more likely in placebo. The OR was estimated from the logistic regression that included treatment as a factor in the model.
CL = Confidence Limit, N1 = total number of subjects with non-missing or imputed data.
Logistic regression is used for macitentan vs. placebo comparison to generate odds ratio, CL, and p-value with treatment as factor in the model.
Log binomial regression is used for macitentan vs. placebo comparison to generate relative risk, and CL with treatment as factor in the model.
Efficacy parameter thresholds include 6MWD >=440m at Week 24, increase in 6MWD >40m at Week 24, WHO FC I-II at Week 24, CI>=2.5 L/min/m2 at Week 16, SVO2 >=65% at Week 16, PVR<500 dyn.sec/cm$^5$ at Week 16, NTproBNP<300 pg/mL at Week 24, mRAP < 8 mmHg at Week 16.
Output: T_EFF_5EV_EMA_FAS

**Table 34 Responder analysis at Week 16/24: Proportion of subjects who achieved ≥ 6 vs < 6 efficacy threshold parameters, FAS**

| | Macitentan 10 mg N=40 | Placebo N=40 | Macitentan 10 mg versus placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Odds-Ratios (OR) | | | Relative Risk (RR) | |
| | n / N1 (%) | n / N1 (%) | OR | 95%CL | p-value | RR | 95%CL |
| at least 6 efficacy parameters thresholds | 8 /40 (20.0) | 2 /40 (5.0) | 4.75 | 0.941, 23.985 | 0.0593 | 4.00 | 0.905, 17.681 |
| less than 6 efficacy parameters thresholds | 32 /40 (80.0) | 38 /40 (95.0) | | | | | |

The odds ratio (OR) >1 indicates that responders were more likely in macitentan, while OR < 1 indicates that responders were more likely in placebo. The OR was estimated from the logistic regression that included treatment as a factor in the model.

CL = Confidence Limit, N1 = total number of subjects with non-missing or imputed data.

Logistic regression is used for macitentan vs. placebo comparison to generate odds ratio, CL, and p-value with treatment as factor in the model.

Log binomial regression is used for macitentan vs. placebo comparison to generate relative risk, and CL with treatment as factor in the model.

Efficacy parameter thresholds include 6MWD >=440m at Week 24, increase in 6MWD >40m at Week 24, WHO FC I-II at Week 24, CI>=2.5 L/min/m2 at Week 16, SVO2 >=65% at Week 16, PVR<500 dyn.sec/cm$^5$ at Week 16, NTproBNP<300 pg/mL at Week 24, mRAP < 8 mmHg at Week 16.

Output: T_EFF_6EV_EMA_FAS

**Applicant's Conclusion:** Overall, the responder threshold analysis supports the clinical relevance of the effect of macitentan in an inoperable CTEPH population. Macitentan treatment increased the proportion of responder subjects for all variables defined, across clinical, functional, hemodynamic, and biochemical evaluations. In addition, macitentan was associated with a higher proportion of subjects meeting multiple combination response criteria, as compared to placebo. This is very relevant, as no single variable has been found to correlate consistently with survival in patients with PAH, and thus a multidimensional
approach is recommended by the current treatment guidelines when monitoring the efficacy of a therapy.

It is also important to highlight some of the additional limitations when comparing the responder analysis performed in MERIT-1 to that performed in CHEST-1. This analysis does not take into consideration the smaller sample size in MERIT-1, the differences in the severity of the CTEPH population between the two studies (more severe patients in MERIT-1), or the use of background PAH advanced therapies in MERIT-1 versus a treatment naïve population in CHEST-1, which could have influenced the available response range to macitentan.

***Rapporteur Assessment***

The applicant has provided several responder analyses with many modifications in the definition of responders compared with the requested analysis published for riociguat based on the CHEST-1 study results. Therefore, across-study comparison (MERIT-1 vs CHEST-1) in terms of responders is limited. These limitations are added to the inherent limitations due to differences in study design and populations.

With respect to PVR (main outcome in MERIT-1 study), 5 additional patients on macitentan and 4 additional patients on placebo had achieved the responder definitionF (PVR < 500 dyn.s.cm$^{-5}$) at week 16 compared to baseline (27.5% vs 27.5% at week 16) (Table 31). On the contrary, in the CHEST-1 study, the proportion of patients achieving the responder definition for PVR had doubled to 50% in the riociguat group but remained similar to baseline levels in the placebo group (26%) [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55].

For 6MWD, 5 additional patients on macitentan and 6 additional patients on placebo had achieved the responder definition for 6MWD (>440 m) at week 24 compared to baseline (Table 31). On the

contrary, in the CHEST-1 study, there was a significant increease in the proportion of patients achieving response (+21%) but no change in the proportion of placebo-treated patients achieving this threshold (+1%) [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55].

In addition, 14 (35%) patients in the macitentan group and 9 (22.5%) in the placebo group had achieved an increase in 6MWD of > 40 m compared to baseline (Figure 7 of the response document). In the CHEST-1 study, twice as many patients in the riociguat group had achieved an increase in 6MWD of >40 m compared with the placebo group (53% vs 24%) [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55].

For WHO FC, 6 additional patients on macitentan and 5 additional patients on placebo improved from WHO FC III at baseline to WHO FC I/II at week 24. On the contrary, in the CHEST study, a larger increase in the proportion of patients achieving WHO FC I/II was observed in the riociguat group (+23%) compared with the placebo group (+9%) [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55].

Some secondary haemodynamic endpoints, like cardiac index, NT-proBNP and mRAP, were clearly in favour of macitentan (Table 31). Similar trends were observed in the CHEST-1 study [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55].

The differences in these haemodinamic secondary endpoints favouring macitentan probably drive the differences observed when combining multiple responder definition criteria.

In summary, the applicant has provided several responder analyses for different endpoints, which are limited mainly due to the small sample size of the MERIT-1 study. The data allows to conclude that there may be significant differences between macitentan and placebo in the rates of responders to some secondary haemodynamic endpoints, but not in responders to PVR or in responders in 6MWD (defined as 6MWD ≥ 440 m), while a non-significant trend was in favour of macitentan for responders in 6MWD defined as an increase > 40 m versus baseline (14 patients vs. 9 patients). On the contrary, in the CHEST-1 study, larger, robust and significant differences were found in favour of riociguat compared to placebo in the rates of responders to PVR, 6MWD and improvement in WHO FC [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55]. These comparisons are, however, fraught with risk, due to different study designs, patients' disease severity and background medications, but highlights the different level of evidence available for riociguat and macitentan in CTEPH. It is the applicant's responsibility to provide such evidence.

**Conclusion**

Issue not solved (supportive of the major objection).

***Question 14***

***Subjects who received placebo in the MERIT-1 study showed a lower beneficial effect after 6 months of treatment in the OLE MERIT-2 study (19.8 m) compared with the macitentan group in MERIT-1 at Week 24 (34.0 m). A plausible explanation for this observation is that patients who received placebo during the blinded treatment period in the MERIT-1 study progressed to more irreversible disease, suggesting that patients can only benefit from treatment with macitentan when macitentan therapy is initiated as early as possible after the development of CTEPH. Notably, the time since diagnosis of CTEPH was 0.44 years in the macitentan group and 0.56 years in the placebo group of the MERIT-1 study. The Applicant is requested to discuss if this can have influenced the efficacy results.***

***Furthermore, Table 14 of the Integrated Summary of Efficacy (Module 5.3.5.3) shows that the mean improvement from OL baseline in patients that were on placebo and are switched***

***to macitentan is of only 2 metres (mean) or 5 metres (median) at 6 months after switching when baseline data for MERIT-2 are considered. Therefore, the analysis of MERIT-2 suggests no effect of macitentan in 6MWD after switching from placebo. The applicant is invited to comment.***

***Summary of MAH answer***
The analysis of a treatment effect of macitentan in MERIT-2, following the switch from placebo (in MERIT-1) suffers from limitations imposed by the lack of randomization and the absence of a control arm at baseline in MERIT-2.

As mentioned in Question 14 above, the response to treatment in inoperable CTEPH may be influenced by the delay in diagnosis to starting PAH advanced therapies, as the population progresses to a more irreversible disease. In the response to this question the applicant has also tested this interesting hypothesis in Section 14.1, before addressing the switch of placebo patients in MERIT-1 to macitentan in MERIT-2 in Section 14.2.

**14.1 Effect of macitentan and degree of disease progression**
To investigate whether the macitentan treatment effect is impacted by the degree of disease severity at treatment start and whether earlier treatment initiation could be even more beneficial, a PAH population with more advanced disease was identified, using a definition based on published data by [Simonneau 2015] distinguishing incident (time since diagnosis ≤ 6 months) vs prevalent (> 6 months) patients.

Applying these definitions to an analysis from MERIT-1 (DB), a difference in mean change from baseline to Week 24 in 6MWD in subjects with initiation of treatment ≤ 6 months after diagnosis vs those with initiation > 6 months after diagnosis could be shown [Table 35], favoring early initiation.

The mean (standard error [SE]) change from baseline to Week 24 in 6MWD for subjects with initiation of treatment ≤ 6months after diagnosis was 47.06 ± 15.44 m and −1.29 ± 16.35 m for macitentan and placebo, respectively, corresponding to a treatment effect (macitentan − placebo) of 48.34 m (95% CLs: 3.16, 93.53) [Table 35]. For subjects with initiation > 6 months after diagnosis, the mean (SE) change in 6MWD was 21.45 ± 16.14 m and 3.04 ± 15.00 m for macitentan and placebo, respectively, with a treatment effect (macitentan − placebo) of 18.41 m (95% CLs: −26.20, 63.02).

**Table 35 Analysis of change from MERIT-1 (DB) baseline to Week 24 in 6MWD (imputed) by time to treatment initiation since diagnosis (≤ 6 months vs > 6 months), FAS**

| | n | Macitentan 10 mg MERIT DB Mean ± SE (m) | n | Placebo MERIT DB Mean ± SE (m) | Treatment difference*: change from baseline Mean (95% CLs) (m) |
|---|---|---|---|---|---|
| **Time since diagnosis** | | | | | |
| ≤6 months | 21 | 47.06 ± 15.14 | 18 | -1.29 ± 16.35 | 48.34 (3.16, 93.53) |
| >6 months | 19 | 21.45 ± 16.14 | 22 | 3.04 ± 15.00 | 18.41 (-26.20, 63.02) |

*Adjusted for 6MWD baseline. p-value for the interaction test (trt*time since diagnosis) is 0.3504.
Source: Appendix 1 Table 57 (T_6MWDAC_TSD_EMA_FAS)
6MWD = 6-minute walk distance; CL= confidence limit(s); DB = double-blind; FAS = Full analysis set; SE = standard error.

This analysis suggests that subjects for whom macitentan is initiated sooner after diagnosis show a greater treatment effect than those for whom treatment initiation is later. This outcome is also reflected in the somewhat lower treatment response observed in subjects who received OL macitentan in MERIT-2 following 6 months on placebo during the DB treatment period in MERIT-1, essentially delaying initiation of macitentan treatment by a minimum of 6 months.

**14.2 Treatment effect in placebo subjects switching to macitentan in MERIT-2**

It is important to note that the 6MWD data as displayed in the referenced table [Module 5.3.5.3 ISE table 14] are based on the same imputation rules as in MERIT-1 (i.e., 0 m for death, LOCF for other missing data).

Four imputed values in the former placebo group (1 death and 3 other missing values) substantially impact the ability to illustrate the treatment effect in this cohort, as comparatively low OL baseline values are carried forward. Also, imputations in the former DB macitentan group (n = 4) potentially impacted the ability to illustrate the macitentan treatment effect [Table 36].

**Table 36 Summary of subjects with missing 6MWD values at Month 6 in MERIT-2**

| | MERIT-1 | | | | MERIT-2 | |
|---|---|---|---|---|---|---|
| Subject Number | Baseline (m) | Week 8 (m) | Week 16 (m) | Week 24 (m) /imputed* | Month 6 (m)/imputed* | Reason for missing data |
| **Subjects who received placebo in MERIT-1** | | | | | | |
| [redacted] | 283 | 275 | 283 | 283* | 283* | Discontinued for lack of efficacy |
| | 162 | 153 | 156 | 160 | 160* | Subject is ongoing (appendiceal abscess SAE at Month 6), unchanged WHO FC |
| | 214 | 267 | 174 | 271 | 0* | death |
| | 237 | 303 | 302 | 265 | 265* | Discontinued due to non-CTEPH related AE (hemoglobin decrease) |
| **Subjects who received macitentan in MERIT-1** | | | | | | |
| [redacted] | 224 | 130 | 95 | 189 | 189* | Discontinued for lack of efficacy, unchanged WHO FC at time of discontinuation |
| | 235 | 310 | 330 | 296 | 296* | Unchanged WHO FC, (vertebral fracture SAE not resolved at Month 12 (Month 6/MERIT-2 OL) |
| | 441 | 435 | 453 | 456 | 456* | Subject is ongoing (ongoing paralysis and vertebral fracture SAE), unchanged WHO FC |
| | 417 | 396 | 378 | 378 | 378* | Discontinued due to tolerability, in WHO FC I at time of discontinuation |

6MWD = 6-minute walk distance; AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; OL = open-label; SAE = serious adverse event; WHO FC = World Health Organization functional class.
Source: Module 5.3.5.3 ISE listing 1 (L_6MWD_FAS); Module 5.3.5.3 ISS Appendix 1 listing 5 (L_AE_FAS), listing 3 (L_DISC_FAS).

In Module 5.3.5.3 ISE table 14, the treatment response in 6MWD of MERIT-1 placebo subjects at Month 6 in MERIT-2, a mean (median) change from MERIT-2 baseline of 2.0 m (5.0 m) is based on a "difference" between 16.6 m and 19.8 m [Table 37]. In this analysis, 16.6 m is the LS mean of change in 6MWD from baseline to Week 24 in MERIT-1 (which is also the new "baseline" for MERIT-2) and 19.8 m is the LS mean of change from DB MERIT-1 baseline to Month 6 in MERIT-2 [Table 37]. The limitation of this analysis is that the treatment effect of 16.6 m (at the end of MERIT-1) was based on observed data excluding 4 placebo subjects with missing values: 2 subjects who died, 1 lost to follow-up, and 1 with AE arthralgia, while the treatment effect of 19.8 m was based on the imputed data at Month 6 in MERIT-2. Hence, different rules were applied for "baseline MERIT-2" and "Month 6 MERIT-2".

To assess the true effect of macitentan on 6MWD following the switch from DB placebo in MERIT-1 to macitentan in MERIT-2, the applicant has considered 2 options: to use imputed data for both MERIT-1 and MERIT-2 or to focus exclusively on observed data [Table 37]. In this analysis, the relevant changes in 6MWD for the MERIT-1 placebo subjects are illustrated by the difference between Week 24MERIT-1 (which is the baseline for MERIT-2) and Month 6 MERIT-2 data. Hence, the changes from "MERIT-2 BL" to

"Month 6 MERIT-2" were 18.8 m (imputed data) and 11.6 m (observed data) [Table 37].

**Table 37 Summary of 6MWD (m) in MERIT-2, FAS**

| | n | Macitentan 10 mg MERIT DB/OL Mean ± SD | n | Placebo/ Macitentan 10 mg MERIT DB/OL Mean ± SD |
|---|---|---|---|---|
| **Imputed data** | | | | |
| **MERIT-2 BL*** | 40 | 35.0 ± 52.52 | **40** | **1.0 ± 83.24** |
| Month 6 (MERIT-2) | 40 | 34.0 ± 52.36 | **36** | **19.8 ± 50.81** |
| **Observed data** | | | | |
| **MERIT-2 BL*** | 40 | 35.0 ± 52.52 | **36** | **16.6 ± 44.95** |
| Month 6 (MERIT-2) | 36 | 37.8 ± 52.16 | **32** | **28.2 ± 32.38** |

*Week 24 in MERIT-1 was also MERIT-2 baseline.
Source: Module 5.3.5.3 ISE table 13 and table 15
6MWD = 6-minute walk distance; BL = baseline; DB = double-blind; FAS = Full analyses set; OL = open-label; SD = standard deviation.

In addition, the estimated mean paired treatment difference in 6MWD for subjects who received placebo during MERIT-1 and macitentan during MERIT-2 (Estimand 3: New PPS/6MWD PPS) was 12 m (95% CLs: −28.6, 52.6), favoring macitentan treatment [Table 72]. The analysis was based on 39 placebo subjects in New PPS/6MWD PPS estimand.

Although the treatment effect with macitentan on 6MWD in MERIT-2 appears lower in subjects who had received placebo in the 6-month DB MERIT-1 study, the results must be viewed in the context of the absence of a placebo control. Another explanation, as suggested in this question, can be that the 6-month placebo treatment in MERIT-1 resulted in a certain degree of disease progression, which could not be fully recovered after initiation of macitentan in MERIT-2.

**Applicant's Conclusion:** The benefit from treatment with macitentan is not limited to patients with a shorter time since diagnosis, as demonstrated in MERIT-1. Treatment with macitentan for 6 months in MERIT-2 to MERIT-1 DB placebo-treated subjects provided clinically meaningful benefit in 6MWD.

***Rapporteur Assessment***

The applicant has provided a post-hoc exploratory subgroup analysis of the exploratory secondary outcome of 6MWD depending on time since CTEPH diagnosis (≤ 6 months vs. > 6 months). The p-value for interaction is 0.3504, thus far beyond of being statistically significant, and therefore it cannot be concluded whether the effect of macitentan may be lower or higher when there is a delay in starting treatment.

The applicant has also provided several post-hoc analyses of the secondary outcome of 6MWD during the open label phase of the MERIT study (MERIT-2). It worth mentioning that there is high variability, as shown by a SD much higher than the point estimate for change in 6MWD in most cases (Table 37). In addition, four imputed values in the former placebo group (1 death and 3 other missing values) substantially impact the ability to illustrate the treatment effect in this cohort, as comparatively low OL baseline values are carried forward. These limitations prevent from concluding whether there was or there was not an increase in 6MWD when patients were switched from placebo to macitentan.

The applicant has explained that the discrepancies between the only 2 meter improvement in MERIT-2 in placebo patients after switching to macitentan shown in table 14 of the Integrated Summary of Efficacy (Module 5.3.5.3) compared with other analyses is due to differences in imputation rules applied for "baseline MERIT-2" and "Month 6 MERIT-2". The results in 6MWD in MERIT-2 are dependent on whether imputed data or observed data are analyzed and also on the imputation rules.

The company insists in showing the analyses that are more favourable to the experimental drug for trying to justify some drug effect, between 11 and 18 metres in MERIT-2 (Table 37). Even in the best case scenario (18 metres), these differences are far beyond the 40 m improvement calculated as the minimally important difference for change in 6MWD (the smallest change or difference in outcome measure, perceived as beneficial, that would justify a change in a patient's medical management) according to recent literature [D'Armini, et al. J Heart Lung Transplant. 2015;34:348-55] [Gabler et al. Circulation 2012;126:349-56] [Mathai et al. Am J Respir Crit Care Med 2012;186:428-33].

In summary, data on 6MWD from MERIT-2 are not assessable due to important limitations (small sample size, high variability, lack of control group, high dependence on whether imputed or observed data are considered and on the imputation methods applied). Although it is counterintuitive that a sick symptomatic patient with CTEPH can benefit from an early start of treatment, the results of MERIT-1/2 study are exploratory and cannot confirm whether the effect of macitentan is higher when started in patients < 6 months since CTEPH diagnosis or > 6 months since diagnosis. Therefore, the uncertainties about the potential benefit from treatment with macitentan in the MERIT-1 study in terms of statistical significance and clinical relevance are applicable to the overall study population, regardless of time since diagnosis, and also to patients in whom start of treatment is delayed for more than 6 months and then are switched to macitentan (MERIT-2).

**Conclusion**

Issue solved (no further information pursued).

***Question 15***

***The point estimate for BDI was far beyond the 0.9 units that are considered the minimal important difference in BDI in patients with PAH [Khair RM, et al. Ann Am Thorac Soc. 2016;13(6):842-9], which is against a meaningful effect in relief of symptoms. The company is invited to provide a post-hoc responder analysis showing the rate of patients with a >0.9 unit improvement vs. baseline (i.e.: above the minimal) per treatment group.***

***Summary of MAH answer***
The following response is divided into two parts in order to i) highlight the limitations in interpretability of the BDI as an individual assessment, and ii) to demonstrate the utility of the requested BDI 'responder' criteria in more objectively assessing 6MWD.

***Interpretability of BDI***
In the applicant's opinion, BDI assessed as a post-walk variable, does not carry any clinical utility in itself. The interdependency of BDI and 6MWT has to be considered when interpreting the BDI score. This is also reflected in a substantial number of controlled studies with PH-targeted medications that have failed to show an effect on BDI as an individual measure.

The BDI assessment in MERIT-1 and most PH studies was performed immediately after the end of the 6MWT [Module 5.3.5.1 D-17.097 section 9.6.1.2], which is in line with published international guidelines [ATS Guidelines 2002, Galiè 2009]. The timing of the assessment makes the BDI interdependent with the level of effort applied for the exercise test, and therefore renders it poorly suited as an individually interpretable value.

In the presence of an overall positive treatment effect on 6MWD, a neutral effect on BDI in both treatment arms essentially validates that the walk test was performed under non-encouraged conditions and can be considered bias-free.

The lack of statistically or clinically significant improvement in BDI score, despite an improvement in exercise capacity, as was observed in MERIT-1 has also been reported in other studies with PAH medications [Barst 2006, Galiè 2005, McLaughlin 2006, Rubin 2002, Simonneau 2008] and in the long-term outcome studies in PAH with macitentan (SERAPHIN) and selexipag (GRIPHON) [D-12.425, D-13.361].

Therefore, the observed neutral effect on BDI in MERIT-1 is in line with results from previous randomized-controlled studies performed in PH. A neutral effect on BDI indicates that the respective 6MWTs were performed under similar conditions and with the same level of effort. As such, they are consistent with the standardization principles applicable to this exercise-related test.

***Responder analysis on BDI***

Responders' according to the referenced minimally important difference for BDI of > 0.9 units were analyzed for their attained 6MWD. In this analysis, a total of 13 (32.5%) and 16 (40.0%) subjects in the macitentan and placebo groups, respectively, met the criteria of an improvement in BDI of > 0.9 units from baseline to Week 24 [Table 38]. For these subjects, the LS mean difference of change from baseline to Week 24 in 6MWD (macitentan – placebo) was 52.22 m (95% CLs: 16.43, 88.01) with no overlap in 95% CLs (37.51 m, 90.56 m) and (−12.08 m, 35.72 m) for macitentan and placebo, respectively
[Table 38].

These data are entirely consistent with the limitations inherent to the BDI, as explained above. Given the interdependency of 6MWT and BDI, controlling for one of the variables (here BDI 'responder', which employed a comparable level of effort into the 6MWT), renders an objective (bias-free) assessment and likely represents the objective 'true' effect of macitentan on 6MWD.

**Table 38 Between-treatment analysis of change from baseline to Week 24 in 6MWD (observed) for subjects with > 0.9 unit improvement in Borg dyspnea index at Week 24 compared to baseline, FAS**

Week 24

| | NDF | DDF | F-value | P-value | Macitentan 10 mg | Placebo | Macitentan - Placebo |
|---|---|---|---|---|---|---|---|
| Number of subjects included in the analysis set | | | | | 40 | 40 | |
| Number of subjects included in the analysis | | | | | 13 | 16 | |
| Type III analysis of effects | | | | | | | |
| Treatment | 1 | 26 | 8.99 | 0.0059 | | | |
| LS mean | | | | | 64.03 | 11.82 | 52.22 |
| SE | | | | | 12.91 | 11.63 | 17.41 |
| 95% CL | | | | | 37.51, 90.56 | -12.08, 35.72 | 16.43, 88.01 |

CL = confidence limit, DDF = Denominator Degrees of Freedom, LS Mean = Least Square Mean, NDF = Numerator Degrees of Freedom, SE = Standard Error

Statistical model is Analysis of Covariance including 6MWD at baseline as a covariate, with Treatment as factor in the model.

Source: Appendix 1 Table 58 (T_6MWDACO_BORGMID_EMA_FAS)

**Applicant's Conclusion:** There is no difference in the number of subjects achieving a 0.9 unit improvement in BDI between macitentan and placebo in MERIT-1. Given the interdependency of BDI and 6MWT, a responder analysis regarding BDI must be viewed in the context of the change in 6MWD. In this analysis, with a similar improvement in BDI, macitentan-treated subjects achieved a statistically significant and clinically meaningful treatment effect of 52.22 m (LS mean), which can be considered a bias-free result.

***Rapporteur Assessment***

The applicant has provided a requested analysis or "responders" in BDI, defined as those with an improvement > 0.9 units versus baseline. In this analysis, there were numerically fewer responders in the macitentan group [13 (32.5%)] than in the placebo group [16 (40.0%)]. The applicant states that: "BDI assessed as a post-walk variable, does not carry any clinical utility in itself", that "The interdependency of BDI and 6MWT has to be considered when interpreting the BDI score", and that "In the presence of an overall positive treatment effect on 6MWD, a neutral effect on BDI in both treatment arms essentially validates that the walk test was performed under non-encouraged conditions and can be considered bias-free".

Therefore, according to the applicant's explanation, it seems that a neutral effect on BDI is the alternative hypothesis to be accepted after rejecting the null hypothesis. However, looking at the MERIT-1 study protocol, BDI was included as secondary endpoint with the null hypothesis being the equivalence between treatments. In addition, BDI was included in the hierarchical testing for efficacy endpoints.

*"To control for multiplicity across the primary and secondary efficacy endpoints and in order to preserve the overall type 1 error at the pre-defined 2-sided significance level of α = 0.05, it was planned to analyze secondary endpoints hierarchically according to the sequence and statistical significance pre-specified in the protocol, based on the following conditions:*

*• The predefined nominal significance level (p < α two sided) was achieved for the primary efficacy endpoint (percent of baseline PVR at rest at Week 16).*

*• For the secondary endpoints, the predefined nominal significance level (p < α two sided) was reached for all the previous endpoints in the sequence (i.e., first for the change from baseline to Week 24 in 6MWD, then for the change in Borg dyspnea index and finally for worsening WHO FC)."*

Furthermore, the submitted analysis of 6MWD in patients that afterwards are responders to BDI is a good example of what should not be done in statistical analysis. As a result, the applicant's conclusion is not valid.

In the response to MO, the applicant also states that "*in the applicant's experience, the Borg dyspnea index (BDI) is not a clinically relevant endpoint in the evaluation of pulmonary hypertension (PH) symptoms. In the published literature as well as in large studies with macitentan or selexipag in PAH (AC-055-302/SERAPHIN and AC-065A302/GRIPHON), no effect on BDI was observed, despite a clinically relevant effect on disease progression."* It is endorsed that the BDI is not as clinically relevant as disease progression. The assessors would have welcomed the provision of disease progression data in the CTEPH population. Unfortunately, no data are available in the new indication. The MAH has not mention that other studies in PAH (Patent-1) and CTEPH (CHEST-1) (Ghofrani et al, N Engl J Med 2013;369:319-29) have shown significant differences in the BDI endpoint in favour of the experimental group.

In summary, responder's analysis of BDI numerically favoured placebo not supporting the benefit of macitentan in relief of symptoms. This finding is also consistent with the lack of effect in terms of responders in WHO FC (see also assessment of Q13), and compares unfavorably with the data available for riociguat, the only approved drug in the CTEPH indication.

**Conclusion**

Issue not solved (see other clinical concern).

***Question 16***

***Quality of Life assessed by PAH-SYMPACT symptom and impact part scores and EQ-5D scores did not show differences in clinical significance between macitentan and placebo. Please comment.***

***Summary of MAH answer***

There is a statistically significant improvement in subjects on macitentan over placebo with regards to the Euro Quality of Life-5D (EQ-5D) Quality of Life (QoL) Health summary state index (HSSI) at Week 24 (−0.05, 95% CLs: −0.10, 0.0; p = 0.0490). The following factors may have contributed to the lack of a consistently clinically significant difference between the macitentan and placebo groups in the PAH-SYMPACTTM and overall EQ-5D-3L QoL assessments:

• In MERIT-1, the disease-specific questionnaire PAH-SYMPACTTM was measured at Baseline, Week 8 and Week 16 only. The maximum treatment effect of macitentan as measured by 6MWD was observed at Week 24. It can be assumed that the full benefit on QoL may have become apparent after Week 16, i.e., at Week 24 or later. This is supported by the results of the EQ-5D, which was additionally measured at Week 24, and for which a statistically significant difference in favor of macitentan was shown on the HSSI score, with an LS mean difference of change from baseline to Week 24 (macitentan vs placebo) of −0.05 (95% CLs: −0.10, 0.0; p = 0.0490). It should be noted that in MERIT-1, negative values represent improvement. The EQ-5D visual analog scale (VAS) showed a similar magnitude of effect in favor of macitentan as the summary index score (6.23, 95% CLs: −0.38, 12.85; p = 0.0644) [Module 5.3.5.1 D-17.097 table 11-18]. In the CHEST-1 study, treatment with riociguat resulted in a statistically significant improvement in EQ-5D score and in the EQ-5D VAS. This was not supported by the change in the disease-specific Living with Pulmonary Hypertension questionnaire score which did not achieve significance [Ghofrani 2013c].

• The placebo-corrected change of 0.13 (95% CLs: 0.06, 0.21; p < 0.0001; n = 259) in EQ-5D observed in the CHEST-1 study, consisted of an improvement of 0.06 in the riociguat arm and a deterioration in QoL of −0.08 in the placebo arm [Ghofrani 2013c].

The change observed with riociguat in CHEST-1 is comparable with that observed with macitentan in MERIT-1, which was also 0.06. However, unlike in CHEST-1, no deterioration in EQ-5D occurred in the placebo arm of MERIT-1. An explanation for this could be that treatment-naïve subjects participated in the CHEST-1 study, for whom the initiation of active therapy was likely to produce a large improvement, as the placebo-treated group was likely to remain unchanged or even deteriorate, thereby magnifying the placebo-corrected treatment effect. This may not be applicable in the MERIT-1 population, most of whom continued to receive background therapy. Thus, in MERIT-1, the placebo-treated subjects generally were less likely to deteriorate during a short trial, and thus the magnitude of placebo-corrected treatment effect was attenuated. This is confirmed by a between-treatment analysis of change from baseline to Weeks 8, 16, and 24 in EQ-5D HSSI score and VAS for subjects with and without PH advanced therapy at baseline [Table 71]. In subjects with PH advanced therapy at baseline, HSSI score improved at Week 24 in both treatment arms (macitentan: −0.073, placebo: −0.028). The same pattern was observed with the VAS, with improvements noted in both treatment arms (macitentan: 9.32, placebo: 5.93). In subjects without PH advanced therapy at baseline, a deterioration in QoL was observed in the placebo arm.

At Week 24, the HSSI score improved (−0.022) in subjects on macitentan without PH advanced therapy at baseline and deteriorated (0.069) in subjects on placebo (between-treatment difference −0.091). Similarly, on the VAS, macitentan subjects improved (8.16) and placebo subjects deteriorated by −1.92 at Week 24 (between-treatment difference 10.09).

**Conclusion:** In summary, there are two factors contributing to the lack of a clinically significant difference between the macitentan and placebo groups in the PAH-SYMPACTTM and overall EQ-5D-3L QoL assessments:

• PAH-SYMPACTTM: This instrument was used at Weeks 8 and 16, and not at Week 24 when the maximum treatment effect of macitentan on 6MWD was observed. This likely limited the chance to capture the potential benefit of macitentan on QoL, as assessed by the PAH-SYMPACTTM.

• EQ-5D: The favorable trend observed with macitentan treatment in the EQ-5D, although similar to the improvement observed with riociguat in CHEST, only partly reached statistical significance. This may be attributed to the high proportion of subjects on concomitant PH advanced therapies at baseline in the MERIT-1 study. It is unlikely that patients on concomitant PH advanced therapies show a large deterioration on placebo when compared to treatment-naïve patients.

***Rapporteur Assessment***

The MAH mentions that was a statistically significant improvement in subjects on macitentan over placebo with regards to the EQ-5D at week 24. Firstly, this was another exploratory endpoint for which statistical significance cannot be inferred. Secondly, the differences were far beyond being considered of clinical relevance.

In addition, according to the protocol, the "main" exploratory QoL variables were the change from baseline to Week 8 and Week 16 in PAH-SYMPACT™ symptom and impact domain scores. No clinically

relevant differences between groups were observed. The applicant states that the more plausible explanation for the lack of differences in PAH-SYMPACTTM is because it was not measured at week 24, when the maximum treatment effect of macitentan was observed. The applicant is encouraged to test this hypothesis in a further confirmatory trial adequately powered to show statistically and clinically relevant differences between groups.

**Conclusion**

Issue solved (no further information pursued).

***Question 17***

***It is unknown why a death due to hemorrhagic stroke in the placebo group of the MERIT-1 study was qualified as a PH-related disease progression. Please, discuss.***

***Summary of MAH answer***
The PT haemorrhagic stroke' was reported for one subject from the Russian Federation (MCN A-CH2015-123491). A full narrative for this subject is provided in the MERIT-1 CSR [Module 5.3.5.1 D-17.097 section 15.4.1.2.1]. This event satisfies the definition established for PH-related disease progression, which included "all-cause death" as one of the components. This endpoint was meant to capture time to clinical worsening.

It was adapted from the 'clinical worsening and disease progression' definition first recommended to be used as an endpoint in Phase 3 PH clinical trials by the Task Force on End Points and Clinical Trial Design at the Fourth World Symposium on Pulmonary Hypertension, which includes all-cause mortality and is also in line with the CHMP endpoint of time to clinical worsening [EMEA/CHMP/EWP/356954/2008, McLaughlin 2009, Frost 2011, Studer 2014].

***Rapporteur Assessment***
The applicant's response is not endorsed.

The exploratory endpoint of time to first PH-related disease progression was wrongly defined in the protocol as synonym of time to clinical worsening. However, these two terms are not synonyms. The PH guideline (EMEA/CHMP/EWP/356954/2008) states:

*Time to Clinical Worsening: The investigation of a composite primary endpoint that reflects, in addition to mortality, time to clinical worsening is encouraged. The composition of this composite endpoint may vary depending on the severity and the aetiology of the disease. The following components are suggested:*

*1. All-cause death.*

*2. Time to non-planned PAH-related hospitalization.*

*3. Time to PAH-related deterioration identified by at least one of the following parameters: i. increase in WHO FC; ii. deterioration in exercise testing iii. signs or symptoms of right-sided heart failure*

Therefore, if patient died due to haemorrhagic stroke, it had to be qualified among "all-cause death", and "clinical worsening", but not as "PAH-related disease progression".

**Conclusion**

Issue solved (no further information pursued).

***Question 18***

***The applicant is requested to clarify, why the Kaplan-Meier curve of time to PH-related disease progression only included 5 events in the placebo group, whereas 7 placebo***

***subjects were reported to have PH-related disease progression.***

***Summary of MAH answer***

The time to the first PH-related disease progression event up to end-of-study [as defined in D-17.097 appendix 16.1.9.1.1 section 9.3] was estimated using the KM method. All events (2 on macitentan and 7 on placebo) were included [D-17.097 table 11-13, table 15-72, appendix 16.1.9.1.1 sections 5.5.3.7 and 9.3]. The KM curve displayed in MERIT-1 includes events reported up to 24 weeks sharp (macitentan: 2 events, placebo: 5 events) [Module 5.3.5.1 D-17.097 figure 11-6]. The remaining 2 events in the placebo group (all cause death and other PH-related disease]) happened on Days 171 and 170, respectively, while the subjects were still receiving placebo treatment in the MERIT-1 study [Module 5.3.5.1 D-17.097 appendix 16.2.5.1 and appendix 16.2.7.1]. As these 2 events occurred beyond Week 24, they are not shown in the graph but were included in the estimation. This information is provided in the MERIT-1 CSR [Module 5.3.5.1 D-17.097 section 11.2.2.6].

***Rapporteur Assessment***

The applicant has clarified that the two of the events in the placebo group occurred beyond week 24 and where not included in the KM curve.

**Conclusion**

Issue solved.

***Question 19***

***Regarding the MERIT-2 study the MAH is requested to explain the apparent lack of consistency between the change in 6MWD at Month 6 for the patients on placebo in MERIT-1 shown in Table 13 and Figure 8 of the JAR.***

***Summary of MAH answer***

Table 13 of the Joint Assessment Report (JAR; i.e., Table 39 below) constitutes the corresponding source for the 6 Month/OL time point in Figure 8 of the JAR (i.e., Figure 8 below), both displaying the 6MWD change from MERIT-1 baseline.

Table 13 of the JAR [Table 39] displays the change in 6MWD from DB baseline (DB MERIT-1) to the Month 6 time point in MERIT-2 applying standard imputation rules to all subjects with a MERIT-2 baseline (0 m for death, LOCF for other missing data). It can be seen that the mean changes from baseline (DB MERIT-1) to Month 6 (MERIT-2) were 19.8 m and 34.0 m [Table 39] for subjects who were previously treated with placebo and macitentan, respectively, in MERIT-1. Mean changes from baseline (DB MERIT-1) to Weeks 8, 16 and 24 are summarized in [Module 5.3.5.3 ISE table 13] and graphically displayed in Figure 8, and are completely aligned.

For the interpretation of Table 39 (Table 13 of the JAR [Module 5.3.5.3 ISE table13]) and discussion on the benefit of switching from placebo to macitentan, please see the response to Question 14.
In summary, there is no lack of consistency between the change in 6MWD at Month 6 in MERIT-2 for subjects who received placebo in MERIT-1, as shown in Table 13 and Figure 8 of the JAR.

***Rapporteur Assessment***

The applicant's response is endorsed. The discrepancy is not between table 13 and figure 8 of the JAR, but between table 13 of the JAR (19.8 to 34 meter improvement) and Table 14 of the Integrated Summary of Efficacy (only 2 meter improvement in 6MWD), which has been discussed in the assessment of Q14.

**Conclusion**

Issue solved.

## Clinical safety aspects

***Question 20***

***The applicant is invited to provide information about planned studies to further assess the safety profile of macitentan in CTEPH standard practice (i.e.: in comparison with riociguat or on top of riociguat) upon an eventual approval of the new indication.***

***Summary of MAH answer***

The applicant agrees that it would be of interest to further characterize the safety profile of macitentan (including in combination with riociguat) in CTEPH in a real–world clinical practice setting. To this end, the applicant proposes to develop a dedicated CTEPH post-marketing observational study.

This study will consist of a comprehensive review of safety events that occur in CTEPH patients treated with macitentan, as monotherapy, in combination with riociguat, or in combination with any other PH-specific therapy, in a real-world setting and followed up in several major European PH national registries (e.g., SPAHR in Sweden, COMPERA in Germany, REHAP in Spain, the French registry, the UK Audit, and the Czech Republic database; final list to be determined in collaboration with the EMA and registry owners).

The prospective observational follow-up of patients newly treated with macitentan, in the context of these existing registries, will describe the safety profile of macitentan in a real-world setting, including all important potential and identified safety risks of macitentan use. This study will be a secondary use of data from existing PH registries and databases that include CTEPH patients newly treated with macitentan. Data collection specific to safety events for macitentan users would be extended for each contributing registry and data will be analyzed by the respective data owners using similar statistical methods. Meta-analysis techniques will be used to combine the aggregated results obtained from all registries / database statistical analyses [Appendix 3 D-18.428].

In the meantime, and since the CTEPH submission to the EMA on 28 August 2018, additional sources of safety data have been further reviewed/analyzed:

1) Post-marketing experience (spontaneous AE reporting) up to 18 October 2018 (18 October 2017 in the Summary of Clinical Safety) including reports from the off-label use of macitentan, in particular in the CTEPH population, and
2) Additional safety data from the combined OPUS and OrPHeUS databases. Please find below an in-depth review of these data.

**Post-marketing experience: data from the Actelion Drug Safety database [Argus]**
A total of 35,038 cases have been received cumulatively for macitentan-treated patients between the International Birth Date (IBD) (18 October 2013) and 17 October 2018, of which 720 had a reported medical history of CTEPH (representing an additional 479 cases with a medical history of CTEPH since the previous submission). Overall, in 3039 out of the 35,038 cases, concomitant use of riociguat was reported. Among the 720 cases with a medical history of CTEPH "CTEPH population", concomitant use of riociguat was reported in 143 cases.

Based on worldwide post-marketing experience (i.e., all AEs received from patients exposed in real-world medical practice and long-term use in the post-authorization phase), the review below presents a summary of cumulative data on macitentan, in cases with/without a medical history of CTEPH, and with/without concomitant use of riociguat.

Despite limitations inherent to the comparison of safety data based on post-marketing sources, the overall nature and distribution of events reported in cases with/without riociguat are consistent, and reflect both the known safety profile of macitentan (headache, anemia, hemoglobin decrease, fluid retention, peripheral edema, hypotension) and events expected in a patient population suffering from PAH and associated comorbidities (dyspnea, PH, RV failure), as well as the known events expected with riociguat as per the product label. No unusual pattern of AEs was observed, and no new concerns were identified.

No exposure data are available for patients who received concomitant treatment with macitentan and riociguat. Therefore, it should be noted that the analysis was based on the nature of the AEs reported and the proportions of these AEs among all events reported in cases with documented concomitant use of these medications (i.e., estimation of reporting rates was not possible).

The results of the analyses of available data (up to 17 October 2018), even though based on limited data (relatively low number of cases received for patients concomitantly receiving macitentan and riociguat, and in particular in patients having a medical history of CTEPH) and the limited information provided (in cases arising from post-marketing sources, i.e., regarding treatment start and stop dates, and the inability to assess temporal association of the reported AEs and concomitant treatments), support that the concomitant use of macitentan and riociguat and the use of macitentan in the CTEPH patient population are not associated with any specific safety signal.

**Additional safety data from OPUS & OrPHeUS databases**

In the application submitted to the EMA on 28 August 2018, results (up to the data cut-off date of 17 April 2018) from the OPUS Registry, a multicenter, prospective, long-term, observational drug registry, were included [Module 5.3.5.4 D-18.259]. To meet the ongoing post-approval safety commitment in the US, OrPHeUS (a multicenter, retrospective, medical chart review) was conducted as a complementary data source to OPUS. In this combined OPUS-OrPHeUS dataset analysis, the sample size of the CTEPH population increased to 144 patients (data provided previously included 45 patients from the OPUS registry alone as of 17 April 2018 [Module 5.3.5.4 D-18.259]).

The safety events (AEs and all-cause deaths) reported in the OPUS and OrPHeUS databases are described below [Module 5.3.5.4 D-18.430].

a) AEs in the OPUS Registry
AE analysis is provided on the OPUS registry dataset only, as in OrPHeUS, AE reporting was not applicable given the retrospective nature of the study. The safety analysis presented below includes data up to the cut-off date of 17 October 2018. AE data for the CTEPH and PAH populations are summarized in Table 40.
Overall, the updated AE data contribute a total exposure period of 28.8 patient-years at risk for an AE for CTEPH patients treated with Opsumit [Table 40]. Reported rates for the occurrence of AEs do not suggest any incremental AE risk associated with Opsumit in CTEPH patients compared to PAH patients [Table 40]. Few patients experienced liver test abnormalities during the exposure period in the CTEPH and the PAH Follow-up Sets [Module 5.3.5.4 D-18.430 table 34; table 35]. One CTEPH patient met the biochemical criteria of a potential Hy's law case during treatment with Opsumit [Module 5.3.5.4 D-18.430 table 38]. The event was not considered to be "reasonably possibly due to Opsumit treatment" as evaluated by the Independent Liver Safety Data Review Board [data on file].

**Table 40 Rates of AE per 100 patient-years during the exposure period in the CTEPH Follow-up Set and the PAH Follow-up Set – OPUS Registry**

| | CTEPH Follow-up Set N = 56 | PAH Follow-up Set N = 1710 |
|---|---|---|
| **AEs** | | |
| Patient experienced at least 1 AE | 37 (66.1%) | 1270 (74.3%) |
| Exposure time (patient-years) | 28.8 | 857.2 |
| Rate of AE per 100 patient-years (95% CI) | 128.6 (93.2, 177.5) | 148.2 (140.2, 156.5) |

AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Source: Module 5.3.5.4 D-18.430 table 39, table 41.

To compare the CTEPH populations treated with Opsumit in combination with riociguat and Opsumit without riociguat in the OPUS Registry CTEPH dataset (N = 31 and 25, respectively), AE data for these two patient subgroups are summarized in Table 41. The proportion of patients reporting at least an AE in the Opsumit with riociguat subgroup was higher than in the subgroup of patients who received

Opsumit without riociguat. The difference was mainly driven by the occurrence of events such as pneumonia (16.1% versus 8%), cough (6.5% versus 0), edema peripheral (12.9% versus 0%), and epistaxis (9.7% versus 0) [Module 5.3.5.4 D-18.430 table 44 and table 45]. Among those, edema peripheral is an identified very common adverse drug reaction for both riociguat and macitentan, and epistaxis is an identified common adverse drug reaction with riociguat.

**Table 41 Rates of AE per 100 patient-years during the exposure period in the CTEPH Opsumit with riociguat and Opsumit without riociguat subgroups– OPUS Registry**

| | Opsumit with riociguat subgroup N = 31 | Opsumit without riociguat subgroup N = 25 |
|---|---|---|
| **AEs** | | |
| Patient experienced at least 1 AE | 23 (74.2%) | 13 (52.0%) |
| Exposure time (patient-years) | 12.7 | 16.0 |
| Rate of AE per 100 patient-years (95% CI) | 180.7 (120.1, 271.9) | 81.1 (47.1, 139.6) |

AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Source: Module 5.3.5.4 D-18.430 table 43.

b) All-cause deaths in the combined OPUS-OrPHeUS dataset

The combined OPUS-OrPHeUS dataset was used to provide all-cause death distribution. All-cause death for the CTEPH and PAH patient sets is summarized in Table 42. Overall, in this 3-fold larger dataset compared to the data submitted previously, the updated all-cause death data contributes a total exposure period of 206.9 patient-years at risk for death for CTEPH patients treated with Opsumit [Table 42]. Reported rates for the occurrence of all-cause death per 100 patient-years for the CTEPH and the PAH Follow-up Sets do not suggest any incremental mortality risk associated with Opsumit in CTEPH patients compared to PAH patients [Table 42].

**Table 42 Rates of death per 100 patient-years during the exposure period in the CTEPH Follow-up Set and PAH Follow-up Set – combined OPUS-OrPHeUS dataset**

| | CTEPH Follow-up Set N = 144 | PAH Follow-up Set N = 4072 |
|---|---|---|
| **Death** | | |
| Number of deaths | 9 (6.3%) | 411 (10.1%) |
| Exposure time (patient-years) | 206.9 | 5584.4 |
| All cause death per 100 patient-years (95% CI) | 4.3 (2.3, 8.4) | 7.4 (6.7, 8.1) |

CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Source: Module 5.3.5.4 D-18.430 table 46, table 47.

All-cause death for the subgroups of patients treated with Opsumit in combination with riociguat and Opsumit without riociguat is summarized in Table 43. Reported rates for the occurrence of all-cause death per 100 patient-years are similar between the two subgroups taking into consideration the overlapping 95% CIs between the 2 patient sets [Table 43].

**Table 43 Rates of death per 100 patient-years during the exposure period in the CTEPH Opsumit with riociguat and Opsumit without riociguat subgroup – combined OPUS-OrPHeUS dataset**

| | Opsumit with riociguat subgroup N = 70 | Opsumit without riociguat subgroup N = 74 |
|---|---|---|
| **Death** | | |
| Number of deaths | 4 (5.7%)* | 4 (5.4%) |
| Exposure time (patient-years) | 79.2 | 119.3 |
| All cause death per 100 patient-years (95% CI) | 5.1 (1.9, 13.5) | 3.4 (1.3, 8.9) |

CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension.
* One additional patient died in this subgroup after discontinuation of the Opsumit with riociguat combination
Source: Module 5.3.5.4 D-18.430 table 48.

**Overall Applicant's conclusion**

No new safety concerns have been identified among the various sources of additional safety data reviewed and summarized above. In addition to the previously submitted data, this supplementary safety information supports the opinion of the Marketing Authorization Holder (MAH) that the macitentan safety profile in CTEPH patients remains unchanged and is very similar to the safety profile observed in PAH patients. The combination of macitentan with riociguat does not appear to be associated with any specific new safety signal.

Whilst the MAH concurs with the Pharmacovigilance Risk Assessment Committee (PRAC) assessment that routine pharmacovigilance should be sufficient to identify and characterize the risks of the product; in order to further characterize the safety profile of macitentan, including in combination with riociguat, in CTEPH in a real–world clinical practice setting, the MAH proposes to develop a dedicated CTEPH post-marketing observational study in collaboration with several existing major European PH national registries as described above [Appendix 3 D-18.428].

***Rapporteur Assessment***
The MAH has provided the additional safety data analyzed since the CTEPH submission to the EMA on 28 August 2018.

1) Post-marketing experience (spontaneous AE reporting) up to 18 October 2018 (18 October 2017 in the Summary of Clinical Safety) including reports from the off-label use of macitentan, in particular in the CTEPH population, and
2) Additional safety data from the combined OPUS and OrPHeUS databases.

It is agreed that the data provided do not raise new safety concerns with the combination of macitentan with riociguat.

The company has collected 720 cases from the Actelion Drug Safety Database Argus with a medical history of CTEPH "CTEPH population" and concomitant use of riociguat in 143 cases. Therefore, there are many potential candidates to be included in a phase III confirmatory study.

**Conclusion**

Issue solved.

***Question 21***

***Analysis of AEs in subpopulations of MERIT-1 shows a higher proportion of subjects with PH advanced therapy at baseline in both treatment groups had edema/fluid retention AESIs (29.2% macitentan vs. 12.0% placebo) compared to subjects without PH advanced therapy***

***(18.8% macitentan vs. 6.7% placebo). Patients on concomitant PH therapies represent a higher risk population with a more advanced disease. Increased risk of AESIs is not unexpected. Anyway, the applicant is invited to discuss whether this increase in AESIs could be due, at least to some extent, to drug-drug PK or PD interactions between macitentan and other drugs used in patients with CTEPH.***

***Summary of MAH answer***
Pharmacokinetic (PK) drug-drug interactions (DDIs) between macitentan and the PH-advanced therapies (beraprost sodium, iloprost, sildenafil, tadalafil and riociguat) used by subjects in the MERIT-1 study are unlikely, based on their known PK characteristics, as described below.

*Inhaled or oral prostanoids*
• A PK interaction between macitentan and beraprost is unlikely, as macitentan does not affect CYP2C8 isoforms and beraprost has no effect on any of the CYP450 isoforms [Opsumit® SmPC, Fukazawa 2008].
• A PK interaction between macitentan and iloprost is unlikely, as *in vitro* studies have shown that CYP450-dependent metabolism plays only a minor role in the biotransformation of iloprost, and no relevant inhibition of drug metabolism via CYP450 enzymes is to be expected with iloprost [Iloprost® SmPC].

*PDE-5 inhibitors*
• Macitentan does not affect the PK of sildenafil and sildenafil does not affect the PK of macitentan, based on results from a dedicated clinical DDI study submitted in the initial marketing authorisation application and reflected in the [Opsumit® SmPC].
• No PK interaction is expected between macitentan and tadalafil, as both compounds are substrates of CYP3A4 and have no clinically relevant inhibitory or inducing effects on this CYP450 [Adcirca® SmPC, Opsumit® SmPC]. A recently published PK study in PAH patients treated with various combinations of ERAs and PDE-5 inhibitors further confirms the lack of clinically relevant DDIs between macitentan and tadalafil [Grünig 2017].

*Soluble guanylate cyclase stimulators*
• No effect of macitentan 10 mg on the PK of riociguat was observed in a DDI study between macitentan and riociguat. The CSR is provided as part of the application [Module 5.3.3.4 D-18.171]. Riociguat and its main metabolite are not inhibitors or inducers of major CYP450 isoforms (including CYP3A4) *in vitro* at therapeutic plasma concentrations [Adempas® SmPC], therefore riociguat is not expected to affect the PK of macitentan.

**Edema/fluid retention - Pharmacodynamic interaction assessement**

Edema/fluid retention are known adverse drug reactions (ADRs) with ERAs, with a frequency reported as 'very common' for both macitentan [Opsumit® SmPC] and ambrisentan [Volibris® SmPC].

In the pivotal trial of macitentan leading to its registration for the treatment of PAH, an AE of peripheral edema was reported in 18.2% of subjects (44/242) treated with macitentan 10 mg compared with 18.1% (45/249) on placebo (median treatment duration of 118 weeks [macitentan 10 mg] and 101 weeks [placebo]) [Pulido 2013]. In subjects receiving background therapy at baseline (mainly PDE-5 inhibitors), an AE of peripheral edema was reported in 19.5% of subjects treated with macitentan 10 mg vs 23.5% in subjects on placebo.

With the ERA ambrisentan, the incidence of edema was 18.5% (24/130) in PAH patients receiving ambrisentan 5 mg and 28.4 % (19/67) in PAH patients receiving ambrisentan 10 mg for 12 weeks [Volibris® Monograph 2018]. An increase in the incidence of peripheral edema (45%) was observed when ambrisentan was administered in combination with the PDE-5 inhibitor tadalafil compared to when ambrisentan and tadalafil were given as monotherapies (38% and 28%, respectively), to PAH patients [Volibris® SmPC].

Fluid retention is also listed as a common ADR for the PDE-5 inhibitor sildenafil [Revatio® SmPC], and facial edema is a common ADR for tadalafil [Adcirca® SmPC]. Peripheral edema is also a common ADR for the sGC stimulator riociguat, which is approved for the treatment of inoperable CTEPH and persistent or recurrent CTEPH after surgical treatment [Adcirca® SmPC].

In the MERIT-1 study, most subjects were receiving a PH advanced therapy at baseline (macitentan: 60% and placebo: 62.5%) [Module 5.3.5.1 D-17.097 table 15-30]. PDE-5 inhibitors were taken by

57.5% and 60% of subjects on macitentan and placebo, respectively, with sildenafil the most frequently used PDE-5 inhibitor in both treatment groups [Module 5.3.5.1 D-17.097 table 15-30].

The proportion of subjects with an AE associated with edema and fluid retention was 25% in the macitentan group and 10% in the placebo group [Table 44]. Similarly, in the subgroup of subjects with PH advanced therapy at baseline, a higher proportion of subjects had an edema/fluid retention AE of special interest (AESI) in the macitentan group (29.2%) than in the placebo group (12%) [Table 44]. In the subgroup of subjects without PH therapy at baseline, the proportion of subjects with an edema/fluid retention AESI was also higher in the macitentan group (18.8%) than in the placebo group (6.7%) [Table 44].

**Table 44 AEs of special interest: edema and fluid retention in MERIT-1, Safety analysis set**

| Preferred Term | Macitentan 10 mg N=40 n (%) | Placebo N=40 n (%) |
|---|---|---|
| **Overall** | | |
| Subjects with at least one AE of edema and fluid retention | 10 (25.0) | 4 (10.0) |
| Oedema peripheral | 9 (22.5) | 4 (10.0) |
| Hydrothorax | 1 (2.5) | 0 |
| Oedema | 1 (2.5) | 0 |
| Ascites | 0 | 1 (2.5) |
| **Subjects with PH advanced therapy at baseline** | **N=24** | **N=25** |
| Subjects with at least one AE of edema and fluid retention | 7 (29.2) | 3 (12.0) |
| **Subjects without PH advanced therapy at baseline** | **N=16** | **N=15** |
| Subjects with at least one AE of edema and fluid retention | 3 (18.8) | 1 (6.7) |

Preferred Terms are based on MedDRA version 19.0.
Source: Module 5.3.5.1 D-17.097 table 15-90, Module 5.3.5.3 ISS Appendix 1 table 38.
AE = adverse event; PH = pulmonary hypertension.

In the macitentan group, the proportion of subjects reporting an AESI of edema/fluid retention was approximately 33% higher in subjects with PH advanced therapy at baseline compared to those without PH advanced therapy at baseline (29.2% versus 18.8%), while in the placebo group, it was approximately 45% higher in subjects with PH advanced therapy at baseline compared to those without PH advanced therapy at baseline (12% versus 6.7%) [Table 44].

It is important to note that in MERIT-1, more subjects in the macitentan group (22.5%) presented edema as a concomitant disease at baseline than in the placebo group (15%) [Module 5.3.5.1 D-17.097 table 15-23]. Also, more subjects in the macitentan group (12.5%) were receiving a dihydropyridine derivative as concomitant therapy compared to the placebo group (5%). Fewer subjects in the macitentan group (10%) were receiving an angiotensin converting enzyme (ACE) inhibitor versus 22.5% in the placebo group, while the same number of subjects were receiving an angiotensin II receptor antagonist (ARB, 7.5%) in both groups [Module 5.3.5.1 D-17.097 table 15-25].

Calcium channel blockers, and specifically dihydropyridine derivatives, are known to trigger the occurrence of peripheral edema [Pedrinelli 2001]. Therefore, the imbalance in terms of occurrence of AESIs related to edema/fluid retention, beside the fact that subjects had more edema at baseline in the macitentan group, may also have been favored by the more frequent concomitant use of ERAs and calcium channel blockers (dihydropyridine) in this group of subjects than in the placebo group.

The addition of a renin-angiotensin system blocker, i.e., ACE or ARB, reduces the risk of edema due to calcium channel blockers. [Makani 2011]. Therefore, the fact that overall, subjects on placebo, and more specifically in the subgroup of subjects with PH advanced therapy at baseline (mostly PDE-5 inhibitors) had fewer events of edema /fluid retention than subjects on macitentan may also be explained by the more frequent concomitant use of a renin-angiotensin system blocker.

In summary,

• PK DDIs between macitentan and the PH-advanced therapies are unlikely.

• Although subjects who received macitentan reported more AEs associated with edema/fluid retention compared to subjects on placebo in the overall population, in the subgroup of subjects with PH advanced therapy at baseline compared to subjects without PH advanced therapy at baseline, there was no disproportionate increase in the number of events on macitentan compared to placebo, arguing against a pharmacodynamic interaction.

• The higher proportion of subjects reporting an AESI of edema/fluid retention in the macitentan group may be explained by the facts that 1) a higher number of subjects had edema as an ongoing medical condition at baseline; 2) a higher number of subjects were receiving dihydropyridine derivatives at baseline; and 3) a low number of subjects were receiving a renin angiotensin system blockade agent.

**Applicant's Conclusion:** based on the above, the increase in edema/fluid retention AESIs is not due to PK or pharmacodynamic DDIs between macitentan and other drugs used in patients with CTEPH.

***Rapporteur Assessment***

There was an increase in the number of events of edema/fluid retention in the overall MERIT-1 population that was consistent in the subgroups by concomitant PH advanced therapies at baseline (yes/no). The low number of events (10 vs. 4 in the overall population; 7 vs. 3 in the subgroup with concomitant PH therapies; 3 vs. 1 in the subgroup without concomitant PH therapies), as well as the presence of concomitant confounding factors (more subjects in the macitentan group presented edema as a concomitant disease at baseline and more subjects in the macitentan group were receiving a dihydropyridine derivative compared to the placebo group) prevent from any meaningful conclusion.

**Conclusion**

**Issue solved (no further information pursued).**

***Question 22***

***The Applicant is requested to clarify that, although considered as treatment-related, hematuria has not been proposed to be included as an ADR in section 4.8 of the SmPC.***

***Summary of MAH answer***
The SAE of hematuria in MERIT-2 that was considered by the investigator to be treatment-related [Module 5.3.5.3 ISS appendix 1 table 24] was reported in a female subject with a medical history of painless gross hematuria for 3 years. The subject was receiving 2 additional pulmonary vasodilators (tadalafil, beraprost), and was anticoagulated with warfarin. The subject experienced hematuria followed by urodynia and dysuria 3 weeks after starting OL macitentan in MERIT-2 and following her participation for approximately 6.5 months in the placebo arm of the DB MERIT-1 study. The final diagnosis of urocystitis was made after a bladder biopsy revealing reactive lesions and cystoscopy findings describing hyperplasia of posterior bladder trabeculae without iverticulum or neoplasia. Macitentan was discontinued 12 days after onset of the event due to an AE of decreased hemoglobin, and therapy including iron supplements was initiated. Two weeks later, hematuria resolved. A subject narrative is already provided [Module 5.3.5.3 ISS appendix 2 section 2.2.6].

An analysis of similar events in the Argus safety database in patients receiving macitentan in clinical trials up to 17 October 2018 identified 9 additional cases of hematuria. None of the events were assessed as related to study medication, and all had a documented use of anticoagulants or antithrombotic drugs. For 8 cases, confounding factors such as urinary tract infections or mechanical trauma were documented and the 9th case was attributed to concomitant use of acetyl-salicylic acid and enoxaparin.

During the 5 years since the IBD of Opsumit (macitentan) for the treatment of PAH (18 October 2013), based on the first approval in the US, an estimated 52,284 patients have been exposed to commercial macitentan worldwide. In the Argus safety database, cumulatively as of 17 October 2018, 33 cases of hematuria and 1 case of hemorrhagic cystitis (27 solicited cases, 7 spontaneous reports) were identified. Of these cases, none were reported as related to macitentan. The median time to onset, where provided, was 170 days (between 1 week and 3.5 years). Confounding factors were documented in all cases: concomitant use of anticoagulants or platelet aggregation inhibitors in 30

cases; a local cause for hematuria in 22 cases (urinary infection: 10 cases, local trauma [e.g., urolithiasis, catheters: 7 cases], and cancer: 5 cases).

Considering the circumstances in the case reported as related (medical history of gross hematuria for 3 years, and concomitant use of anti-coagulant [warfarin] and prostanoids [such as beraprost] that may predispose to development of bleeding events), as well as the analyses conducted in the Argus safety database that did not identify further plausibly related cases, a causal association between hematuria and macitentan appears unlikely. Also, the safety profile of macitentan is well characterized based on data from placebo-controlled studies and post-marketing sources. There had been no evidence of hematuria or other bleeding events associated with the use of macitentan.

***Rapporteur Assessment***

It is agreed that the single case of hematuria reported as related to macitentan in the MERIT-1 study provides insufficient evidence for establishing a causal association with macitentan, also taking into account that the patient had prior history of hematuria and that there was no causal association between macitentan and haematuria in other placebo-controlled studies and post-marketing sources. Therefore, haematuria is not proposed to be included as an ADR in section 4.8 of the SmPC.

***Conclusion***

***Issue solved.***

## RMP

***Question 23***

Taking into account the GVP V Rev2 the MAH is asked to further discuss and review whether changes to the list of safety concerns for macitentan are needed.

***Summary of MAH answer***

No changes to the list of safety concerns for macitentan are needed. In particular, MERIT data do not demonstrate any additional important risks compared to those described in the Risk Management Plan (RMP) for PAH.

All safety concerns were reviewed for consistency with the actual definitions as per Good Pharmcovigilance Practice (GVP) V Rev2 (in effect as of 31 March 2017), i.e.,

• Important risks are undesirable clinical outcomes likely to impact the risk-benefit balance of the product and would usually warrant further evaluation as part of the PV plan and/or risk management activities. For identified risks, there is sufficient scientific evidence that they are caused by the medicinal product. For potential risks, there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but there is currently insufficient evidence to conclude that this association is causal.

• Important missing information refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilization or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far.

The summary of important safety concerns is provided in the table below:

| | |
|---|---|
| Important identified risks | Anaemia, decrease in haemoglobin concentration<br>Hepatotoxicity<br>Teratogenicity<br>Symptomatic hypotension |
| Important potential risks | Thrombocytopaenia<br>Leukopaenia<br>Menstrual disorders (primarily bleeding)<br>Ovarian cysts<br>Pulmonary oedema associated with PVOD<br>Testicular disorders and male infertility<br>Off-label use (including in paediatric patients) |
| Important missing information | Paediatric patients<br>Elderly patients aged > 75 years<br>Patients with moderate to severe hepatic impairment<br>Patients with severe renal impairment and/or undergoing dialysis |

PVOD = pulmonary veno-occlusive disease.

Each of the important risks (identified as well as potential), and all topics of "missing information" are closely monitored, with detailed periodic review and assessment of new and cumulative events in Periodic Safety Update Reports (PSURs). Additional measures for specific safety concerns are summarized below.

Important identified risks:

The SmPC for macitentan contains warnings and/or recommendations for evaluations prior to the start of macitentan and during therapy for anemia, hepatotoxicity, and teratogenicity (pregnancy prevention and early detection); these 3 topics are also addressed in detail in the educational materials for macitentan.

Symptomatic hypotension has been re-classified from a potential to an identified risk following the PRAC recommendation dated 5 May 2017(PRAC PSUR Assessment Report of the 6th Opsumit Periodic Benefit-Risk Evaluation Report (PBRER) covering the period 18 April 2016 to 17 October 2016), on the basis of the cumulative data provided and taking into account that hypotension was already listed in section 4.8 of the SmPC.

Important potential risks:

Thrombocytopenia and leukocytopenia are listed as ADRs; no specific monitoring recommendations are provided. Menstrual disorders and ovarian cysts are not mentioned in the SmPC but are subject to targeted questionnaires in PV surveillance. The most recent PRAC recommendations dated 17 May 2018 (PRAC PSUR Assessment Report of the 7th Opsumit PBRER covering the period 18 October 2016 to 17 October 2017) include a comment that the characterization of these 4 important potential risks remains unchanged. For menstrual disorders and ovarian cysts, the PRAC Rapporteur assessment specifies that they should be maintained as important potential risks for macitentan.

The SmPC for macitentan contains warnings regarding PVOD and male fertility.

Important missing information:

Missing information refers to populations under-represented in, or excluded from, the pivotal clinical trial, i.e., pediatric patients, elderly patients above 75 years, or patients with renal or with hepatic impairment. Periodic and cumulative reviews have been provided in PSURs regarding these patient populations. The PRAC Rapporteur consistently commented that no new safety concern emerged based on the data presented. The clinical trial program currently ongoing in pediatric patients with PAH will provide controlled information on the characterization of the safety profile of macitentan in this population.

Note:

The applicant is taking the opportunity to mention in section Part II SVII.3.1 of the RMP the additional risk minimisation activities that are in place since the initial marketing authorization in 20 December 2013 to prevent the important identified risks (anaemia, teratogenicity and hepatotoxicity), as requested in the EMA Guidance on format of the RMP (EMA/PRAC/613102/2015 Rev.2).

The following statement is identified in tracked changes: *The following additional risk minimisation activities are in place: educational tools that include prescribing checklist, Heath Care Professional (HCP) brochure and patient card; and the controlled distribution system (Part V.2).*

The applicant is also taking the opportunity to align the exposure in section SV.1.2 Exposure with the PBRER/PSUR (data cut-off 17 October 2017) used in the RMP.

***Rapporteur Assessment***

The MAH has discussed whether changes to the list of safety concerns for macitentan are needed as requested. It is acknowledged that safety data from studies in CTEPH do not show any additional important risk compared to those described in the RMP for PAH.

Taking into account the GVP V Rev2, the MAH has not proposed any changes to the list of safety concerns approved for macitentan. However, the assessors consider that the important risks Thrombocytopenia and Leukocytopenia could be removed from the list of safety concerns in line with the GVP V Rev2. Safety information on both risks is included in section 4.8 of the PI as ADRs with frequency common and no specific monitoring is required. No additional pharmacovigilance activities are ongoing or planned to address these risks. Moreover, safety postmarketing available information to date (safety data up to 17 October 2018 provided in last PSUR currently under assessment) does not show any new relevant issue on both risks. Therefore, we are of the opinion that both risks could be removed from the list of safety concerns of RMP for macitentan. The MAH is reminded that new safety information on these potential risks, that would no longer be categorised as important in the RMP, is expected to be included in the PSURs as per GVP module VII. No further changes to the list of safety concerns are considered necessary.

Lastly, the changes noted by the applicant in Part II SVII.3.1 and section SV.1.2 of RMP version 9.3 are acceptable.

***Conclusion***
**Issue not solved.**

***Question 24***

***The MAH should include the FUQ for the safety concern "Teratogenicity" as routine pharmacovigilance activity in all the pertinent sections of RMP as appropriate.***

***Summary of MAH answer***

The applicant confirms that each pregnancy is followed up to final outcome using the Actelion Drug Safety Pregnancy Form as a routine pharmacovigilance activity. Maternal and baby information are both collected in this form to closely monitor compliance with the labelling pregnancy contraindication and further characterize the risk of teratogenicity, if reported. The Actelion Drug Safety Pregnancy Form to collect Pregnancy information is included in the annex 4 of the macitentan RMP.

***Rapporteur Assessment***

The MAH has not updated all the pertinent sections of RMP to include FUQ for the safety concern "Teratogenicity". In this regard, the table V3 "summary of risk minimisation measures" should include this FUQ. In addition, it is also noted in this table that for the safety concerns "Menstrual disorder (primary bleeding) and "Ovarian cysts" in the column pharmacovigilance activities the text included should be amended according to the "Guidance on the format of the RMP in the EU in integrated format" Rev.2.0.1 for consistency.

***Conclusion***
**Issue not solved.**

***Question 25***

***The MAH should provide the specific follow up forms in full in annex 4- Specific adverse drug reaction follow-up forms.***

***Summary of MAH answer***

The applicant is providing in Annex 4 of the macitentan RMP the following specific adverse drug reaction follow-up forms:

• Actelion Drug Safety Pregnancy Form to collect Pregnancy information (including maternal and baby information)

• Target follow-up questionnaire (TFUQ) to collect information on menstrual disorders

• TFUQ to collect information on ovarian cysts.

***Rapporteur Assessment***

The MAH has included the specific follow up forms in full in annex 4- Specific adverse drug reaction follow-up forms as requested.

***Conclusion***
**Issue solved.**

***Question 26***

***The Annex 6 should be updated taking into account only the risks that need additional risk minimisation measures and the key messages of educational material.***

***Summary of MAH answer***

As stated in the response to Question 23, no changes to the list of safety concerns for macitentan are proposed in this application. In particular, MERIT data do not demonstrate any additional important risks compared to those described in the RMP for PAH and therefore, no additional measures compared to those in place for PAH are proposed for CTEPH.

An updated Annex 6 of the macitentan RMP is being submitted and is aligned with the Annex II.D of Opsumit. In Annex 6, anemia, teratogenicity, and hepatotoxicity are included, the identified risks for which additional risk minimization measures have been put in place since the initial approval of Opsumit on 20 December 2013. The key messages of the educational materials have also been aligned with Annex II.D.

***Rapporteur Assessment***

The MAH has updated the annex 6 as requested including the approved key messages of the additional risk minimisation measures for macitentan in line with the Annex II D.

***Conclusion***

**Issue solved.**

***Question 27***

***The elements of the public summary of the RMP will require revision following the conclusion of the procedure.***

***Summary of MAH answer***

The applicant confirms that the public summary of the RMP will be updated according to the conclusion of the procedure.

***Rapporteur Assessment***

The MAH has confirmed that the public summary public summary of the RMP will be updated according to the conclusion of the procedure.

***Conclusion***

**Issue solved** (at this stage).

# Annex 3: Rapporteur proposed Second Request for Supplementary Information (second RSI)

## *Major objections*

## Clinical efficacy aspects

1. The benefit shown in the MERIT-1 study is currently insufficient to grant an indication in patients with inoperable CTEPH:

    a. The effect of macitentan on 6MWD in the primary analyses and the sensitivity analyses based on different missing data imputation techniques shows that the effect estimates statistics are not robust and differences are difficult to interpret (see also assessment of Q3, Q4): a1) The main analysis of change in 6MWD using ANCOVA is biased by high variability (SD in mean change in 6MWD from baseline is more than two-fold higher than the mean value) probably due to the presence of extreme values. Therefore, an analysis focused on median would have been more appropriate. Please, discuss. In order to rule out that the effect has been driven by extreme values, please also provide a graphical representation illustrating the 6MWD data distribution by treatment group (MS comment); a2) In addition, the applicant is invited to comment about the difference in standard deviations in change in 6MWD between the FAS and PP populations, despite no patient was excluded for the PP population in the macitentan group.

    b. The point estimate for the effect in 6MWD favoured placebo in most countries, while the trend towards a benefit was only achieved in Russia, Ukraine and Thailand (see assessment of Q11). Particularly in Ukraine, the difference in favour of macitentan was an impressive 122.5 m improvement versus placebo. In this respect: b1) Please, provide the interaction p-value by country for the effect on 6MWD and analyse the results of 6MWD including country as covariate; b2) The applicant is requested to provide a narrative for patient treated with macitentan in a centre in Ukraine, who improved 160 metres in 6MWD from baseline to week 24. Please, also discuss about the chance for a patient with inoperable CTEPH to improve 160 metres from baseline to week 24; b3) As sensitivity analysis, the applicant is requested to show MERIT-1 study results: by excluding that patient; and by excluding that centre in Ukraine.

    c. The high number of important protocol deviations in more than 50% of patients and the fact that these deviations were not at random (much higher in the placebo group) add uncertainties on whether study conduct and oversight was adequate and goes against the robustness of the results. The applicant is invited to discuss on the potential causes for these not at random protocol deviations.

    d. A request for GCP inspection has been adopted for the following sites of clinical trial AC-055E201, MERIT-1, regarding the heterogeneity of the data presented and the large number of protocol violations reported:

        In 3 sites

The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the RSI.

### *Other concerns*

### Clinical aspects

2. The macitentan effect on other clinical endpoints (i.e.: dyspnoea, disease progression, change in WHO functional class) was neither statistically nor clinically relevant. The additional responders' analyses submitted are also supportive of a lack of clinically meaningful effect (see also assessment of Q13 and Q15). The applicant is invited to comment.

### Non clinical aspects

3. The Applicant should clarify how prevalence of CTEPH in Great Britain was calculated or use prevalence data from a reliable source as Orphanet. Additionally PAH and CTEPH, prevalence data should be updated with the most recent published data of European population (1st January of 2018) and $PEC_{surfacewater}$ value should be recalculated with the the new $F_{pen}$ values.

### RMP

4. The table V3 "summary of risk minimisation measures" should be amended :

   - to include the FUQ for the safety concern "Teratogenicity" .

   - to include the required pertinent text for the safety concerns "Menstrual disorder ( primary bleeding) and "Ovarian cysts" in the column pharmacovigilance activities as per the "Guidance on the format of the RMP in the EU in integrated format"( Rev.2.0.1 31 October 2018).

5. Thrombocytopenia and Leukocytopenia should be removed from the list of safety concerns of the RMP for macitentan. All pertinent sections of RMP should be updated accordingly. The MAH is reminded that new safety information on these potential risks no longer categorized as important in the RMP is expected to be included in the PSURs as per GVP module VII.

6. In the event that the extension of indication to include the treatment of patients with CTEPH is not approvable, the MAH should commit to submit a variation procedure to implement the recommended changes of the RMP concerning the GVP module V- Rev 2 included in this AR.

# Annex 4: Product Information annotated with Rapporteur comments

The MO precludes granting the new indication. As a result, proposed changes in sections 4.1, 4.2 and 5.1 are not acceptable and no PI is attached.