24 October 2013
EMA/457699/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opsumit

International non-proprietary name: MACITENTAN

Procedure No. EMEA/H/C/002697/0000

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Product information

Name of the medicinal product:	Opsumit
Applicant:	Actelion Registration Ltd. Chiswick Tower, 13th Floor 389 Chiswick High Road London W4 4AL United Kingdom
Active substance:	MACITENTAN
International Nonproprietary Name/Common Name:	MACITENTAN
Pharmaco-therapeutic group (ATC Code):	other anti-hypertensives, ATC code: C02KX04
Therapeutic indication(s):	Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	10 mg
Route(s) of administration:	Oral use
Packaging:	Bottle (HDPE) and blister (PVC/PE/PVdC/Alu)

Package size(s):	15 tablets and 30 tablets

Table of contents

List of abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
ALT	alanine aminotransferase
APAH	Associated PAH
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
BSEP	Bile salts export pump
CEC	Clinical Event Committee
CHMP	Committee for Medicinal Products for Human Use (Europe)
CL	Confidence limit
CI	cardiac index
CI	confidence interval
Cmax	Maximum concentration
CTD	Connective Tissue Disorder
CV	coefficient of variation
DBIL	Direct bilirubin
DBP	Diastolic blood pressure
DDI	drug-drug interaction
dPAP	Diastolic pulmonary artery pressure
DRA	Drug Regulatory Affairs (department)
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EM(E)A	European Medicines (Evaluation) Agency
EOS	End of study
EOT	End of double-blind treatment
ERA	Endothelin Receptor Antagonist
ET	Endothelin
FC	Functional Class
FPAH	Familial Pulmonary Arterial Hypertension
GC	Gas Chromatography
GQM	Global Quality Management (department)
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
IC50	Concentration that causes 50% inhibition
Ki	Inhibition constant
i.v.	intravenous
ICF	Informed consent form
ICH	International Conference on Harmonisation
IPAH	Idiopathic Pulmonary Arterial Hypertension
LSM	least squares mean
MAH	Marketing Application Holder
MDR	Multidrug resistant protein
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure
mRAP	mean right atrial pressure
NIH	National Institute of Health
NNT	Number needed to treat

NT-pro-BNP	N-terminal pro-B type natriuretic peptide
NTCP	Na^+-taurocholate cotransporting polypeptide
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
OD	Once daily
OL	Open Label
PAH	Pulmonary Arterial Hypertension
PBPK	Physiologically Based Pharmacokinetic
PD	Pharmacodynamic
PDE5I	phosphodiesterase type 5 inhibitor
P-gp	P glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PPH	Primary Pulmonary Hypertension
PRAC	Pharmacovigilance Risk Assessment Committee
PVR	Pulmonary Vascular Resistance
QoL	Quality of Life
QSAR	Quantitative Structure-Activity Relationship
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCPS	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	standard deviation
SDAC	Statistical Data Analysis Center
SiSBP	Sitting systolic blood pressure
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA queries
SOC	system organ class
SOP	Standard operating procedure
sPAP	Systolic pulmonary artery pressure
SUSAR	Suspected unexpected serious adverse reaction
SvO2	Mixed venous oxygen saturation
T1/2	half life
Tmax	Time to reach Cmax
TPR	Total Pulmonary Resistance
TTC	Threshold of Toxicological Concern
ULN	Upper Limit of Normal
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actelion Registration Ltd. submitted on 25 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Opsumit, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 January 2012.

The medicinal product "macitentan" was designated by the European Commission as an orphan medicinal product for the treatment of pulmonary arterial hypertension under number EU/3/11/2009 on 29 September 2011.

The applicant initially applied for the following indication:

Opsumit is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in patients of WHO Functional Class II to IV to reduce morbidity and mortality. Opsumit is effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease (see section 5.1).

The finally approved indication is:

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

*Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1)."***The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Opsumit (macitentan) was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Following the CHMP positive opinion on this marketing authorisationn, the committee for Orphan Medicinal products (COMP) reviewed the designation of of Opsumit as an Oprphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency website: ema.europa.eu/Find medicine/Rare disease designations.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/0087/2012] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products approved for the same condition.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance macitentan contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen-Cilag S.p.A.
Via C. Janssen
IT-04010 Borgo San Michele
Latina
Italy

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Pieter de Graeff

The application was received by the EMA on 25 October 2012.

- The procedure started on 21 November 2012.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013 .
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 March 2013.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 March 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 July 2013.
- The summary report of the inspection carried out at the following sites of SERAPHIN study site 8401 – Mexico and site 5101- China and MAH facilities Actelion Switzerland between 19 February 2013 and 12 April 2013 was issued on 15 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 July 2013.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2013.
- PRAC RMP Advice and assessment overview, adopted on 5 September 2013.
- During the CHMP meeting on 19 September 2013 outstanding issues were addressed by the applicant during an oral explanation before the CHMP and the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 September 2013.
- PRAC RMP Advice and assessment overview, adopted on 10 October 2013.
- During the meeting on 24 October 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Opsumit.
- The CHMP adopted a report on similarity of macitentan with ambrisentan, bosentan, sildenafil and iloprost on 24 October 2013.

2. Scientific discussion

2.1. Introduction

Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Although the pathogenesis of PAH is not completely understood, it likely involves an imbalance in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants that are probably consequences of pulmonary endothelial cell dysfunction and/or injury.

PAH is defined by right-heart catheterization showing a precapillary pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise, with a pulmonary artery wedge pressure < 15 mmHg). There is a female-to-male preponderance (1.7:1), with patients most commonly presenting in the third and fourth decades, although the age range is from infancy to greater than 60 years.

The annual incidence of idiopathic pulmonary hypertension has been estimated within 1 or 2 cases per million individuals per year. This is well within the criteria defined for the prevalence of orphan diseases.

The median life expectancy from the time of the diagnosis in patients with idiopathic PAH (IPAH), before the availability of disease-specific (targeted) therapy, was 2.8 years through the mid-1980. PAH is a rare, progressive, life-threatening disease with a poor prognosis.

Current clinical classification of PAH comprises apparently heterogeneous conditions, which share comparable clinical and hemodynamic pictures and virtually identical pathologic changes of the lung microcirculation. PAH includes idiopathic (IPAH, formerly termed primary pulmonary hypertension) and familial forms (FPAH), PAH associated with various conditions (APAH), such as scleroderma and other connective tissue diseases (CTD), congenital heart defects with systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus infection, exposure to drugs and toxins and other more rare settings: thyroid disorders, glycogen storage disease, Gaucher´s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (Sickle disease especially), myelo-proliferative disorders, splenectomy, PAH associated with significant venous or capillary involvement and finally, persistent pulmonary hypertension of the newborn.

The functional classification is the measure of the limits imposed on a patient by a disease. It is a critical element of the assessment of patients with PAH. There are two classification systems that, in practice, are used interchangeably when characterizing patients with PAH:

A. New York Heart Association (NYHA) functional classification

- **Class 1:** No symptoms with ordinary physical activity.
- **Class 2:** Symptoms with ordinary activity. Slight limitation of activity.
- **Class 3:** Symptoms with less than ordinary activity. Marked limitation of activity.
- **Class 4:** Symptoms with any activity or even at rest.

B. World Health Organization (WHO) functional assessment classification

- **Class I:** Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- **Class II:** Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class III:** Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class IV:** Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Variables associated with poor survival includes, among others, a NYHA/WHO Functional Class (FC) III or IV and the presence of Raynaud's phenomenon. Patients with a NYHA/WHO Class I or II have a median survival of 59 months (approximately 5 years), while patients with a NYHA/WHO Class III have a median survival of 32 months (2.6 years), and patients with a NYHA/WHO Class IV have a median survival of 6 months. For Primary Pulmonary Hypertension (PPH), the US National Institute of Health (NIH) registry showed survival rates for untreated patients of 68%, 48%, and 34% after 1, 3, and 5 years from diagnosis, respectively. Although advances in therapies and patient management have improved these rates, there is still no known cure for PPH or other forms of PAH.

Symptoms of PAH include dyspnoea (most commonly), fatigue, chest pain or discomfort, dizziness, syncope, near syncope, edema, leg edema, and palpitations. When the disease is advanced, the clinical manifestations include cyanosis, dyspnoea on exertion, hemoptysis, atypical chest pain or angina pectoris, syncope, heart failure, arrhythmias and cerebrovascular accidents.

General measures recommended for patients with PAH is to engage in activities appropriate to their physical capabilities in order to prevent deconditioning and worsening of overall function. At present, conventional treatment for patients with PAH includes calcium-channel blockers, anticoagulants, diuretics and oxygen. In addition, two phosphodiesterase-5 inhibitors (sildenafil, tadalafil), two oral endothelin-receptor antagonists (ERA) (bosentan, ambrisentan), an intravenous prostacyclin (epoprostenol), an inhaled prostacylin (iloprost) and a subcutaneous prostacyclin (treprostinil) have also been licensed for the treatment of PAH in various European countries. Of these, sildenafil (Revatio®), tadalafil (Adcirca®), bosentan (Tracleer®), ambrisentan (Volibris®) and iloprost (Ventavis®) have been authorised through the centralised procedure. Sildenafil, tadalafil and ambrisentan are indicated for patients with primary and CTD-associated PAH, while bosentan is indicated for patients with primary PAH, scleroderma-associated PAH, and PAH associated to congenital systemic-to-pulmonary shunts and Eisenmenger's physiology. Iloprost is indicated only for patients with primary PAH. Four of these medicinal products are licensed for patients with NYHA FC II and III disease severity (sildenafil, tadalafil, bosentan and ambrisentan), whereas the remaining ones are licensed for patients with

NYHA class III only. An additional ERA, sitaxentan (Thelin®), was withdrawn from the market in 2010 due to concerns about liver toxicity.

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. In vitro, macitentan selectively inhibits the binding of ET-1 to ET_A and ET_B receptors as well as the effects mediated by these receptors in functional assays.

Macitentan belongs to the class of endothelin receptor antagonists (ERA), but has a molecular structure, physicochemical properties, receptor-binding kinetics, and efficacy in nonclinical models that differentiate it from previously authorized compounds.

The selection of macitentan for development as a dual ERA was further guided by the compound's pharmacokinetic characteristics which are consistent with once-daily (OD) dosing, its favourable drug-drug interaction profile, and its low propensity to inhibit intrahepatic bile salt transport, which is believed by the applicant to translate into a favourable liver safety profile.

2.2. Quality aspects

2.2.1. Introduction

Opsumit is a film-coated tablet containing an active substance not previously authorised in the EU at the time of the submission of this application.

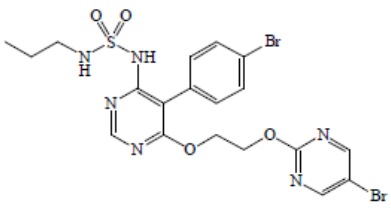
The finished product is presented as film-coated tablets, containing 10 mg of macitentan. Other ingredients are: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate, polysorbate 80, polyvinyl alcohol, titanium dioxide, talc, soya lecithin, xanthan gum (see section 6.1 of the SmPC).

The product is available in blisters and bottles as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance macitentan appears as white to off-white crystalline powder insoluble in water and aqueous solutions in room temperature at pH 1.2, 4, 6.8, 7, 9 and is slightly soluble in methanol and ethanol.

The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide, corresponding to the structural formula below:



The molecular formula is $C_{19}H_{20}Br_2N_6O_4S$ and its relative molecular mass 588.27 g/mol. Its pKa is 6.2 and the partition coefficient LogD is 2.9 (lipophilic). The molecule is achiral thus having no

stereoisomers. Several polymorphic forms have been described including different solvates. All macitentan batches manufactured so far for clinical studies and commercial purposes correspond to the same stable polymorphic form which is a true polymorph with a melting point of 135°C. It is the thermodynamically most stable form at room temperature. Long-term stability studies on several clinical and registration batches showed no polymorphic change of macitentan after up to 36 months of storage at 30 °C / 65% RH. Results of the dynamic vapour sorption of macitentan show that it is not hygroscopic.

Manufacture

Macitentan is manufactured in three chemical steps and a last milling step, which were all described in sufficient detail. A flow diagram for the synthesis of macitentan is provided, including starting materials, intermediates, solvents and reagents for each stage. The rationale for the choice of the starting materials is considered acceptable. The manufacturing process development includes a detailed description of the optimisation steps for the active substance. The two last chemical steps were optimised thereby limiting the formation of impurities and increasing the yield. The applicant has applied the design of experiments approach and applied a multivariate analysis with the identified key parameters of the process step. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterisation. Batch analysis data show that the active substance can be manufactured reproducibly.

Specification

Macitentan specification includes tests and limits for appearance (visual), colour (visual), clarity and colour of solution (Ph. Eur.), identification (IR, HPLC), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), water content (Ph. Eur.), residual solvents (GC), related substances (HPLC), assay (HPLC), particle size distribution (laser light diffraction) and microbial purity (Ph. Eur.).

Potential impurities that could be present in the starting material are either controlled in the starting material itself or in the intermediate. Potential genotoxic impurities were evaluated for genotoxic concern by *in silico* QSAR analyses for those showing genotoxic alerts. The results of these analyses showed no concern. The potential genotoxicity of the starting material has been further investigated and was found negative in a full Ames test. The calculated TTC is 150ppm (10mg daily dose), however the starting material was not detected in the last two campaigns. Since the starting material was found negative in the Ames test, negative results from the *in silico* genotoxicity predictions on its impurities are enough to consider them too as non-genotoxic. Therefore, no routine controls below the TTC value are deemed necessary for these two impurities on the starting material or on the active substance.
Overall, the discussion on the potential genotoxic impurities is considered sufficient. The limits for impurities are in line with European Guidance (NfG on impurities - ICH topic Q3A (R2).
The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three registration batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The stability of macitentan active substance was investigated on three registration batches under accelerated (40 °C / 75% RH) and long-term (30 °C / 65% RH) storage conditions.
Stability data of another three clinical batches were produced by the same manufacturer using the same route of synthesis as the registration batches were also presented as supportive data.

During stability testing the following characteristics are tested: appearance, colour, clarity and colour of a solution, water, assay, related substances, microbial quality (not routinely tested), and particle size distribution (not routinely tested). All analytical methods were the same as those used at release; they were shown to be stability indicating.
After storage for six months at 40 °C / 75% RH and 48 months at 30 °C / 65% RH, no change in the physical and chemical characteristics was observed.

Photostability testing (forced degradation testing according ICH Q1B) was carried out on one batch in line with the relevant Guideline ICH Topic Q1B Photostability Testing of New Active Substances and Medicinal Products. A confirmatory photostability study was performed on one recent batch. The results were consistent with those obtained from the initial studies and show macitentan is stable to light in the solid state but degradation was observed in solution in all solvents tested. The method is considered stability indicating.

Overall, the stability data support the proposed retest period and storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Prior to the initiation of formulation development studies, an excipient compatibility study with the active substance was performed. It was concluded that all excipients investigated could be used for further development. The selected excipients are well-known for use in pharmaceutical products and are commonly used excipients in film-coated tablet formulations.

A capsule formulation in different strengths was initially developed to provide dose flexibility. This formulation was used in early Phase 1 studies as well as in one Phase 2 study. For the formulation and manufacturing process development the physicochemical properties of the active substance were taken into account. A tablet formulation was developed from the capsule and was optimised with regard to the effect of key formulation attributes on stability and tablet characteristics. The dissolution profiles of 10 mg capsule and 10 mg film-coated tablets were compared and were found equivalent. In addition, a clinical pharmacology comparison study between macitentan 10 mg capsules and macitentan 10 mg film-coated tablets was performed in healthy subjects. The study showed that the PK of macitentan and its active metabolite were comparable for the two formulations. Given that the intended use is a chronic, multiple-dose regimen, the minor difference found in C_{max} of macitentan between the two formulations was not considered relevant. The results adequately supported comparability of data obtained with the two formulations and that no dose adaptation was needed when switching from the capsule to the tablet formulation in the development of the product. The film-coated tablets were therefore used in clinical Phases 1, 2 and 3.

The dissolution method has been shown to be discriminatory with regard to the factors that can vary during manufacture and are likely to or have shown to affect the performance and with regard to distinguishing tablets which have been exposed to accelerated or inappropriate storage conditions.

According to ICH Q6A guideline, the specification for solid oral dosage forms normally includes a test to measure the release of active substance from the finished product. According to the decision tree #7(1), a single-point dissolution acceptance criterion with a lower limit was included in the specifications for Opsumit.

Following the selection of the wet granulation method the process has been optimised with regard to the granulation parameters and the tablet characteristics. The manufacturing parameters were further adapted as appropriate for the equipment intended for full-scale manufacture at proposed site for commercial manufacture. The process used is not associated to conditions that could generate a conversion of the desired polymorphic form of the active substance into other polymorphs.

Adventitious agents

The manufacturing processes of neither the active substance nor the finished product involve any materials of human or animal origin apart from lactose, which fulfils the necessary requirements. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

The manufacture of macitentan film-coated tablets involves conventional wet granulation and coating processes. No critical steps were identified. However, suitable in-process controls have been introduced at each manufacturingstep to ensure reproducible quality for the finished product. The manufacturing process is adequately described and as it is considered to be a standard process, validation data do not have to be incorporated in the dossier before registration. A satisfactory process validation protocol has been submitted. The process validation at commercial scale will be performed by the proposed manufacturer prior to marketing the product.

Product specification

The finished product release specifications include appropriate tests for appearance and colour (visual), identification (HPLC and IR), water content (Ph. Eur.), tablet mass (gravimetry), assay (HPLC), content uniformity (Ph. Eur.), degradation products (HPLC), dissolution (Ph. Eur.) and microbiological quality (Ph. Eur.).
Analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are submitted for three registration batches. The batch analysis data are within the set specification limits and show that Opsumit film-coated tablets can be manufactured reproducibly.

Stability of the product

The stability of Opsumit 10 mg film-coated tablets was investigated in three registration batches stored in the both proposed blister and bottle packaging intended for the market under accelerated (40°C ±2°C / 75% ±5% RH) and long term conditions (25°C ±2°C / 60% ±5% RH

and 30°C ±2°C / 75% ±5%RH). All relevant characteristics such as appearance, colour, average mass of 10 tablets, water content, content, dissolution, degradation products and microbial quality were determined. The HPLC methods used are identical to those used for the release and have been shown to be stability indicating.
Up to 18 months data were available and no significant changes of the physical, chemical and pharmaceutical characteristics were observed. A slight increase of the level of the main degradation product is observed after three months at 40 °C/ 75% RH. However under long term conditions no significant changes of the physical, chemical and pharmaceutical characteristics were observed.

In addition, up to 60 months supportive stability data were presented from the clinical batches. These batches were produced by a different manufacturer but have the same composition and the same manufacturing process as the registration batches. The composition of the commercial film-coated tablets is also the same as the ones used in clinical studies. The blister of the clinical batches was different to that of the registration ones.
A comparison was performed between the stability data from the clinical and registration batches for each packaging configuration (bottle, blister) and storage condition. The main quality attributes susceptible to change during stability , i.e., assay, amount of degradation product and dissolution, were evaluated. No significant change in the dissolution rate is observed for either the clinical or the registration batches packed into blisters. Results with regard to the degradation between the clinical and the registration batches are similar.

In-use stability testing has been conducted on one Opsumit registration batch in bottles. Appearance of the tablets, assay, related substances as well as dissolution were evaluated. All methods used are the same as the analytical methods used at release. For all parameters tested, no significant difference is observed.

Photostability has been investigated on one registration batch in accordance with ICH Q1B guideline. During photostability testing the following characteristics were tested: appearance, colour, content and degradation products. All methods were the same as the analytical methods used at release and the results were evaluated against the current specifications. No significant differences could be observed between the samples exposed to intense light and the control samples. No increase in related substances was observed in any of the samples. Therefore, Opsumit film-coated tablets can be considered as photostable and thus in accordance with the ICH Q1B guideline it is not necessary to store the finished product protected from light.

Overall, the stability data support the proposed shelf life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. Development of the finished product had to take into account the particular characteristics of the active substance. The choice of formulation, of excipients and the manufacturing process has been justified. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

The nonclinical safety program for macitentan includes studies on general toxicity, carcinogenicity, reproductive toxicity, juvenile toxicity, mutagenicity, and phototoxicity, as well as safety pharmacology. The testing strategy was primarily based on the ICH M3 guideline and other applicable ICH nonclinical safety guidelines.

2.3.1. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacology assays show that macitentan is able to inhibit the binding of endothelin-1 (ET-1) to its receptors endothelin A (ET_A) and endothelin B (ET_B), to inhibit ET_A or ET_B receptor–mediated functional responses as intracellular accumulation of Ca and IP_1 and ET-1 induced contraction of isolated tissues (rat aorta and trachea). However, the free therapeutic plasma concentrations of macitentan (2.5 nM) is in the range of the concentration that causes 50% inhibition (IC_{50}) and K_b values for the ET_A receptor (IC_{50}=0.5 nM, K_b=0.81 nM), but it is lower than the values for the ET_B receptor (IC_{50}=391 nM, K_b=128 nM). Since macitentan is highly bound to plasma protein, the K_b and IC_{50} for ET_B receptor were calculated based on the unbound fraction of macitentan in the culture medium. The values (IC_{50}=13 nM, K_b=24 nM) are also higher than the free plasma concentrations of macitentan in PAH patients treated with 10 mg of macitentan. Therefore, based on *in vitro* studies macitentan can be regarded as an ERA that is approximately 100-fold more selective for ET_A as compared to ET_B. On the other hand, plasma ET-1 concentration, a marker of ET_B blockade, was increased in animals and humans after treatment with macitentan, indicating that ET_B receptor is inhibited by macitentan *in vivo*.

Macitentan has relatively slow dissociation kinetics, when compared to other products in its class (ambrisentan and bosentan). This results in a prolonged receptor occupancy. The slow dissociation of macitentan from the receptors leads to an inhibition that is insurmountable to (high levels of) ET-1 when macitentan concentrations are >1-10 nM, which is below clinical plasma levels. *In vivo* pharmacodynamics studies were conducted in rats. The pharmacodynamic effects of macitentan have been investigated in normal rats and in rat disease models in which ET-1 plays a pathological role.

Macitentan reduced systemic arterial blood pressure only in rat models of hypertension associated with an increased expression of ET-1 (DOCA-salt and Dahl salt-sensitive rats) but not in healthy (normotensive) rats (with no activation of the ET system). The duration of this response depended on the dose. The data indicate that macitentan exhibits a sustained duration of action when compared to ambrisentan and bosentan. The slow release of macitentan from the receptor and the fact that increases in ET-1 concentration do not result in displacement of macitentan from the receptor, as well as the formation of an active metabolite, ACT-132577 (M6), with a relatively long half-life time might all contribute to this difference. The dose at which maximal effect of macitentan treatment was observed varied somewhat between studies, however at 10 mg/kg maximal or almost maximal effects were seen. At this dose C_{max} and AUC in the rat are within the range of those in humans receiving 10 mg.

Two circulating macitentan metabolites have been identified in humans: ACT-132577 (active metabolite M6) and ACT-373898 (inactive metabolite on endothelin receptors M5). ACT-132577 is approximately 8-fold less potent than macitentan on ET_A and 2-fold less potent on ET_B. Similar to macitentan, the free therapeutic plasma concentrations of ACT-132577 (7.4 nM) is lower than the IC_{50} and Kb values for the ET_B (IC_{50} total=987 nM, Kb total=319 nM, IC_{50} free=94 nM, Kb free=139 nM). Based on the high exposure, and prolonged half-life this metabolite most likely contributes to the in vivo efficacy of macitentan treatment.

The dependence of a hemodynamic effect following macitentan treatment on activation of the ET-system as seen in rat models of hypertension is also seen in humans. Also in humans, the clinical efficacy of macitentan is dependent on local ET system activation as 10 mg macitentan/day decreases blood pressure in patients with essential hypertension but not in healthy subjects.

In dogs, macitentan treatment did result in reduction in systemic blood pressure (see safety pharmacology). It thus appears that dogs are more sensitive than humans, and rats may be a better predictive model for effects of macitentan on blood pressure.

Repeated oral administration of macitentan was not associated with tachyphylaxis and cessation of treatment did not result in a rebound effect. Macitentan was able to further decrease blood pressure when given on top of the other ET receptor antagonists (bosentan or ambrisentan). Conversely, these compounds were not able to cause additional blood pressure reduction when given on top of macitentan.

In animal models of pulmonary hypertension (monocrotaline-induced and the bleomycin-induced rat models) macitentan reduced pulmonary arterial pressure, pulmonary arterial wall thickness, right ventricular hypertrophy and increased survival. The first clear effect on mean (5 minutes) pulmonary artery pressure (mPAP) was generally seen at a dose of 1 mg/kg and the (almost) maximal effect at 10 mg/kg, which is similar to the effective doses found in the systemic

hypertension rat models. A further increase in dose did not result in significant additional effect, only in the duration of the effect. In none of the *in vivo* studies heart rate was affected.

Secondary pharmacodynamic studies

Only one secondary pharmacodynamics study was provided showing that macitentan did not bind to a panel of 63 receptors and enzymes. No unexpected risks have been identified in animal or clinical studies. Therefore further non-clinical studies on additional pharmacological targets are not deemed necessary.

Safety pharmacology programme

Potential safety pharmacology effects were evaluated on central nervous system, respiratory function and the cardiovascular system.

The only observation was a decrease in arterial blood pressure in dogs at all tested doses. This effect was not observed in healthy rats, but more importantly also not in humans.

Combined treatment of macitentan with a PDE5 inhibitor (sildenafil or tadalafil) induced additive effects on maximal blood pressure reduction and synergistic effects on the extent and duration (ABC) of mean arterial pressure reduction in hypertensive rats.

2.3.2. Pharmacokinetics

The pharmacokinetic and metabolic profiles of macitentan have been characterized in rats and dogs.

The analytical method to measure the plasma concentrations of macitentan and its metabolites ACT-132577 (M6, active) and ACT-373898 (M5, inactive), independently or in combination, were validated using LC-MS/MS. Stability of macitentan and ACT-132577 in plasma was demonstrated for at least 1 year and stability of ACT-373898 was demonstrated for up to 2 years.

In vitro data showed that macitentan permeates rapidly through membranes and is not a substrate of human P-gp. Macitentan was absorbed slowly after oral dosing in the rat, whereas peak plasma concentrations were reached 2 h post-dose in dog.

Oral bioavailability was about 80% in the dog and about 30% in the rat, which increased to 89% at higher doses. After IV administration, macitentan showed a low plasma clearance in rat and dog. The volume of distribution was 1-2 L/kg in rats and about 1 L/kg in dogs, which indicates reasonable distribution into tissues. Exposure to macitentan increased dose-proportionally following IV administration in rat and dog and after oral administration in dog.

Following oral administration in rat, exposure increased more than proportionally between 1 and 30 mg/kg. This non-proportional behaviour may be caused by saturation of metabolic clearance. Non-linearity was not observed in humans and therefore this finding seems of limited relevance.

Particle size had a significant effect on macitentan exposure indicating drug dissolution in the gastrointestinal tract as a limiting factor for oral absorption. Macitentan has an active circulating metabolite, ACT-132577, which has comparable pharmacokinetic properties as macitentan. Only systemic plasma clearance was lower than macitentan, resulting in a longer half-life. Following

repeated doses, the exposure to macitentan and the metabolite ACT-132577 increased less than dose-proportionally in mice, rats and dogs. There was no plasma accumulation of macitentan or ACT-132577 observed. In contrast, a decrease in the systemic exposure of macitentan and ACT-132577 was observed in rat and dog. This effect can be explained by auto-induction of macitentan metabolism in rat and dog, while auto-induction in mouse was not exhibited. Auto-induction is not expected in humans.

Binding to plasma proteins is high in all species examined for macitentan (>99%), and for the metabolites ACT-132577 (98.3-99.9%) and ACT-373898 (91.0-98.5%). Partitioning of either macitentan or ACT-132577 into red blood cells was limited in any of the species investigated. Drug-related radioactivity distributed into most tissues within 2 hours after oral administration. Highest tissue concentrations were measured in liver, kidney, plasma, blood and lung. Macitentan-related radioactivity also distributed into the brain, although to a limited extent (tissue-plasma ratio: 0.02-0.06). After 7 days, drug-related radioactivity was still observed in half of the tissues examined, suggesting some accumulation in these organs when using macitentan daily.

Extensive *in vitro* metabolism was observed resulting in one major metabolite ACT-132577 retaining pharmacological activity. No human specific metabolites were observed *in vitro*. In both the pre-clinical species (rat and dog) and humans macitentan is extensively metabolised before excretion. The applicant investigated the biotransformation pattern in plasma, urine, and faeces of rat, dog and humans and in bile of rat and dog. Data from the excreta indicate that the biotransformation pattern could be different between the non-clinical species and humans. However, as macitentan and its two circulating metabolites ACT-132577 and ACT-373898 were present in rat and dog in comparable or higher absolute amounts than in humans, they are adequately covered in the animal toxicity programme.

The predominant route of elimination of drug-related radioactivity was via feces in rats and dogs (67-81%) independent of the route of administration. The recovery of the majority of the dose in feces suggests biliary elimination as the major route of excretion. [^{14}C]Macitentan-derived material was excreted in milk of rats. Concentrations of radioactivity in milk were below the plasma concentrations until 48 hours post-dose. However, 96 hours post-dose the milk-plasma ratio was 2.0.

The interactions of macitentan and its major human metabolite ACT-132577 with a panel of drug transporters (P-gp, OATPB1, OATPB3, OCT1, OCT2, OAT1, OAT3, BSEP, NCTP, MATE-1 and MATE-2) have been studied in order to investigate potential drug-drug interactions. Macitentan (but not ACT-132577) could be an inhibitor of drug transporter BCRP at clinically relevant intestinal concentrations.

Macitentan and its metabolites ACT-080803 (M3) and ACT-132577 (M6) are not inducers of CYP3A4 at clinically relevant concentrations.

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields the pharmacologically active metabolite ACT-132577. This reaction is dependent on the cytochrome P450 system, mainly CYP3A4 (approximately 99%) with minor contributions of CYP2C8, CYP2C9 and CYP2C19. Other metabolic pathways yield products without pharmacological activity. Several members of the CYP2C family, namely CYP2C8, CYP2C9 and CYP2C19, as well as CYP3A4, are involved in the formation of these metabolites.

Potentially drugs that are inhibitors of CYP3A4 could have an effect on the metabolism of macitentan and thus could lead to drug-drug interactions. Multiple clinical studies were performed regarding potential drug-drug interactions with other drugs (warfarin, sildenafil, ketoconazole, rifampicin, and cyclosporin). (see clinical section).

No clinically relevant interactions were observed for macitentan and its active metabolite M6 with drugs that are inhibitors of CYP3A4. However, concomitant treatment with rifampicin, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite. Reduced efficacy of macitentan in the presence of a potent inducer of CYP3A4 such as rifampicin should be considered.

2.3.3. Toxicology

Mice and rats were used for the single dose toxicity studies and mice, rats and dogs for the repeated-dose toxicity studies. Rats and rabbits were used for the reproductive toxicity studies, and rats and mice for the carcinogenicity studies. In mice, rats and rabbits, macitentan was administered orally by gavage whereas dogs received drug-containing capsules. Impurities and metabolites were toxicologically qualified in these studies and in the in vitro and in vivo genotoxicity studies.

Single dose toxicity

Single doses of up to 2000 mg/kg by oral gavage in mouse and rat indicate that macitentan has low potential for acute toxicity. Mice showed transient overt symptoms including ptosis and/or slightly subdued behaviour during the first hour after administration, whereas rats showed no remarkable findings.

Repeat dose toxicity

Repeat-dose toxicity studies with macitentan were performed by oral administration for time intervals up to 13 weeks in mice, 26 weeks in rats, and up to 39 weeks in dogs. The pharmacodynamic target and the major pathways of macitentan metabolism in humans were all represented in these species. Thus the choice of mice, rats, and dogs was appropriate for the toxicity evaluation of macitentan. In addition, a two-week study was performed in rabbits to establish suitable dosages for the pilot embryo-fetal toxicity studies in this species.

Safety margins or exposure margins were calculated based on combined exposure to macitentan and the pharmacologically active metabolite ACT-132577 in males and females. Male rats were less exposed to the drug after treatment with the same doses than females.

Macitentan was well tolerated from chronic treatment up to relatively high dose levels. Drug-related mortality was observed in the 13-week toxicity study in male Wistar rats after 2 weeks of treatment at 1500 mg/kg/day. Prolonged clotting times led to excessive bleeding and mortality.

In the 4-week dog toxicity study at 500 mg/kg/day, one dog died due to drug-related anorexia. The mortality rate increased in the carcinogenicity studies at 400 mg/kg/day in female mice and at 250 mg/kg/day in female rats after approximately 1 year of treatment. A cause of death could not be established.

Overt symptoms were limited to the high doses and included occasional breathing difficulties, piloerection, coldness, unsteady gait and subdued behaviour in mice, hunched posture, prostrate position, laboured respiration, coldness of limbs; haemorrhages in rats, and decreased food consumption, reduced activity; subdued behaviour; and a rise in body temperature in dogs. In rabbits, there was a severe reduction in body weight and food consumption and a concomitant treatment-related morbidity, but the low dose of 25 mg/kg/day was well tolerated.

In the mouse, rat, and dog toxicity studies, the heart, liver, and testes were identified as the main organs affected by treatment with macitentan. Minor or secondary changes were observed in RBC, the haemostatic system, thyroid, kidney, uterus, ovary and nasal cavity.
Arterial intimal thickening characterized by proliferation of the intimal layer was found in dogs treated with macitentan at doses ≥30 mg/kg/day, independently of the treatment duration. The right and, less often, the left coronary arteries were the preferred target. These findings were often associated with breaks of the internal elastic lamina. After subacute (4-week) treatment with doses higher than 50 mg/kg/day, atrial fibrosis with chronic inflammation, epicarditis, and neovascularization were also observed. Thus, the cardiac NOEL was established at 5 mg/kg/day in all three studies, providing an acceptable safety margin (>5.8) to maximal human exposure at 10 mg/day.

Public literature suggests that the observed coronary arteriopathy is a class effect of endothelin receptor antagonists in dogs. I*n vivo* studies described in the pharmacology section show that macitentan decreases arterial blood pressure in dogs in a dose-dependent manner. As result of exaggerated pharmacology on ET_A receptors (inhibition of vasoconstriction), marked hypotension, sustained vasodilatation in the coronary vascular bed and reflex tachycardia may alter flow dynamics and lead to increased shear stress and tension on the coronary wall with subsequent microscopic trauma. Although the effect of macitentan on the heart rate is limited in dogs, provided literature suggests that the dog is a species particularly sensitive to hemodynamic changes and related coronary vascular and myocardial effects. Coronary and myocardial lesions were not observed in rats or mice. Clinically, data regarding MACE and ECG do not raise any concerns regarding the long term cardiovascular safety of macitentan.

The effects on the liver included increased weight and centrilobular hypertrophy. These findings are considered to be an adaptation to the increased metabolic demand and enzyme induction by macitentan. The increased incidence of hepatodiaphragmatic herniation observed only after 104 weeks of treatment in rats was considered to be related to the induced life-long liver hypertrophy.

In mice, focal hepatocellular necrosis and increased plasma levels of the liver enzymes (AST, ALT) were observed in dose-range finding studies of 2- and 13-weeks' duration performed for the mouse carcinogenicity study. These findings were associated with bile duct proliferation and gall bladder hyperplasia, accumulation of pigmented macrophages and granulocytic infiltration. The necrotic foci and the associated inflammatory reaction in the liver were in some cases accompanied by increased polymorphonuclear leukocyte counts in lymph nodes and increased granulopoiesis in the bone marrow.

A dose-range finding study in B6C3F1-mice revealed that CD-1 are more susceptible to hepatocellular necrosis than B6C3F1 mice.

The slightly decreased concentrations of albumin, cholesterol, bilirubin and/or urea and increased concentrations of triglyceride in plasma further point to a slightly decreased liver function.

In vitro cytotoxicity studies in mouse and human liver slices did not measure mitochondrial toxicity and only found cytotoxicity at concentrations far above the *in vivo* concentration at clinical therapeutic dose in humans. Thus, the liver toxicity found in the repeated dose studies can be explained by indirect mechanisms and therefore does not provide specific evidence for mitochondrial toxicity.

Bosentan but not ambrisentan inhibited human hepatic transporters, which have been discussed as a potential mechanism for the increased hepatotoxicity observed for this agent in humans. However, macitentan and metabolite M6 are not expected to interfere with hepatic and bile salt transport.

Drug-related effects on the male reproductive system were identified in rats and dogs. The alterations found included dilation of seminiferous tubules, tubular degeneration and hypospermatogenesis. The NOAELs for dilation of seminiferous tubules in rats were 50 mg/kg/day (8.2 fold the exposure in patients treated with 10 mg/day of macitentan) in the 13-week toxicity study, 250 mg/kg/day (11.6 fold the exposure in patients treated with 10 mg/day of macitentan) in 26-week rat toxicity studies and it was not determined, but it is lower than 10 mg/kg/day (4.2 fold the exposure in patients treated with 10 mg/day of macitentan) in the 104-weeks carcinogenicity study. These findings suggest that the testicular risk increases after chronic treatment. In the 39-week dog toxicity study, the NOEL was established at 5 mg/kg/day (5.8 fold the exposure in patients treated with 10 mg/day of macitentan). Seminology showed an increased percentage of morphologically abnormal sperm at 50 and 250 mg/kg/day, only in the 26-week rat study (NOEL was 10 mg/kg/day, 2.3 fold the exposure in patients). It is difficult to assess the clinical relevance of hypospermatogenesis and tubular degeneration because individual cases have been reported in different rats and dogs studies, including animals from control groups. The chronic treatment also induced an increase in the prostate weight at 250 mg/kg/day (NOEL was 50 mg/kg/day, 8.2 fold the exposure in patients treated with 10 mg/day of macitentan) in rats. Adverse effects induced by macitentan in rat male reproductive organs were reversible.

Haematological alterations as decreased haematocrit, RBC count and haemoglobin and increased WBC and platelet were observed in different mice, rat and dog toxicity studies. The changes were minimal, found at doses that indicate acceptable safety margins for humans (8.2 in rats, 5.8 in male dogs and 17 in female dogs) and reversible.

A prolonged aPTT was observed in male rats treated with 250 mg/kg/day during 13 or 26 weeks. The finding is considered to have limited relevance to humans as it was observed only at high dose levels that provide safety margins higher than 7, in only one species and only in males.

The observed increased thyroid weight, possibly a reflection of follicular cell hypertrophy, seems to be a secondary effect of drug-metabolizing enzyme induction in the liver. A similar effect has also been reported with bosentan, which is also an inducer of P450 enzymes.. A benign follicular cell adenoma was recorded for the thyroid of one male rat and a cystic follicular hyperplasia for one female rat treated with high doses of macitentan. Although both these findings can be seen as a spontaneous background change, an association with the treatment-related follicular cell hypertrophy cannot be excluded. A treatment-related altered thyroid function (mild thyroid

hormone imbalance in male rats) has been reported for bosentan, but not for ambrisentan. Thus far, there is no evidence of bosentan affecting thyroid function (thyroxin, TSH) in humans.

The kidney was also affected by macitentan in Wistar rats. Treatment longer than 13 weeks at ≥50 mg/kg/day induced an increase in male kidney weights Treatment during 26 weeks increased the incidence of hyaline/pigment droplets in males at ≥ 50 mg/kg/day and in females at 250 mg/kg/day. The alterations were reversible and the NOEL for kidney damage was established at 10 mg/kg/day (2.3 fold the exposure in patients treated with 10 mg/day of macitentan).

An increased incidence of endometrial cysts in the uterus, associated with increased uterus weights, was observed in the mouse carcinogenicity study at ≥100 mg/kg/day providing a safety margin of 46, and in the rat carcinogenicity study at all doses tested. However, uterine cysts in senescent rats are considered of limited clinical relevance because the mechanism leading to this finding may be due to specific rat hormonal changes induced by macitentan.

Additionally, angiomatous change in the rat ovaries was found at the highest dose (250/50 mg/kg/day) tested. The NOAEL for the ovary effects was established at 50/25 mg/kg/day, 13.4 fold the exposure level in humans treated with 10 mg of macitentan.

Finally, proliferation of nasal mucosa and increased incidence of inflammatory infiltration were seen in nasal cavities in mouse carcinogenicity study at all dose levels. Hyaline inclusions and increased secretion were found at doses ≥ 30 mg/kg/day. Similar effects on the nasal cavity have also been observed in animals treated other ERAs. However, nonclinical data macitentan do not indicate a higher risk with macitentan than with ambrisentan, bosentan or sitaxentan, based on the number of affected species, the time of onset and severity of nasal cavity findings.

Genotoxicity

The genotoxic potential of macitentan was evaluated using a conventional battery of tests: genetic mutation in bacteria and in L5178Y mouse lymphoma cells, chromosomal aberration in human lymphocytes and rat micronucleus in vivo. All in vitro and in vivo tests were performed according to the ICH requirements (CHMP/ICH/126642/08. Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human use (ICH S 2 (R1)) and resulted negative. Thus, it can be concluded that macitentan is not genotoxic.

The metabolite of macitentan ACT-373898 (M5) and the impurity ACT-080803 (degradation product in the active substance) are not mutagenic.

Carcinogenicity

No oncogenic potential was evident in mice or rats after 104 weeks of treatment with macitentan at doses that provide a safety margin for carcinogenicity ≥ 20.

The combination of reproductive and developmental toxicity studies allowed evaluating all states advised in the ICH S5 guideline.

Reproduction Toxicity

The NOEL for male and female fertility and early embryonic development in rats was 250 mg/kg/day. However, the observed effects of macitentan on testes (tubular dilatation, tubular atrophy and hypospermatogenesis) during long-term treatment could affect the reproduction. Testes were also target organs of macitentan in the offspring (F1) of females treated during pregnancy and lactation and in juvenile treated animals. In both studies, the fertility was also affected. Additionally, testicular toxicity has not been adequately assessed in clinical trials. Thus, effects of macitentan on male human fertility cannot be excluded.

Macitentan showed clear dose-dependent teratogenic effects in rats and rabbits. In both species there were cardiovascular and mandibular arch fusion abnormalities. The observed effects are class effects of ET receptor antagonists. A NOEL for embryo-fetal development was not established. In line with other ERAs, a pregnancy contraindication is included in the SmPC.

Pharmacokinetic studies in rats have shown that macitentan is excreted into milk. Therefore, macitentan, like other ERAs, is also contraindicated during breast-feeding.

Other toxicity studies

The juvenile toxicity study did not show new target organ toxicity as compared to adult animals but juvenile animals are more sensitive to macitentan than adults. Effects on development and on reproductive variables were found at doses that suppose an exposure level 6.7 and 3.8 fold, respectively, the levels reached in humans treated with 10 mg/day of macitentan. Risk for human development and reproduction cannot be discarded.

All impurities which were present in former batches and the proposed specification of future batches of macitentan are regarded as appropriately qualified.

In an in vitro system using Balb/c 3T3 fibroblast cell cultures, macitentan exhibited weak phototoxicity at high concentrations. An in vivo study in hairless rats showed no phototoxic effects up to the high dose level of 60 mg/kg/day corresponding 24-fold the human exposure at 10 mg per day. It can be concluded that there is no relevant risk of phototoxicity for patients treated with macitentan at 10 mg per day.

2.3.4. Ecotoxicity / environmental risk assessment

The MAH submitted information related to the environmental risk assessment. After review of the data, the CHMP considered the need to perform Log Know determination using a different method.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of macitentan to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

The applicant has agreed with the recommendation to perform a log Kow determination for macitentan, according to the slow stirring method (OECD 123).

2.3.5. Discussion on non-clinical aspects

Macitentan has been developed as an oral therapy for the long-term treatment of pulmonary arterial hypertension (PAH). Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death. Although the pathogenesis of PAH is not completely understood, it likely involves an imbalance in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants that are probably consequences of pulmonary endothelial cell dysfunction and/or injury.

Macitentan is able to block the binding of ET-1 to ET_A and ET_B receptor. Although the pathophysiology of PAH is not fully understood, ET-1 and its receptors ET_A and ET_B are up-regulated in PAH, are considered mediators of the pathological changes leading to the disease and are targets for currently available PAH-specific therapies. Therefore, the development of Opsumit in the treatment of PAH is justified from a mechanistic perspective.

The pharmacological studies provided by the applicant support that macitentan is an inhibitor of ET_A and ET_B receptors and it inhibits the effects mediated by these receptors, as intracellular accumulation of Ca and IP_1 and induced contraction of isolated tissues (rat aorta and trachea). However, the free therapeutic plasma concentrations of macitentan (2.5 nM) and ACT-132577 (M6) (7.4 nM) are lower than the IC_{50} and K_b values for the ET_B receptor. Thus, based on *in vitro* data macitentan can be regarded as an ERA that is approximately 100-fold more selective for ET_A as compared to ET_B. On the other hand, plasma ET-1 concentration, a marker of ET_B blockade, was increased in animals and humans after treatment with macitentan, indicating that ET_B receptor is inhibited by macitentan *in vivo*.

Efficacy of macitentan was demonstrated in animal models of systemic hypertension, pulmonary hypertension and pulmonary fibrosis. Comparative efficacy studies have shown that macitentan could provide a therapeutic advantage over the currently available therapies bosentan and ambrisentan.

The metabolite ACT-132577 is also active. It is approximately 8-fold less potent than macitentan on ET_A and 2-fold less potent on ET_B, and it may contribute to the overall pharmacological effect of macitentan *in vivo*.

Safety pharmacology studies did not revealed any adverse neurobehavioral or respiratory effects.

Arterial intimal thickening characterized by proliferation of the intimal layer was found in dogs treated with macitentan at doses ≥30 mg/kg/day, independently of the treatment duration. *In vitro* and *in vivo* studies show that macitentan decreases arterial blood pressure in dogs in a dose-dependent manner. The effect of macitentan on blood pressure is limited to dogs, and provided literature suggests that the dog is a species particularly sensitive to hemodynamic changes and related coronary vascular and myocardial effects. Coronary and myocardial lesions

were not observed in rats or mice. Clinically, data regarding MACE and ECG do not raise any concerns regarding the long term cardiovascular safety of macitentan.

Combined treatment of macitentan with phosphodiesterase 5 inhibitor (sildenafil) increased the duration of blood pressure-lowering effect induced by the monotheraphy in hypertensive rats. Other relevant pharmacodynamic drug interactions have been monitored in the clinical setting, and therefore additional non-clinical studies are not warranted.

The pharmacokinetic and metabolic profile of macitentan was characterized in the rat and the dog.

Macitentan metabolism in rats and dogs shows large similarities to the pattern observed in man and all human metabolites were present in animals, supporting the relevance of these species for the preclinical safety program of macitentan, although data from the excreta indicate that the biotransformation pattern could be different between the non-clinical species.

The primary metabolism of macitentan is catalyzed by P450 enzymes, mainly by CYP3A4 with contributions of CYP2C8, CYP2C9 and CYP2C19.

The potential interactions of macitentan and its major human metabolite M6 with a panel of transporter (P-gp, OATPB1, OATPB3, OCT1, OCT2, OAT1, OAT3, BSEP, NCTP, MATE-1 and MATE-2) have been studied in order to characterize potential drug-drug interactions. Macitentan (but not ACT-132577) could be an inhibitor of BCRP at clinically relevant intestinal concentrations. Macitentan and its metabolites ACT-080803 and ACT-132577 are not inducers of CYP3A4 at clinically relevant concentrations.

Macitentan passed into the milk of lactating rats. Therefore, macitentan is contraindicated in lactation.

Macitentan was well tolerated from chronic treatment up to relatively high dose levels.

In the mouse, rat, and dog toxicity studies, the heart, liver, and testes were identified as the main organs affected by treatment with macitentan. Minor or secondary changes were observed in RBC, the hemostatic system, thyroid, uterus, kidney and nasal cavity. The clinical relevance of testicular findings (tubular dilation, tubular atrophy and hypospermatogenesis) is unknown and a potential risk for male fertility cannot be discarded based on these animal studies.

There were no evidences of genotoxic and carcinogenic potential associated with macitentan.

Macitentan showed clear dose-dependent teratogenic effects in rats and rabbits. In both species there were cardiovascular and mandibular arch fusion abnormalities. The observed effects are to be class effect of ET receptor antagonists. In line with other ERAs, a pregnancy contraindication is included in the SmPC.

The juvenile toxicity study did not show new target organ toxicity as compared to adult animals but juvenile animals are more sensitive to macitentan than adults. The SmPC in section 5.3 provides adequate information related to the juvenile toxicity findings.

The MAH submitted information related to the environmental risk assessment. After review of the data, the CHMP considered the need to perform Log Kow determination using a different method.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of macitentan to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

The applicant has accepted the recommendation to perform a log Kow determination for macitentan, according to the slow stirring method (OECD 123).

2.3.6. Conclusion on non-clinical aspects

From a non-clinical point of view, Opsumit would be recommended for approval. The SmPC appropriately reflects the non clinical data submitted with macitentan.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

A routine inspection has been conducted for the pivotal study SERAPHIN, at two Clinical Investigator sites in Mexico (19-22 February, 2013) and China (19-22 March 2013), and at the Sponsor site (Actelion) in Switzerland (8-12 April 2013). The final Integrated Inspection Report (IIR) (**INS/GCP/2012/027;** EMEA/H/C/002697) is dated on 15 May 2013.

The inspectors' conclusion is that the study has been conducted in compliance with GCP at the sites and that the study report can be used for evaluation and assessment of the application.

- Tabular overview of clinical pharmacology studies

Table O-PK-01. Completed clinical pharmacology studies

Study	Characteristics
Single-ascending dose AC-055-101	**Objectives:** Investigation of the PK, PD, safety and tolerability of macitentan in male subjects. **Enrolled:** 56 healthy subjects **Evaluable PK:** 42 macitentan-treated subjects. **Evaluable PD & safety:** 56 subjects (42 on macitentan, 14 on placebo). **Demographics:** Male; Caucasian; Age: 19–49 years; Weight: 55.4–98.0 kg; BMI: 19.4–27.8 kg/m2. **Treatments:** Single oral capsule dose; Macitentan (6 subjects/group): 0.2, 1, 5, 25, 100, 300, 600 mg; Placebo (2 subjects/group). **Design:** single-ascending dose placebo-controlled, double-blind.

Study	Characteristics
Multiple-ascending dose AC-055-102	**Objectives:** Investigation of the PK, PD, safety and tolerability of macitentan in male subjects. **Enrolled:** 32 healthy subjects; **Evaluable PK:** 24 macitentan-treated subjects. **Evaluable PD & safety:** 32 subjects (24 on macitentan, 8 on placebo). **Demographics:** Male; Caucasian; Age: 20–50 years; Weight: 58.2–97.4 kg; BMI: 19.6–28.0 kg/m2. **Treatments:** Once daily oral, capsule dose for 10 days; Macitentan (6 subjects/group): 1, 3, 10, 30 mg; Placebo (2 subjects/group). **Design:** Multiple-ascending dose, placebo-controlled, double-blind.
Tablet–capsule biocomparison study AC-055-108	**Objectives:** Biocomparison of tablet and capsule formulations of macitentan in healthy male subjects. Safety and tolerability. **Enrolled:** 12 healthy subjects. **Evaluable PK:** 11 subjects. **Evaluable safety:** 12 subjects. **Demographics:** Male; Caucasian, 10 subjects; Hispanic, 1 subject; Black, 1 subject. Age: 20–44 years; Weight: 66.0–78.0 kg; BMI: 19.5–27.0 kg/m2. **Treatment A:** Single oral, macitentan 10 mg, tablet. **Treatment B:** Single oral, macitentan 10 mg, capsule. **Design:** Open-label, 2-way crossover.
Absorption, distribution, metabolism, and excretion AC-055-104	**Objectives:** Investigation of the mass balance, PK, metabolism and safety in healthy male subjects. **Enrolled and Evaluable (PK & safety):** 6 healthy subjects. **Demographics:** Male; Caucasian; Age: 47–62 years; Weight: 68.8–88.1 kg; BMI: 24.7–27.4 kg/m2. **Treatments:** Single oral, 14C-macitentan 10 mg capsule. **Design:** Open-label.
Effect of food intake AC-055-103	**Objectives:** Investigation of the effect of food on the PK of macitentan in male subjects. Safety and tolerability. **Enrolled and Evaluable (PK & safety):** 10 healthy subjects. **Demographics:** Male; Caucasian; Age: 26–36 years; Weight: 62.1–97.4 kg; BMI: 20.5–27.3 kg/m2. **Treatments:** Single oral, macitentan 10 mg capsule on 2 occasions. **Design:** Open-label, 2-way cross-over, single dose (once in fed state and once in fasted state).

Study	Characteristics
Macitentan-warfarin Drug-drug interaction AC-055-105	**Objectives:** Investigation of the effect of macitentan on the PK and PD of warfarin in healthy male subjects. Safety and tolerability. **Enrolled:** 14 healthy subjects. **Evaluable PK & PD:** 12 macitentan-treated subjects (excluded 2 macitentan-treated subjects: 1 did not receive warfarin dose in one administration during treatment A; 1 did not receive Treatment B). **Evaluable safety:** 14 macitentan-treated subjects (Treatment A), 13 subjects (Treatment B). **Demographics:** Male; Caucasian; Age: 24–45 years; Weight: 60.7–89.4 kg; BMI: 20.1–26.6 kg/m2. **Treatment A:** Oral macitentan, capsule. 30 mg o.d. (Day 1), 10 mg o.d. (Days 2–8). Concomitant oral warfarin 25 mg (Day 4). **Treatment B:** Single oral warfarin, dose 25 mg (Day 1). **Design:** Open-label, 2-way, crossover.
Macitentan-sildenafil Drug-drug interaction AC-055-106	**Objectives:** Evaluation of PK interactions between macitentan and sildenafil in healthy male subjects. Safety and tolerability. **Enrolled and Evaluable (PK & safety):** 12 healthy subjects. **Demographics:** Male; Caucasian, 10 subjects; Asian, 2 subjects; Age: 20–33 years; Weight: 70–86 kg; BMI: 20.9–28.1 kg/m2. **Treatments:** **Treatment A:** Oral macitentan capsule. 30 mg o.d. (Day 1), 10 mg (Days 2–4). **Treatment B:** Oral sildenafil, 20 mg t.i.d. (Days 1–3). Single 20 mg dose (Day 4). **Treatment C:** Oral macitentan 30 mg o.d. (Day 1), 10 mg o.d. (Days 2–4). Concomitant sildenafil 20 mg t.i.d. (Days 1–3). Single 20 mg dose (Day 4). **Design:** Open-label, 3-way crossover.
Macitentan-ketoconazole Drug-drug interaction AC-055-107	**Objectives:** Investigation of the effect of ketoconazole on the PK of macitentan in healthy male subjects. Safety and tolerability. **Enrolled:** 12 healthy subjects. **Evaluable PK:** 10 macitentan-treated subjects. **Evaluable safety:** 10 macitentan-treated subjects (Treatment A), 11 macitentan-treated Subjects (Treatment B). **Demographics:** Male, Caucasian; Age range: 22–38 years; Weight: 63.0–85.5 kg; BMI: 19.0–28.4 kg/m2. **Treatment A:** Single oral macitentan 10 mg capsule dose. **Treatment B:** Ketoconazole 400 mg o.d. for 24 days. Concomitant single oral macitentan 10 mg dose (Day 5). **Design:** Open-label, 2-way crossover
Macitentan-cyclosporine, macitentan-rifampicin Drug-drug interaction AC-055-111	**Objectives:** Investigation of the effects of cyclosporine and rifampicin on the PK of macitentan in healthy male subjects. **Enrolled and Evaluable (PK & safety):** **Part A:** 10 healthy subjects; **Part B:** 10 healthy subjects. **Demographics:** **Part A:** Male, Caucasian; Age range: 18–40 years; Weight range: 55.0–85.0 kg; BMI range: 18.1–26.5 kg/m2. **Part B:** Male, Caucasian; Age range: 20–44 years; Weight range: 61.0–83.0 kg; BMI range: 21.3–25.1 kg/m2. **Treatments:** **Part A:** Oral macitentan tablet. 30 mg OD (D1), 10 mg OD (D2-17). Concomitant oral cyclosporine A 100 mg BID (D6-17). **Part B:** Oral macitentan 30 mg o.d. (Day 1), 10 mg o.d. (Days 2–12). Concomitant rifampicin 600 mg o.d. (Days 6–12). **Design:** Open-label, 2-part, 1-sequence crossover.
Ethnic sensitivity study AC-055-109	**Objectives:** Investigation of the PK, safety and tolerability of macitentan in healthy Japanese and Caucasian subjects. **Enrolled and Evaluable (PK & safety):** 20 healthy subjects. **Demographics:** **Japanese** (10 subjects); 5 male, 5 female; Age: 21–32 years; Weight: 49.4–62.9 kg; BMI: 19.4–23.6 kg/m2. **Caucasian** (10 subjects); 5 male, 5 female; Age: 19–44 years; Weight: 50.9–66.7 kg; BMI: 19.1–22.5 kg/m2. **Treatments:** Single oral, macitentan 10 mg tablet. **Design:** Open-label, parallel group.
Hepatic impairment AC-055-110	**Objectives:** Investigation of the PK, safety and tolerability of macitentan in subjects with mild, moderate, or severe hepatic impairment due to liver cirrhosis. **Enrolled:** 32 subjects; **Evaluable PK:** 31 subjects; **Evaluable safety:** 32 subjects. 24 subjects with hepatic impairment [8 mild (Child-Pugh A), 8 moderate (Child-Pugh B), 8 severe (Child-Pugh C)] and 8 healthy subjects. **Demographics:** Sex: 20 male; 12 female; Ethnicity: Caucasian; Age range: 34–66 years; Weight range: 62.0–106.0 kg; BMI range: 20.0–31.9 kg/m2. **Treatments:** Single oral macitentan 10 mg tablet. **Design:** Open-label, parallel group.
Renal impairment AC-055-112	**Objectives:** Investigation of the PK in patients with impaired renal function. Safety and tolerability. **Enrolled and Evaluable (PK and safety):** 8 patients with severe renal impairment, 8 healthy subjects. **Demographics:** 8 subjects with severe renal impairment (creatinine clearance range: 16.1–29.0 mL/min), 8 healthy subjects (creatinine clearance range: 89.9–107.4 mL/min); 8 male, 8 female; Caucasian; Age: 36–60 years; Weight: 63.0–90.4 kg; BMI: 22.2–31.1 kg/m2. **Treatments:** Single oral macitentan 10 mg tablet. **Design:** Open-label, parallel group
Spermatogenesis AC-055-113	**Objectives:** Investigation of the effect of macitentan on spermatogenesis, sperm quality and serum hormone concentrations of the hypothalamus-pituitary-adrenal and gonadal axes. PK, safety and tolerability. **Enrolled:** 84 healthy subjects. **Evaluable testicular safety & other safety variables:** All 84 subjects. **Evaluable PK:** 65 subjects. **Demographics:** Male; Caucasian (56), Black (25), other (3); Age: 18–44 years; Weight: 51.0–110.2 kg; BMI: 18.3–30.0 kg/m2.

Study	Characteristics
	Treatments: Once daily oral macitentan 10 mg tablet or placebo for 12 weeks. **Design:** Double-blind, placebo-controlled, parallel group.
Thorough QT study AC-055-114	**Objectives:** Investigation of the effect of repeated daily doses of 10 mg and 30 mg macitentan on the QT/QTc interval in healthy male and female subjects. **Enrolled:** 64 healthy subjects. **Evaluable PK:** 62 subjects (Treatments A–D). **Evaluable safety (cardiodynamic):** 64 subjects (Treatments A–B), 63 subjects (Treatments C–D). **Evaluable PK/cardiodynamic:** 62 subjects (Treatments A–D). **Demographics:** 26 male, 38 female; Caucasian, 63 subjects; Hispanic, 1 subject; Age: 23–55 years; Weight: 50.1–98.5 kg; BMI: 19.1–28.0 kg/m2. **Treatments:** Oral macitentan tablet. **Treatment A:** 8-day o.d. placebo, matching macitentan with single (open-label) moxifloxacin 400 mg (Day 8). **Treatment B:** 8-day o.d. macitentan 10 mg. **Treatment C:** 8-day o.d. macitentan 30 mg. **Treatment D:** 8-day o.d. placebo matching macitentan. **Design:** Double-blind, double-dummy, placebo-controlled, 4-way crossover, with open-label. Active comparator.

b.i.d. = twice daily; BMI = body mass index; o.d. = once daily; PD = pharmacodynamic; PK = pharmacokinetic; t.i.d. = three times daily.
[a] = Ongoing study, will not be completed at data cut-off for regulatory filing
[b] = Study conducted in patients.

Macitentan has been studied in an adequate program of pharmacology studies, which provide comprehensive information on pharmacokinetic (PK) and metabolism, effects of intrinsic factors and concomitant use of other drugs, and important pharmacodynamic (PD) characteristics. A total of 14 completed clinical pharmacology studies are included in the application. A brief summary is provided in Table O-PK-01. Additional relevant PK/PD information that is discussed in this section was generated in study AC-055-201 in patients with essential hypertension (Study AC-055-201) and in a PK/PD sub-studies to the pivotal Phase 3 study AC-055-302 SERAPHIN (study AC-055-302) and its open-label extension AC-055-303 SERAPHIN OL.

Two formulations of macitentan were used in clinical studies, a capsule formulation for early clinical development and a film-coated tablet formulation, which was used in a number of Phase 1 studies, in the Phase 2 study in IPF, and in the pivotal Phase 3 study in PAH. The film-coated tablet formulation used in the confirmatory clinical study (SERAPHIN) is identical to the to-be-marketed formulation.

2.4.2. Pharmacokinetics

Macitentan has been studied in a total of 14 completed clinical pharmacology studies. Additional relevant PK/PD information was generated in study AC-055-201 in patients with essential hypertension and in a PK/PD sub-studies of the pivotal Phase 3 study AC-055-302 SERAPHIN and its open-label extension AC-055-303 SERAPHIN OL .

Concentrations of macitentan and its active metabolite ACT-132577 in human plasma were determined using liquid chromatography coupled to tandem mass spectrometry method (LC-MS/MS). All analyses were performed in the same laboratory and during the studies a partial validation was performed, mainly by analysing quality samples. In the studies after 2009 incurred samples analysis was performed. The studied PK parameters (C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, and $AUC_{0-\infty}$) as well as statistical methods are the usual ones in PK studies and are considered appropriate.

Bioequivalence between tablets and capsules (study AC-055-108)

The MAH performed an open label two-way cross-over tablet–capsule biocomparison study (AC-055-108) aiming at comparing the film-coated tablets (intended to-be-marketed formulation) and capsule formulations (used in early clinical development and the Phase II study in hypertension) in 12 healthy subjects.

Maximum plasma concentrations of the film-coated tablets (intended to-be-marketed formulation, used in a number of Phase 1 studies, in the Phase 2 study in IPF, and in the pivotal Phase 3 SERAPHIN study in PAH) were slightly lower (19%) than capsules (used in early clinical development and the Phase II study in hypertension). However, the relative difference in AUC is small (ranging between 5% to7%), and the corresponding 90% CI for AUC falls within bioequivalence limits. Therefore, results of PK studies conducted with capsules may be extrapolated to tablets.

Absorption

Bioavailability

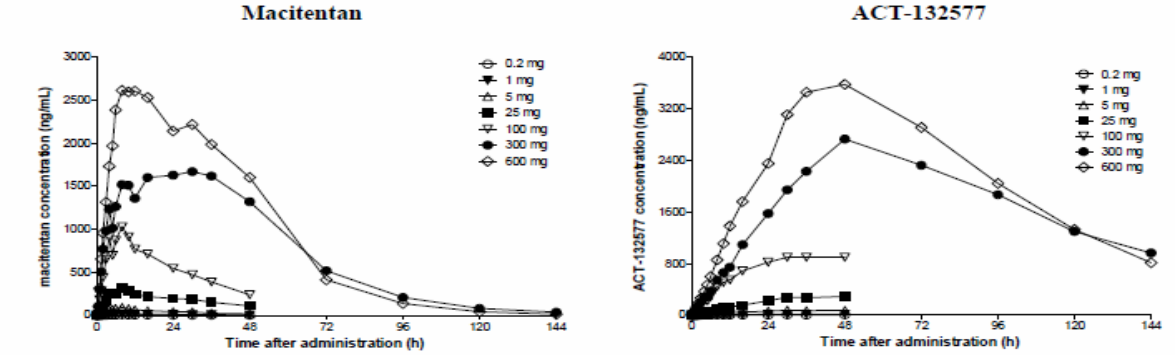
The absolute bioavailability of macitentan could not be established, as the development of an i.v. formulation was not technically feasible. Maximum plasma concentrations of macitentan are achieved about 8 hours after oral administration. Thereafter, plasma concentrations of macitentan and its active metabolite decrease slowly, with apparent elimination half-lives of approximately 16 hours and 48 hours, respectively (Table O-PK-02 and Figure O-PK-01).

Table O-PK-02. Study AC-055-101: Plasma PK parameters of macitentan in healthy subjects after administration of a single dose of 0.2, 1, 5, 25, 100, 300, or 600 mg

Treatment	N	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-48} (ng.h/ml)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$t_{1/2}$ (h)
0.2 mg	6	4.0 (2.6, 6.2)	8 (8—12)	85.9 (52.4, 141)	NC*	NC	NC
1 mg	6	17.9 (12.4, 25.9)	8 (4—10)	439 (271, 711)	NC*	NC	NC
5 mg	6	93.4 (79.1, 110)	8 (4—8)	2056 (1855, 2278)	NC*	NC	NC
25 mg	6	335 (264, 425)	8 (4—30)	8810 (7412, 10,472)	NC*	NC	NC
100 mg	6	999 (643, 1552)	8 (4—12)	25,281 (18,775, 34,040)	NC*	NC	NC
300 mg	6	1847 (1409, 2422)	30 (10—48)	67,109 (48,751, 92,380)	102,017 (76,088, 136,783)	103,007 (76,650, 138,428)	17.5 (14.1, 21.8)
600 mg	5**	2967 (2233, 3943)	12 (8—30)	96,530 (70,006, 133,102)	126,882 (82,617, 194,865)	127,104 (82,657, 195,450)	13.4 (11.3, 15.9)

Data are geometric means (and 95% CI) or for t_{max} the median (and range).
AUC_{0-48} = area under plasma concentration-time curve from 0 to 48 h after drug administration; AUC_{0-t} = area under plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quanification; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from zero to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; N = number of subjects; NC = not calculated; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration.
*AUC_{0-t} equals AUC_{0-48} for these dose groups.
** For 1 subject, no reliable estimate of $t_{1/2}$ could be determined.
Source: van Giersbergen 2005a Table 6.

Figure O-PK-01. Study AC-055-101: Mean plasma concentration versus time profiles of macitentan and ACT-132577 in healthy subjects (n = 6 per group) after administration of a single macitentan dose of 0.2, 1, 5, 25, 100, 300, or 600 mg



Source: van Giersbergen 2005a Figure 1.

Influence of food (study AC-055-103)

In healthy subjects, the exposure to macitentan and its active metabolite was unchanged in the presence of food and, therefore, macitentan is proposed to be taken with or without food. The breakfast that was provided followed the FDA guidance for Food-Effect Bioavailability and Fed Bioequivalence Studies.

Distribution

Macitentan and ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for macitentan and ACT-132577, respectively (Study AD-055-101). Macitentan and its active metabolite are highly bound to plasma proteins (>99%), primarily to albumin (Study B-04.025).

Metabolism

Macitentan undergoes biotransformation by hydroxylation, with the CYP3A4 isoenzyme as the major contributor (Studies B-04.022, B-04.093 and B-04.099). Two circulating macitentan metabolites have been identified in humans: ACT-132577 (active metabolite) and ACT-373898 (inactive metabolite). ACT-132577 is approximately 8-fold less potent than macitentan on ET_A and 2-fold less potent on ET_B. The main metabolite is ACT-132577 (active M6), present at approximately 71% of total drug exposure in plasma. No particularly relevant consequences of polymorphism in CYP3A4 are expected.

Elimination

The major excretion route of macitentan in humans, in the form of metabolites, is via urine, accounting for about 50% of the dose (four metabolites, with the metabolite M323u as the most abundant one), while approximately 24% of the administered dose was recovered in faeces (five metabolites, with the metabolite ACT-080803 M5 the most abundant one) (study AC-055-104). Neither unchanged macitentan nor the active metabolite ACT-132577 were recovered in urine.

Dose proportionality and time dependencies

After repeated administration, the pharmacokinetics of macitentan are dose-proportional up to and including 30 mg (study AC-055-102). In healthy subjects, the accumulation factor for macitentan was 1.4–1.7 when comparing the AUC_{0-24} on Days 1 and 10. The expected accumulation of the active metabolite ACT-132577 based on the half-life was approximately 3.5. However, the accumulation found in healthy subjects after repeated dosing was relatively large, 7-10 times (study AC-055-102). The applicant has clarified that the differences in accumulation ratio of the metabolite ACT132577 based on half-life and the accumulation found *in vivo* after repeated dosing are due to differences in equations applied. In patients, no trend for time-dependency was noted (study AC-055-302). Inter-subject variability was low in healthy subjects and moderate in patients.

PK in the target population

Based on trough concentrations, exposure to macitentan in patients with PAH (study AC-055-302) was approximately 2-fold greater than in healthy subjects ((study AC-055-102) or patients with essential hypertension (Table O-PK-03). ACT-132577 trough plasma concentrations were higher in patients with PAH and essential hypertension (Study AC-055-201) when compared to healthy subjects treated with 10 mg macitentan (study AC-055-102).

Table O-PK-03. Studies AC-055-302, AC-055-201: Summary statistics of macitentan and ACT-132577 trough plasma concentrations (ng/mL)

	AC-055-302 (PAH)				AC-055-201 (essential hypertension)			
	Macitentan		ACT-132577		Macitentan		ACT-132577	
Dose group	Month 6	EOT	Month 6	EOT	Week 4	Week 8	Week 4	Week 8
3 mg								
n	49	142	49	142	46	39	46	39
mean	92.1	76.4	253.0	309.6	65.3	67.3	237.9	246.5
SD	52.6	61.4	103.8	175.3	39.1	34.8	128.4	122.0
CV%	57.1	80.4	41.0	56.6	-	-	-	-
median	89.0	61.0	251.0	294.0	-	-	-	-
min	-	-	-	-	0.0	0.0	0.0	0.0
max	-	-	-	-	176	132	762	509
10 mg								
n	41	154	41	154	48	44	48	44
mean	291.5	208.2	837.4	842.6	164.3	170.9	727.9	805.0
SD	155.2	138.7	328.2	413.1	108.4	85.6	383.1	273.9
CV%	53.3	66.6	39.2	49.0	-	-	-	-
median	276.0	200.0	822.0	857.5	-	-	-	-
min	-	-	-	-	0.0	0.0	0.0	2.3
max	-	-	-	-	462	384	1600	1330

CV = Coefficient of variation; EOT = end-of-treatment; n = number of patients; PAH = pulmonary arterial hypertension; SD = standard deviation.
Source: D-12.473 Tables 5, 6, 9, and 10.

Table O-PK-04. Study AC-055-102: Summary statistics of macitentan and ACT-132577 trough plasma concentrations (ng/ml) on Day 10

	Healthy subjects	
Dose group	Macitentan	ACT-132577
3 mg		
n	6	6
mean	51.8	214
SD	22.2	92.7
min	25.6	151
max	87.9	399
10 mg		
n	6	6
mean	131	585
SD	34.3	132
min	96.7	412
max	184	747

n = number of subjects; SD = standard deviation.
Source: D-06.044 Tables 21 and 22.

A PK sub-study within study AC-055-303 (SERAPHIN-OL), the open-label extension to the SERAPHIN study, was undertaken to allow a more precise dose selection for clinical trials in children and was recently clinically completed. For this, 20 patients from the SERAPHIN-OL study were confined to the clinic for 24 hours, during which samples for a PK profile evaluation were taken, thus allowing for determination of Cmax and AUC_T of macitentan and ACT-132577. The findings indicated that plasma exposure to macitentan and its active metabolite ACT-132577, measured over a 24 h dosing interval, were increased by approximately 10–30% between PAH patients and healthy subjects. These findings are reflected in the SmPC.

Special populations

Renal impairment (Study AC-055-112)

The relative increase in exposure to macitentan and the active metabolite observed in patients with severely impaired renal function (24% and 58% higher than those in healthy subjects) was below that achieved at the highest well-tolerated macitentan dose of 300 mg reported in the SAD study (AC-055-101). There was an 8-fold increase in the exposure to the inactive metabolite ACT-373898, which is expected not to be of clinical relevance, based on available data in animals. However, the clinical significance in humans is unknown. In addition, no data are available in PAH patients with severe renal impairment.

Hepatic impairment (Study AC-055-110)

Overall, the exposure to macitentan and its active metabolite is decreased by 20% in patients with hepatic impairment, without differences according to the degree of impairment. The differences in other PK parameters between hepatically impaired and normal subjects are even more irrelevant. Therefore, no dose-adjustment in hepatic impairment is deemed necessary. It is possible that the PK of a drug differs between a hepatically impaired subject population and a healthy population treated concomitantly with a strong CYP3A4 inhibitor. On the basis of the hepatic impairment study AC-055-110, the applicant hypothesises that the decrease in intrinsic hepatic clearance due to a decrease in enzyme-capacity is compensated by the increase in the unbound fraction leading to an unchanged hepatic drug clearance.

Gender

Females tend to have a longer t1/2 and higher plasma through concentration for both macitentan and ACT-132577, leading to differences in exposure when compared to males (Study AC-055-109). However, the small difference observed could be confounded by body-weight differences (female subjects had a body weight 12% lower than that of the male subjects).

Race

There were no large differences between the races involved in the studies with this product. Japanese subjects tend to have lower exposures to macitentan and ACT-132577 than Caucasians, although the 15% relative difference seems not to be of clinical relevance (Study AC-055-109). Therefore, it can be concluded that the different races do not show clinically relevant differences in the pharmacokinetics of macitentan.

Weight

Analysis by weight category (< 50 kg, 50–99 kg, and > 100 kg) did not indicate a clinically relevant effect of weight on exposure to macitentan at Month 6 or EOT. A decrease of trough plasma concentrations of ACT-132577 with weight was suggested in the 10 mg dose group at Month 6, but this observation could have been driven by the limited number of patients with a weight above 100 kg.

Elderly

The number of elderly patients included in the clinical development of macitentan is provided in table below. In the 14 dedicated PK studies, no subjects > 65 were included. The PK studies were performed in a healthy subject population and the upper allowed age limit for inclusion varied between 45 and 65 years of age. The SmPC reflects that there is limited clinical experience in patients over the age of 75 years, and therefore macitentan should be used with caution in this population (see also "PK in the target population").

Table O-PK-05. Number of elderly patients included in the clinical development programme of macitentan

	Age 65–74	75–84	Age 85+
PK Trials	0	0	0
Controlled Trials			
AC-055-201	44	10	0
AC-055A201	57	11	0
AC-055-302	48	12	0
Non-controlled Trials			
AC-055-303	60	24	1

Children:

Twenty patients between the ages of 12 and < 18 years were enrolled in SERAPHIN study. Characterisation of PK could not be performed. Additional data would be needed in order to support paediatric use (Refer to the clinical efficacy and safety part).

Pharmacokinetic interaction studies

Drug-drug interactions

in vitro studies showed that the metabolism of macitentan to its active metabolite is catalysed by CYP3A4 and to a minor extent by CYP2C19 (Studies B-04.022, B-04.093 and B-04.099). Macitentan and its active metabolite were neither a substrate nor an inhibitor of CYP isoenzymes, multi-drug resistance protein (P-gp, MDR-1), or organic anion transporting polypeptides (OATP1B1 and OATP1B3), and did not interact with proteins involved in hepatic bile salt transport (i.e. BSEP, NTCP). In vivo DDI studies with warfarin (study AC-055-105), sildenafil (study AC-055-106) and cyclosporine (study AC-055-111) showed no relevant PK interaction with macitentan. In addition, there was a 2-fold increase in macitentan exposure with concomitant ketoconazole, a strong CYP3A4 inhibitor (Study AC-055-107) and a decrease by 79% in macitentan exposure with concomitant rifampicin, a potent inducer of CYP3A4 (Study AC-055-111). However, ketoconazole was only administered once daily dose and therefore the inhibitory effect is not considered to represent a worst-case scenario due to the short half-life of ketoconazole in comparison to macitentan. In post-hoc analyses, the predicted increase was

approximately 3.0-fold in the presence of ketoconazole 200 mg twice daily using physiologically based pharmacokinetic (PBPK) modelling.

No specific drug-drug interaction studies with hormonal contraceptives have been conducted. However, the lack of interaction with sildenafil indicates that no clinically relevant pharmacokinetic interactions between macitentan and other CYP3A4 substrates would occur. Overall, macitentan seems to have a low potential for interactions with other medicinal products.

Exposure relevant for safety information

In dose-ascending studies conducted in healthy subjects (Studies AC-055-101 and 102), dose-dependent increases in the incidence of AEs were observed, with headache the most frequently reported adverse event.

The relationship between exposure (trough plasma concentrations) and safety in PAH patients was characterized using a logistic regression model (PK/PD Modelling Report AC-055-302) based on the data from study AC-055-302 (SERAPHIN). However, for adverse events, only the relationship between exposure and AEs leading to study drug discontinuation was explored. Only a small number of patients had an AE leading to study drug discontinuation (n = 26) in this analysis. On the other hand, there was an inverse relationship between macitentan trough plasma concentrations and changes in hematocrit and haemoglobin levels, but no concentration-dependent impact on changes in liver function tests could be established. Post-hoc logistic regression models were applied to explore the relationship between exposure and treatment-related AEs. The median macitentan trough concentrations in the 3 mg and 10 mg dose groups (89 and 276 ng/mL) predicted increases in the probability to have an AE of anaemia from 1.77% (placebo subjects) to 2.09% and 2.96%, respectively. No trend was observed for infrequent AEs (n<30 for the SMQs teratogenicity, thrombocytopenia, leucopenia, menstrual disorder, and ovarian cysts) or for hepatic events (n = 86).

2.4.3. Pharmacodynamics

Mechanism of action

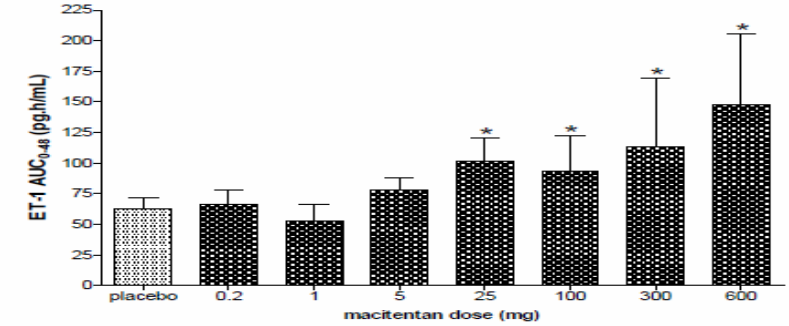
Macitentan is an orally active potent endothelin receptor antagonist, approximately 100-fold more selective for ETA as compared to ETB (refer to the non-clinical part).

Primary and Secondary pharmacology

Primary pharmacology

Binding of an ERA to ETB receptors causes an increase in plasma ET-1 levels, which can be used as a marker of pharmacological effect and potency on the ETB receptor. This effect of ERAs is of rapid onset. A dose-related effect of macitentan to increase plasma ET-1 levels was demonstrated in nonclinical in vivo studies, as well as after a single dose in humans (study AC-055-101) (Figure O-PD-01).

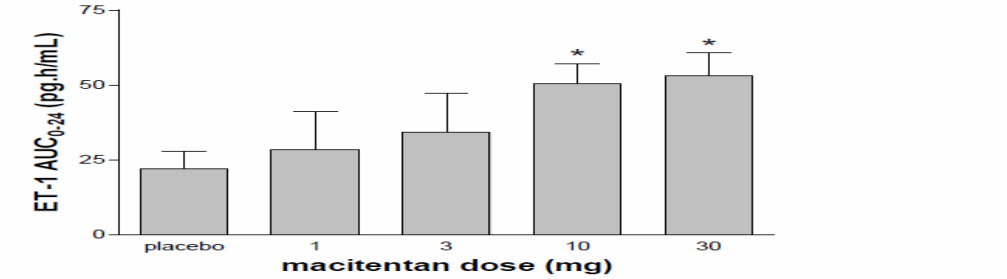
Figure PD-01. Study AC-055-101: Effect of macitentan on plasma ET-1 concentrations.



Each bar represents the arithmetic mean and SD. N = 6 for the different macitentan doses and 14 for the placebo group.
* $p < 0.05$ when compared to placebo.
AUC_{0-48} = area under the plasma concentration-time curve from time 0 to 48 h after drug administration; ET-1 = endothelin-1; SD = standard deviation.
Source: van Giersbergen 2005a Figure 3.

In the multiple-ascending dose study in healthy subjects (study AC-055-102), plasma ET-1 concentrations at steady-state showed a dose-dependent increase, with no further increase beyond the 10 mg OD dose (Figure O-PD-02), indicating full receptor blockade at this dose level.

Figure O-PD-02. Study AC-055-102: Effect of macitentan on plasma ET-1 concentrations



Each bar represents the arithmetic mean and SD. N = 6 for the different macitentan doses and N = 8 for the placebo group.
*$p < 0.05$ when compared to placebo (derived by exploratory statistical analyses).
AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 h after drug administration; ET-1 = endothelin-1; SD = standard deviation.
Source: D-06.044 Figure 5.

Macitentan has a circulating active metabolite (ACT-132577) that is also a dual ERA, is on average approximately 5-fold less potent than macitentan, and may contribute to the clinical effect.

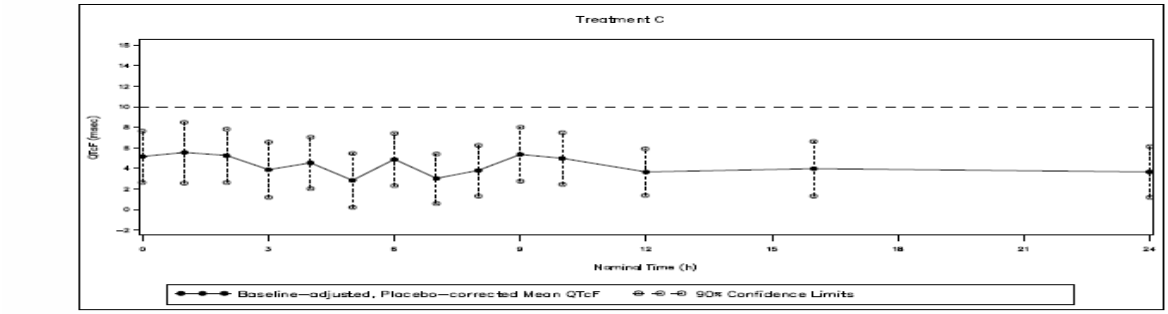
Secondary pharmacology

Thorough TQT study (AC-055-114)

A Thorough QT study AC-055-114 was conducted to investigate the effect of repeated daily doses of 10 mg and 30 mg macitentan on the QT/QTc interval in healthy male and female subjects. This was a double-blind, double-dummy, placebo-controlled, 4-way crossover, with open-label with moxifloxacin as active comparator. 64 healthy subjects were enrolled.

The results demonstrate that macitentan did not affect cardiac repolarization in nonclinical studies or in a thorough TQT study.

Figure O-PD-03. Study AC-055-114: Baseline-adjusted, placebo-corrected mean QTcF and 90 % CI over time, 30 mg macitentan.



Treatment C: 30 mg macitentan; CI = confidence interval.
Baseline defined as time-matched value on Day 1 pre-dose.
Source: D-12.322 Figure 4.

Testicular safety (study AC-055-113)

The results of a dedicated study in healthy subjects, as well as evidence from non-clinical studies, cannot exclude with reasonable confidence the possibility that macitentan would have any major effect on sperm concentration or sperm motility and morphology.

Relationship between plasma concentrations and effect

In the PK/PD model, increasing macitentan concentrations were associated with longer time from baseline to morbidity/mortality event and with an increase in 6 minute walk distance (6MWD).

However, no clear separation between the macitentan 3 mg and 10 mg doses could be observed. The proportion of subjects with an event who provided PK data at EOT was small. Thus, the results should be interpreted cautiously and no firm conclusion should be drawn. Increasing macitentan concentrations were associated with reductions in PVR, mPAP, and TPR and an increase in cardiac index. However, no relationship was established for mRAP and mixed venous oxygen saturation (SvO2). The most important dose-related AE was anaemia/ haemoglobin decrease.

In conclusion, based on the results from the pivotal SERAPHIN study, no population/population subset has been identified for which a dose below 10 mg could be recommended, without the risk of compromising the benefit that can be obtained with macitentan 10 mg.

Pharmacodynamic interactions

In healthy volunteers (study AC-055-106), the administration of macitentan and sildenafil led to an increase in headache and hypotension as compared with each of the drugs administered alone. In the double-blind PAH population, headache was reported at an incidence of 13.2% and 13.6% in the macitentan 3 mg and 10 mg groups, respectively, and at 8.8% in the placebo group. The incidence of headache in patients with concurrent PAH therapy was 14.0% (23/164) and 13.6% (21/154) on macitentan 3 and 10 mg, respectively, versus 10.5% (16/153) on placebo. These data do not indicate a higher incidence of headache associated with the administration of macitentan in patients receiving concurrent PAH therapy. Subgroup evaluation of the PT 'hypotension' in the double-blind PAH population showed that the incidence of hypotension in patients with concurrent PAH therapy was 6.1% (10/164) and 4.5% (7/154) on macitentan 3 and 10 mg, respectively, versus 3.3% (5/153) on placebo. In the subgroup not treated with a specific PAH therapy, the incidence of hypotension was 4.7% (4/86) and 9.1%

(8/88) in macitentan 3 and 10 mg, respectively, versus 6.3% (6/96) on placebo. These data do not suggest a higher incidence of hypotension AEs associated with the administration of macitentan in patients receiving concurrent PAH therapy.

2.4.4. Discussion on clinical pharmacology

Macitentan has been studied in a total of 14 completed clinical pharmacology studies. Additional relevant PK/PD information was generated in study AC-055-201 in patients with essential hypertension and in a PK/PD sub-study to the pivotal Phase 3 study AC-055-302 SERAPHIN.

Pharmacokinetics

Concentrations of macitentan and its active metabolite ACT-132577 in human plasma were determined using a validated liquid chromatography coupled to tandem mass spectrometry method (LC-MS/MS). The analytical method was demonstrated to be precise and accurate. The studied PK parameters (Cmax, tmax, t1/2, AUC0-t, and AUC0-∞) as well as statistical methods are the usual ones in PK studies and are considered appropriate. It is considered that results of PK studies conducted with capsules (used in early clinical development and the Phase 2 study in hypertension) may be extrapolated to film coated tablets (intended to-be-marketed formulation, used in a number of Phase 1 studies, in the Phase 2 study in IPF, and in the pivotal Phase 3 SERAPHIN study in PAH).

Absorption

The absolute bioavailability of macitentan could not be established, as the development of an i.v. formulation was not technically feasible. Maximum plasma concentrations of macitentan are achieved about 8 hours after administration. Thereafter, plasma concentrations of macitentan and its active metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively. In healthy subjects, the exposure to macitentan and its active metabolite was unchanged in the presence of food and, therefore, macitentan may be taken with or without food. This information is adequately reflected in the SmPC section 5.2.

Distribution

Macitentan and ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50L and 40L for macitentan and ACT-132577, respectively. Macitentan and its active metabolite are highly bound to plasma proteins (>99%), primarily to albumin.

Biotransformation / metabolism

Macitentan undergoes biotransformation by hydroxylation, with CYP3A4 isoenzyme as the major contributor. The main metabolite is ACT-132577 (active M6), present at approximately 71% of total drug exposure in plasma. No particularly relevant consequences of polymorphism in CYP3A4 are expected. In vitro studies showed that the metabolism of macitentan to its active metabolite is catalysed by CYP3A4 and to a much minor extent by CYP2C19. Macitentan and its active metabolite were neither a substrate nor an inhibitor of CYP isoenzymes, multi-drug resistance protein (P-gp, MDR-1), or organic anion transporting polypeptides (OATP1B1 and OATP1B3), and did not interact with proteins involved in hepatic bile salt transport (i.e. BSEP, NTCP).

Exposure

Plasma exposure to macitentan and its active metabolite ACT-132577, measured over a 24 h dosing interval, were increased by approximately 10–30% between PAH patients and healthy subjects. As the total daily exposure expressed in AUC is a more relevant reflection of exposure during chronic use than the Ctrough, the applicant proposed to reflect this information in section 5.2 of the SmPC as follows:

"The pharmacokinetics of macitentan and its active metabolite have mainly been documented in healthy subjects. Exposure to macitentan in patients with PAH was approximately 1.2-fold greater than in healthy subjects. The exposure to the active metabolite in patients, which is approximately 5-fold less potent than macitentan, was approximately 1.3-fold higher than in healthy subjects. The pharmacokinetics of macitentan in PAH patients were not influenced by the severity of the disease."

The proposed SPC amendments are considered appropriate by the CHMP.

After repeated administration, the pharmacokinetics of macitentan are dose-proportional up to and including 30 mg. In patients, no trend for time-dependency was noted. Inter-subject variability was low in healthy subjects and moderate in patients.

In conclusion, this information is appropriately reflected in the SmPC as follows:

After repeated administration, the pharmacokinetics of macitentan are dose proportional up to and including 30mg.

Elimination

The major excretion route of macitentan in humans, in the form of metabolites, is via urine, accounting for about 50% of the dose, while approximately 24% of the administered dose was recovered in faeces. Neither unchanged macitentan nor the active metabolite ACT-132577 were recovered in urine.

Pharmacodynamics

Macitentan is an orally potent endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more for selective for ET_A than ET_B in vitro. Macitentan has a circulating active metabolite (ACT-132577) that is also a dual ERA, is on average approximately 5-fold less potent than macitentan, and may contribute to the clinical effect.

In the PK/PD model, increasing macitentan concentrations were associated with longer time from baseline to morbidity/mortality event and with an increase in 6MWD. However, no clear separation between the 2 macitentan doses could be observed. The proportion of subjects with an event who provided PK data at EOT was small. Thus, the results should be interpreted cautiously and no firm conclusion should be drawn. Increasing macitentan concentrations were associated with reductions in PVR, mPAP, and TPR and an increase in cardiac index. However, no relationship was established for mRAP and SvO2.

Data from ET receptor antagonism in clinical pharmacology studies and from decreased blood pressure in a phase II study in patients with essential hypertension provides an adequate rationale for dose selection for the pivotal study in patients with PAH.

Macitentan did not affect cardiac repolarization in nonclinical studies or in a thorough TQT study.

In healthy volunteers (study AC-055-106), the administration of macitentan and sildenafil led to an increase in headache and hypotension as compared with each of the drugs administered alone. In the double-blind PAH population, headache was reported at an incidence of 13.2% and 13.6% in the macitentan 3 mg and 10 mg groups, respectively, and at 8.8% in the placebo group. The incidence of headache in patients with concurrent PAH therapy was 14.0% (23/164) and 13.6% (21/154) on macitentan 3 and 10 mg, respectively, versus 10.5% (16/153) on placebo. These data do not indicate a higher incidence of headache associated with the administration of macitentan in patients receiving concurrent PAH therapy. Subgroup evaluation of the PT 'hypotension' in the double-blind PAH population showed that the incidence of hypotension in patients with concurrent PAH therapy was 6.1% (10/164) and 4.5% (7/154) on macitentan 3 and 10 mg, respectively, versus 3.3% (5/153) on placebo. In the subgroup not treated with a specific PAH therapy, the incidence of hypotension was 4.7% (4/86) and 9.1% (8/88) in macitentan 3 and 10 mg, respectively, versus 6.3% (6/96) on placebo. These data do not suggest a higher incidence of hypotension AEs associated with the administration of macitentan in patients receiving concurrent PAH therapy. The median macitentan trough concentrations in the 3 mg and 10 mg dose groups (89 and 276 ng/mL) predicted increases in the probability to have an AE of anaemia from 1.77% (placebo subjects) to 2.09% and 2.96%, respectively. No trend was observed for infrequent AEs (n<30 for the SMQs teratogenicity, thrombocytopenia, leucopenia, menstrual disorder, and ovarian cysts) or for hepatic events (n = 86). Appropriate information has been included in the SmPC.

Special populations

Renal impairment:
The relative increase in exposure to macitentan and the active metabolite observed in patients with severely impaired renal function (24% and 58% higher than those in healthy subjects) was below that achieved at the highest well-tolerated macitentan dose of 300 mg reported in the SAD study. No data are available in PAH patients with severe renal impairment.

In conclusion, as a precautionary measure, additional warnings are required for patients with severe renal impairment and in patients undergoing dialysis. (see SmPC).

Hepatic impairment

Overall, the exposure to macitentan and its active metabolite is decreased by 20% in patients with hepatic impairment, without differences according to the degree of impairment. The differences in other PK parameters between hepatically impaired and normal subjects are even more irrelevant. Therefore, no dose-adjustment in hepatic impairment is deemed necessary. It is possible that the PK of a drug differs between a hepatically impaired subject population and a healthy population treated concomitantly with a strong CYP3A4 inhibitor. On the basis of the hepatic impairment study AC-055-110, the applicant hypothesises that the decrease in intrinsic hepatic clearance due to a decrease in enzyme-capacity is compensated by the increase in the

unbound fraction leading to an unchanged hepatic drug clearance. Hepatic and liver function are further discussed in the clinical safety part. In summary, information related to hepatic function is appropriately reflected in the SmPC (see contra indication, warnings, undesirable effects sections)and in the RMP.

Gender/race/weight

Females tend to have a longer t1/2 and plasma through concentration for both macitentan and ACT-132577, leading to differences in exposure when compared to males. However, the small difference observed could be confounded by body-weight (female subjects had a body weight 12% lower than that of the male subjects). In conclusion, no specific information is warranted in the SmPC.

There were no large differences between the races involved in the studies with this product. Therefore, it can be concluded that, in the different races, macitentan does not show clinical relevant pharmacokinetics differences.

Analysis by weight category (<50 kg, 50–99 kg, and >100 kg) did not indicate a clinically relevant effect of weight on macitentan exposure at Month 6 or EOT. . A decrease of trough plasma concentrations of ACT-132577 with weight was suggested in the 10 mg dose group at Month 6, but this observation could have been driven by the limited number of patients with a weight above 100 kg.

Elderly population

In the 14 dedicated PK studies, no subjects >65 were included. The PK studies were performed in a healthy subject population and the upper allowed age limit for inclusion varied between 45 and 65 years of age. The SmPC adequately reflects that there is limited clinical experience in patients over the age of 75 years, and therefore macitentan should be used with caution in this population.

Paediatric population

Twenty patients between the ages of 12 and <18 years were enrolled in SERAPHIN study. Characterisation of PK could not be performed. Therefore, no conclusion can be drawn and additional data are needed to support any paediatric indication.

Interaction studies

In vivo DDI studies with warfarin, sildenafil and cyclosporine showed no relevant interaction with macitentan. In addition, there was a 2-fold increase in macitentan exposure with concomitant ketoconazole once daily (a strong CYP3A4 inhibitor) and a decrease by 79% in macitentan exposure with concomitant rifampicin (a potent inducer of CYP3A4). In post-hoc analyses, the predicted increase was approximately 3.0-fold in the presence of ketoconazole 200 mg twice daily, using physiologically based pharmacokinetic (PBPK) modelling.

In conclusion, a potential increase in macitentan exposure when using strong CYP3A4 inhibitors could be of clinical relevance. In view of the non-clinical and clinical data, it is therefore acceptable to reflect this information in the SmPC in sections 4.4, and 4.5 accordingly.

In sections 4.4 and 4.5 the following warnings are mentioned:

“Caution should be exercised when macitentan is administered concomitantly with strong CYP3A4 inhibitors”. A warning is also added in case of concomitant use with strong CYP3A4 inducers, to mention that reduced efficacy of macitentan could occur.

No specific drug-drug interaction studies with hormonal contraceptives have been conducted. However, the lack of interaction with sildenafil indicates that no clinically relevant pharmacokinetic interactions between macitentan and other CYP3A4 substrates would occur. Overall, macitentan seems to have a low potential for interactions with other medicinal products.

In dose-ascending studies conducted in healthy subjects (Studies AC-055-101 and 102), dose-dependent increases in the incidence of AEs were observed, headache being the more frequently reported adverse event. The relationship between exposure (trough plasma concentrations) and safety in PAH patients was characterized using a logistic regression model based on the data from study AC-055-302 (SERAPHIN). However, for adverse events, only the relationship between exposure and AEs leading to study drug discontinuation was explored. Only a small number of patients had an AE leading to study drug discontinuation (n = 26) in this analysis. On the other hand, there was an inverse relationship between macitentan trough plasma concentrations and changes in haematocrit and haemoglobin levels; anaemia/haemoglobin decrease being the most important dose-related AE.

No concentration-dependent impact on changes in liver function tests could be established. Based on the results from the pivotal SERAPHIN study, no population/population subset has been identified for which a dose below 10 mg could be recommended, without risk of compromising the benefit that can be obtained with macitentan 10 mg.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of macitentan has generally been well characterized. However, some additional clarifications and SmPC amendments were considered necessary in some particular subpopulations (lack of appropriate PK data in children) and situations (PK interaction with ketoconazole ; uncertainty about testicular safety; and hepatic impairment/toxicity). The agreed SmPC adequately reflects the current knowledge of the product from a pharmacological perspective (see product information).

2.5. Clinical efficacy

This application is based on a single, long-term, pivotal Phase 3 study, AC-055-302/SERAPHIN. There are no other ongoing Phase 3 studies in the sought indication. Study AC-055-201 in patients with essential hypertension contributed data on the dose-response for hemodynamic efficacy of macitentan and, thus, to the dose selection for the Phase 3 study in PAH (Table O-E-01), and will be discussed under “Dose response study” section of this report. Studies SERAPHIN OL (AC-055-303) and MUSIC (AC-055B201) in patients with idiopathic pulmonary fibrosis (IPF) contributed long-term safety and tolerability data for the proposed dose of 10 mg macitentan OD, and will be discussed only in the “Clinical safety” section of this report.

Table O-E-01. Overview of phase 2 and 3 clinical trials with macitentan

Study [Doc No]	Study objectives	Patients enrolled	Treatment/dose (mg)	Treatment duration	Type of control/blinding
Main studies					
AC-055-201 (*Phase II study*)	Efficacy and safety of macitentan in patients with mild to moderate essential hypertension.	466 enrolled, 379 randomized	Placebo run-in	3–4 weeks	Placebo single-blind run-in Placebo and active controlled (enalapril 20 mg), double-blind treatment.
			Macitentan 0.3 mg Macitentan 1 mg Macitentan 3 mg Macitentan 10 mg Enalapril 20 mg Placebo Placebo	8 weeks	
AC-055-302 SERAPHIN *(Phase III study)*	Efficacy and safety of macitentan in patients with PAH	742	Macitentan 3 mg Macitentan 10 mg Placebo	Up to 3.6 years	Placebo, double-blind.
Supportive studies					
AC-055-303[a] (SERAPHIN OL)	Long-term safety of macitentan in patients with PAH	550	Macitentan 10 mg	N/A	Uncontrolled.
AC-055B201 (MUSIC)	Efficacy and safety of macitentan in patients with IPF.	178 randomized	Macitentan 10 mg	12 months (Period 1) + variable duration (Period 2)	Placebo-controlled, double-blind.

N/A = not applicable; IPF = idiopathic pulmonary fibrosis; OL = open-label; PAH = pulmonary arterial hypertension.
[a] Ongoing study.

2.5.1. Dose response studies

No dedicated dose-finding study was conducted in patients with PAH. Instead, the applicant's strategy was to employ PD data on ET-1 levels (see "pharmacodynamics" section) and hemodynamic efficacy data on blood pressure (BP) reduction in patients with mild to moderate essential hypertension to determine the doses to be tested in the Phase 3 clinical outcome study in patients with PAH (SERAPHIN). The underlying assumption was that a dose shown to be efficacious in systemic hypertension would also be hemodynamically effective in PAH, as previously observed with the ERA bosentan (Krum, 1998).

Dose response study AC-055-201: A multi-center, double-blind, randomized, placebo- and active-controlled, parallel group, dose-ranging study to evaluate the efficacy, safety and tolerability of ACT-064992 in subjects with mild-to-moderate essential hypertension.

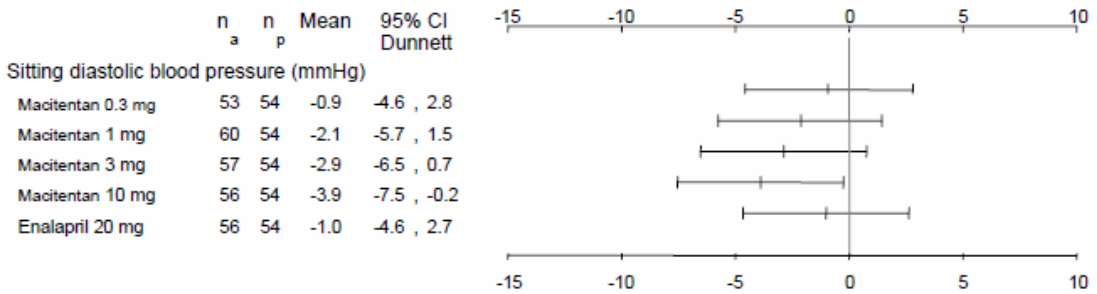
Population and baseline characteristics

A total of 314 subjects were enrolled. The per-protocol set for evaluation of the primary endpoint included placebo (n = 54), macitentan doses 0.3 mg (n = 54), 1 mg (n = 60); 3 mg (n = 57); 10 mg (n = 56) and enalapril (n = 56). Baseline values were balanced between treatment groups; subjects with rather mild hypertension were included (SiDBP at randomization 97.6 ± 2.5 mmHg [mean ± SD]).

Efficacy

Treatment with the 10 mg dose of macitentan was associated with a statistically significant reduction vs placebo in SiDBP at trough (Figure O-E-01). The response to macitentan seemed dose-dependent and most of the BP reduction was reached within 4 weeks of treatment. Secondary and exploratory analyses of control and response rates showed similar treatment effects and trends.

Figure OE-01. Study AC-055-201: Change in sitting diastolic blood pressure from baseline to end of double-blind period (placebo-adjusted).



CI = confidence interval.
Source: D-06.142 Figure 3.

PK/PD results

Pharmacokinetic analysis showed that exposure in terms of C_{trough} to both ACT-064992 and ACT-132557 was dose-proportional over the dose range tested. Pharmacodynamic results showed a pronounced effect on endothelin-1 (ET-1) levels in the 3- and 10-mg ACT-064992 dose groups. When pharmacokinetic (PK) and SiDBP at trough data are included in a mathematical model, the 10 mg dose seemed to be close to the plateau of the pharmacological effect.

Safety

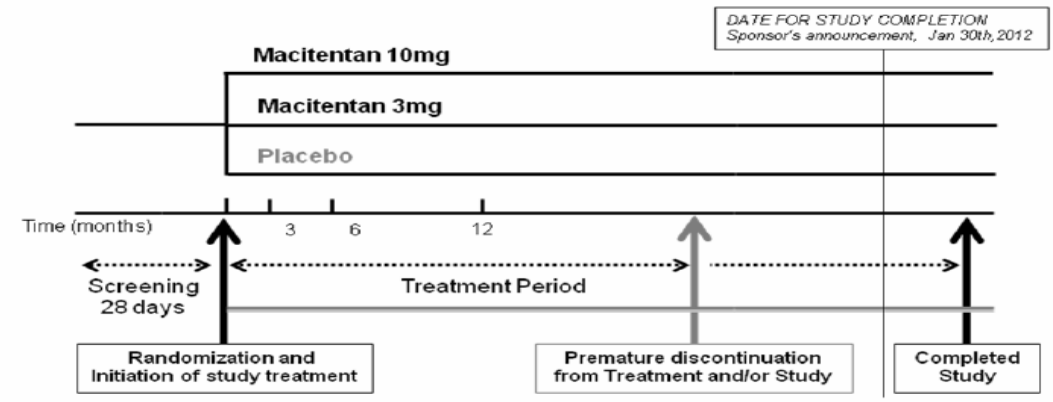
In study AC-055-201 in patients with essential hypertension, there were five cases of increases in liver transaminases >3×ULN, which led to the Sponsor's decision to end the study earlier than planned (see section 4 of current report for further discussion on hepatotoxicity).

2.5.2. Main study

Study AC-055-302 (SERAPHIN; Module 5.3.5.1): Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to improve cliNical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, Phase III study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension.

The clinical evidence based on the results of the efficacy and safety of macitentan in the treatment of patients with PAH is derived from study AC-055-302/SERAPHIN (Table O-E-01). This was a pivotal placebo-controlled, global Phase 3 study, which enrolled 742 patients with symptomatic PAH, randomized in a 1:1:1 ratio to macitentan 3 mg OD, macitentan 10 mg OD, or placebo OD (Figure O-E-03).

Figure O-E-03. SERAPHIN study design.



End of treatment (EOT) is the date of discontinuation from treatment. Patients could discontinue study treatment at any time following randomization. EOT coincided with the end of study for patients who were ongoing on study drug on the date of study completion (30 January 2012 announced by Actelion).

End of study (EOS) is the date of discontinuation from study.

Study completers are patients who were still in the study (alive and available for a visit/to be contacted) on the date of study completion, independent of whether or not the patients had discontinued the study treatment prematurely or had been enrolled into the SERAPHIN open label study following a morbidity event.

The primary objective of the long-term, event-driven SERAPHIN study was to demonstrate that macitentan reduces the risk of morbidity and mortality events during treatment in patients with PAH. The study was conducted in 158 centres in 39 countries, between 25 May 2008 (first patient enrolled) and 15 March 2012 (last patient last visit).

Methods

The study included a screening period (up to 28 days) followed by a treatment period from randomization to the EOT visit. EOS occurred when the target of 285 events confirmed by the Clinical Event Committee (CEC) was expected to have been achieved. The EOT visit either coincided with the EOS visit for patients who were still on double-blind study treatment or occurred earlier in case of premature discontinuation of study drug. Patients were encouraged to remain in the study after EOT up to the EOS visit. Vital status follow-up at EOS was performed for all patients who had not prematurely discontinued from the study (i.e., died, withdrawn consent or had been declared lost to follow-up). Patients who prematurely discontinued study treatment (double-blind) due to worsening of PAH and obtained written approval from Actelion, and patients who completed the study as scheduled, could enter the open-label extension study, SERAPHIN OL. For patients who had opted not to participate or who were not eligible to participate in the open-label extension study, SERAPHIN OL, a 28-day safety follow-up after EOT was performed.

Study Participants

A total of 699 patients were planned to be randomized and 742 patients were actually randomized (1:1:1 ratio) to macitentan 3 mg (250 patients), macitentan 10 mg (242 patients) or placebo (250 patients).

Diagnosis and main criteria for inclusion

Patients aged 12 years or older at study entry, with a confirmed diagnosis of symptomatic PAH in modified WHO FC II to IV were eligible. The PAH aetiology was required to be within groups 1.1 to 1.3 of the Venice classification, i.e., idiopathic PAH, familial PAH, PAH related to collagen vascular disease, PAH associated with simple congenital systemic-to-pulmonary shunts (at least 1 year post surgical repair), HIV infection, or drugs and toxins.

Randomization into the study required a PAH diagnosis confirmed by hemodynamic evaluation showing:

Mean pulmonary artery pressure (mPAP) >25 mmHg

Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤15 mmHg

Pulmonary vascular resistance (PVR) at rest ≥ 320 dyn×sec/cm^5

Patients were required to have a 6-minute walk distance (6MWD) ≥ 50 m at baseline.

Exclusion criteria

There were a total of 23 exclusion criteria. Of interest, patients with PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and, combined and complex systemic-to-pulmonary shunts, corrected or non-corrected, were excluded. The criterion of "PAH associated with congenital heart disease" in the indication was amended to acknowledge that it was limited to "PAH associated with corrected simple congenital heart disease.

Study treatments

Altogether, 742 patients were randomized to macitentan 3 mg, macitentan 10 mg, or matching placebo in a 1:1:1 ratio. Patients received macitentan or placebo tablets OD, in addition to their usual PAH treatment (if applicable and allowed by the protocol).

Patients randomized into the study were either naïve to a PAH-specific treatment or could be undergoing treatment with oral phosphodiesterase inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine, provided that the dose had been stable for at least 3 months prior to randomization. Any change of dose in the absence of PAH worsening was strongly discouraged during the study. Concomitant treatment with oral diuretics was allowed, provided the patient had been on stable dose for at least 1 month prior to randomization. Optimization of the dose of oral diuretics was allowed during the treatment period.

Prohibited concomitant medications

1) ERAs (e.g., bosentan and ambrisentan) unless they were initiated for clinical worsening of PAH and after study drug discontinuation; 2) Intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil) unless they were initiated for a morbidity event; 3) Specific immunosuppressants: calcineurin or mTOR inhibitors (e.g., cyclosporine A and tacrolimus, everolimus, sirolimus); 4) CYP3A inducers (carbamazepine, rifampin, rifabutin and St John's wort); 5) Any investigational drug other than the study drug.

Objectives

The primary objective of the study was to demonstrate that either dose (3 mg or 10 mg) of macitentan reduces the risk of morbidity and mortality in patients with symptomatic PAH.

Secondary objectives of the study were:

To demonstrate that either dose (3 mg or 10 mg) of macitentan improves exercise capacity, WHO functional class (FC), and reduces the risk of death due to PAH or hospitalization for PAH up to end-of-treatment (EOT) in patients with symptomatic PAH.

To demonstrate that either dose (3 mg or 10 mg) of macitentan reduces the risk of death of all causes up to EOT and up to end-of-study (EOS).

To evaluate the safety and tolerability of macitentan in patients with symptomatic PAH.

Outcomes/endpoints

Primary efficacy endpoint

The primary objective of reduction in the risk of a morbidity or mortality event was assessed as the time from start of treatment to the first morbidity or mortality event up to EOT, defined as follows:

Death, or onset of a treatment-emergent adverse event (AE) with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or

Atrial septostomy or hospitalization for atrial septostomy, or

Lung transplantation or hospitalization for lung transplantation, or

Initiation of intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of intravenous or subcutaneous prostanoids, or

Other worsening of PAH, defined by the combined occurrence in a patient of all the following three events:

At least 15% decrease in the 6MWD from baseline, confirmed by two 6-minute walk tests (6MWT), performed on separate days, within 2 weeks of each other.

AND

Worsening of PAH symptoms that included at least one of the following: Increase in WHO FC, or no change in patients in WHO FC IV at baseline; Appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy

AND

Need for new treatment(s) for PAH that included the following: Oral or inhaled prostanoids (e.g., iloprost); Oral phosphodiesterase inhibitors (e.g., sildenafil); Endothelin receptor antagonists (e.g., bosentan, ambrisentan) only after discontinuation of the study treatment; Intravenous diuretics

The observation period for the primary endpoint started with first drug intake and ended at EOT + 7 days. Patients who prematurely discontinued study treatment without a morbidity or mortality event were censored at the time of study treatment discontinuation plus 7 days. Patients without an event at EOS (declared by the sponsor on 30 January 2012) were censored for the primary endpoint at their last visit in the study. An independent clinical event committee (CEC) reviewed all morbidity and mortality events in a blinded fashion and adjudicated (qualified or disqualified) these events for the main analysis of the primary endpoint. Furthermore, the CEC also adjudicated the type of primary endpoint event and confirmed whether a mortality event was due to PAH.

Secondary efficacy endpoints

- Change in 6MWD from baseline to Month 6
- Proportion of patients with improvement in modified WHO FC from baseline to Month 6
- Time to death due to PAH or hospitalization for PAH up to EOT that included (The protocol-defined endpoint was clarified in the Statistical Analysis Plan (SAP) prior to unblinding): Death due to PAH (as identified by CEC) up to EOT + 7 days, or onset of a treatment-emergent AE with a fatal outcome due to PAH occurring up to 4 weeks after EOT, or Hospitalization for PAH up to EOT + 7 days.
- Time to death of all causes up to EOT that included (The protocol-defined endpoint was clarified in the SAP prior to unblinding): Death of all causes up to EOT + 7 days, or onset of a treatment-emergent AE with a fatal outcome occurring up to 4 weeks after EOT (The protocol-defined endpoint was clarified in the Statistical Analysis Plan (SAP) prior to unblinding).
- Time to death of all causes up to EOS (This protocol defined exploratory endpoint was changed to a secondary endpoint in the SAP).

Exploratory endpoints investigated the effects of macitentan on changes in 6MWD, Borg dyspnea index and WHO FC at each assessed time-point, quality of life (QoL), and N-terminal pro-B type natriuretic peptide (NT-pro-BNP) levels.

Pharmacodynamic endpoints investigated the effects of macitentan on changes in PVR, mean right atrial pressure (mRAP), mean pulmonary pressure (mPP), cardiac index (CI), total pulmonary resistance (TPR) and mixed venous oxygen saturation from baseline to Month 6 in a sub-study to the overall protocol.

Pharmacoeconomic endpoints:

Number per year of all-cause and PAH-related hospitalizations from baseline up to EOT; Number per year of in-patient hospital days for all causes and PAH-related causes from baseline up to EOT.

Sample size

The anticipated sample size for this study was 699 patients randomized to treatment using a 1:1:1 ratio. A total of 285 events were needed to detect a hazard ratio for macitentan/placebo of 0.55 for at least one dose group over an estimated maximum study duration of 4.1 years (using

a hazard rate of 0.43 in the placebo group, an expected hazard ratio of 0.05 per year for attrition and an accrual rate of 200 patients per year). For sample size calculations, type-I error was set to 0.005 (two-sided, Bonferroni correction to ensure an overall alpha level of 0.01) and power was set to 90% A planned blinded sample size re-estimation was performed 3 months before the end of expected recruitment which led to a revised expected hazard rate of 0.28 in the placebo group, resulting in the decision to increase the initial planned sample size (n = 525) to 699 to maintain the planned study duration. The planned sample re-sizing had no impact on the results in the primary endpoint and change in 6MWD, according to ancillary analyses provided by the applicant.

Randomisation

Patients who satisfied the eligibility criteria were randomized in a 1:1:1 ratio to receive macitentan (3 mg or 10 mg) or placebo using a centralized randomization system via Interactive Voice Response (IVR) or Interactive Web Response (IWR). An independent service provider was responsible for the central randomization services. A unique 4-digit randomization number was assigned to each patient. Randomization was stratified by centre and the block size used was a combination of 3 and 6. The randomization code was to be unblinded/broken by Actelion GQM and made available for data analysis only after study closure, i.e., when the study was completed, the protocol violations were determined, and the clinical database was declared complete, accurate and locked. The password was requested by an authorized person at Actelion GQM on 23 April 2012 and the randomization code was made available for analysis on 26 April 2012.

Blinding (masking)

This study was performed in a double-blind fashion. The two dose strengths of macitentan and placebo were indistinguishable and all study drug kits were packaged in the same way. The SDAC (Statistical Data Analysis Center) had access to the randomization codes and was responsible for the overall preparation of the data for review by the DSMB and for preparing interim reports for review by the DSMB based on the data generated by Actelion. The investigator and study staff, the patients, the monitors, and Actelion employees and contractors remained blinded to the study drug allocation until the database closure on 26 April 2012.

Statistical methods

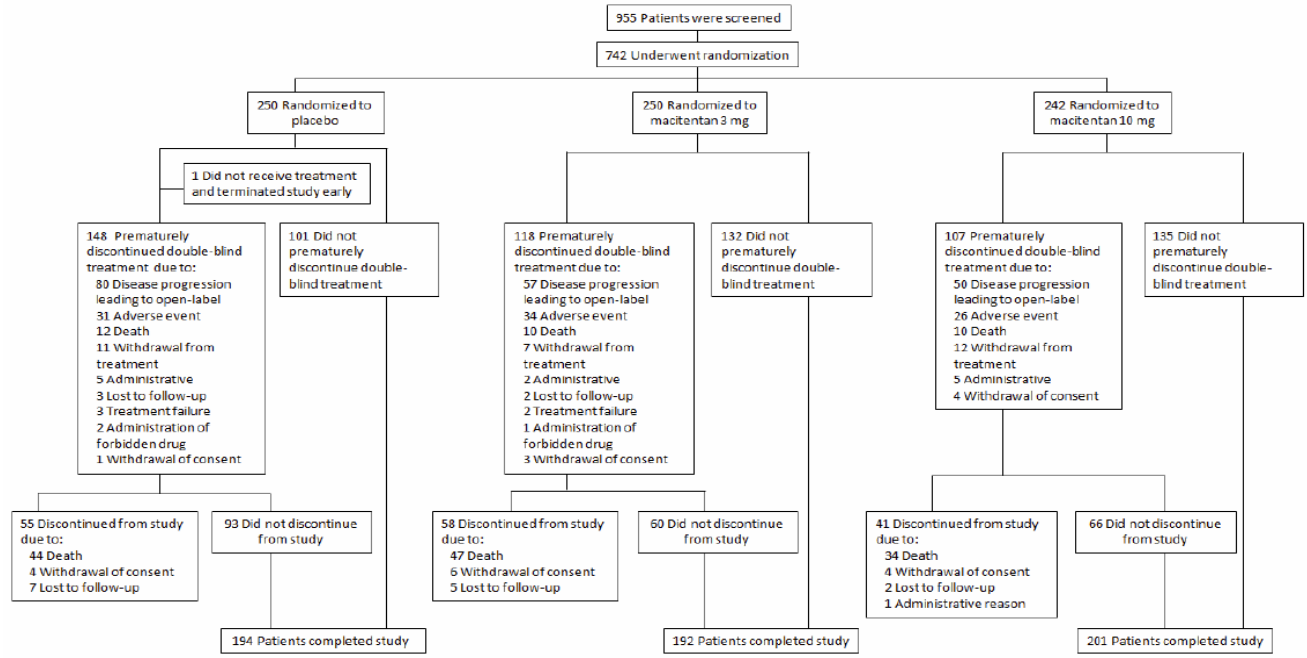
The null hypothesis was that, independently for each dose group of macitentan (3 mg and 10 mg), there was no difference between macitentan and placebo for the risk of first occurrence of a morbidity or mortality event up to EOT (the primary endpoint). To keep the study-wise type-I error to a two-sided 0.01 ‘conclusive’ (and highly statistically significant) level in the presence of multiple tests, each comparison of active dose versus placebo was tested at a nominal type-I error level of 0.005 (two-sided) according to Bonferroni’s approach, with testing starting from the primary endpoint. The study could also be declared ‘positive’ at a global significance level of 0.05 (statistically significant). According to Bonferroni’s approach, the comparison of each active dose versus placebo was to be tested at a nominal type-I error level of 0.025 (two-sided), with testing starting from the primary endpoint. The secondary endpoints were analyzed hierarchically for each dose group in the sequence of change in 6MWD (Wilcoxon rank sum test), change in WHO

FC (Fisher's exact test), time to death or hospitalization due to PAH up to EOT, and time to death of all causes up to EOT and EOS (all logrank test). No further alpha adjustment was necessary for the secondary endpoints due to the hierarchical testing procedure. No confirmatory claims can be based on variables that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected. Efficacy endpoints were analyzed using the All-randomized set (all randomized patients irrespective of whether or not they received study drug). The logrank test with no adjustment for covariates was used to compare the treatment effect of macitentan versus placebo for the primary endpoint. The treatment effect was estimated using Cox's proportional hazard model. All time to event variables were estimated using the Kaplan-Meier method. The exploratory endpoints were analyzed descriptively. Safety data were analyzed descriptively using the All-treated set (all randomized patients who received study drug).

Participant flow

A total of 955 patients were screened from 158 centres in 39 countries and 742 patients from 151 centres in 39 countries were randomized in a 1:1:1 ratio to the macitentan 3 mg (n = 250), macitentan 10 mg (n = 242) and placebo groups (n = 250) (Figure O-E-04). A total of 590 patients (79.5%) completed the study as planned. The proportion of patients who prematurely discontinued the study was 22.4% in the macitentan 3 mg group, 16.9% in the macitentan 10 mg group, and 22.0% in the placebo group. Death was the main reason for patients not being able to complete the study in all three groups (18.8% macitentan 3 mg, 14.0% macitentan 10 mg, 17.6% placebo). Other reasons for premature discontinuation from the study included withdrawal of consent (2.4% macitentan 3 mg, 1.7% macitentan 10 mg, 1.2% placebo) and loss to follow up (1.2% macitentan 3 mg, 0.8% macitentan 10 mg, 2.8% placebo).

Figure O-E-04. Disposition of patients



Premature discontinuation from treatment or EOT is the date of discontinuation from treatment. Patients could discontinue study treatment at any time following randomization. EOT coincided with EOS for patients who were still on study drug on the date of study completion (30 January 2012, announced by Actelion).
Premature discontinuation from study: Patients no longer alive/willing/available to provide vital status following sponsor's announced EOS (30 January 2012, announced by Actelion).
Study completed: Patients from whom vital status could be collected following sponsor-announced EOS independent of an earlier discontinuation from the treatment.

Recruitment

Russia and China were the only countries contributing more than 20 patients per group. There was a significant difference in patient recruitment by region before and after sample size re-sizing. Most patients from Asia and North-America were recruited after sample size re-sizing, while in the remaining regions most patients were recruited before sample size re-sizing.

Conduct of the study

Four protocol amendments were made and the most important was amendment 3 related to increase in sample size (See "sample size" subsection).

Baseline data

A summary of the demographic characteristics for the 'All-randomized set' is provided in Table O-E-02. In general, the demographic characteristics across the three treatment groups were well matched. There was a predominance of females and the median age was approximately 45 years. Approximately 14% of the patients were elderly (age > 65) and 3% were adolescents (12-17 years). Average body mass index (BMI) was approximately 25 kg/m^2. Ethnically, the patients were predominantly Caucasian or Asian, reflecting the fact that the majority were recruited at centres in Europe and Asia.

Table O-E-02. Summary of patient demographics, All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
SEX [n (%)]				
n	249	248	242	739
Males	65 26.1%	61 24.6%	48 19.8%	174 23.5%
Females	184 73.9%	187 75.4%	194 80.2%	565 76.5%
AGE (years)				
n	249	248	242	739
Mean	46.7	44.5	45.5	45.6
Standard deviation	17.03	16.26	14.99	16.13
Standard error	1.08	1.03	0.96	0.59
Median	46.0	43.0	45.0	45.0
Q1 , Q3	32.0 , 61.0	31.0 , 57.0	34.0 , 56.0	33.0 , 58.0
Min , Max	13.0 , 85.0	12.0 , 80.0	13.0 , 76.0	12.0 , 85.0
AGE [n (%)]				
n	249	248	242	739
< 18	7 2.8%	7 2.8%	6 2.5%	20 2.7%
18 - 64	199 79.9%	208 83.9%	209 86.4%	616 83.4%
>= 65	43 17.3%	33 13.3%	27 11.2%	103 13.9%
BMI (kg/m^2)				
n	249	248	242	739
Mean	25.2	25.8	25.6	25.5
Standard deviation	5.11	6.36	6.06	5.86
Standard error	0.32	0.40	0.39	0.22
Median	24.6	24.8	24.4	24.6
Q1 , Q3	21.6 , 28.1	21.2 , 29.6	21.7 , 28.2	21.6 , 28.7
Min , Max	14.9 , 49.0	15.2 , 61.9	15.4 , 52.1	14.9 , 61.9
RACE [n (%)]				
n	249	248	242	739
Caucasian/white	131 52.6%	137 55.2%	135 55.8%	403 54.5%
Black	8 3.2%	5 2.0%	6 2.5%	19 2.6%
Asian	71 28.5%	69 27.8%	65 26.9%	205 27.7%
Hispanic	37 14.9%	37 14.9%	35 14.5%	109 14.7%
Other	2 0.8%	-	1 0.4%	3 0.4%
LOCATION [n (%)]				
n	249	248	242	739
US	23 9.2%	25 10.1%	19 7.9%	67 9.1%
Non-US	226 90.8%	223 89.9%	223 92.1%	672 90.9%
REGION [n (%)]				
n	249	248	242	739
North America	30 12.0%	30 12.1%	23 9.5%	83 11.2%
Western Europe/Israel	50 20.1%	41 16.5%	48 19.8%	139 18.8%
Eastern Europe/Turkey	59 23.7%	63 25.4%	62 25.6%	184 24.9%
Asia	68 27.3%	70 28.2%	68 28.1%	206 27.9%
Latin America	42 16.9%	44 17.7%	41 16.9%	127 17.2%

Source: Table 62

The mean time from PAH diagnosis to randomization in the study population was 2.7 years (Table O-E-03). Idiopathic PAH was the most common aetiology (55%) followed by PAH due to collagen vascular disease (30%) and PAH due to congenital shunts (8%). It is worth mentioning that the term “congenital shunts” corresponds to PAH associated to corrected simple congenital systemic-to-pulmonary shunts, since patients with PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and combined and complex systemic-to-pulmonary shunts were excluded. . In the indication this subpopulation was limited to “PAH associated with corrected simple congenital heart disease”. Familial (heritable) PAH and PAH due to HIV infection and drugs and toxins represented 3% or less.

Table O-E-03. Summary of baseline characteristics, All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
Time from PAH diagnosis (days)				
n	247	247	241	735
Mean	942	1079	951	991
Standard deviation	1362.0	1659.1	1325.1	1456.9
Standard error	86.7	105.6	85.4	53.7
Median	460	425	476	462
Q1 , Q3	180 , 1279	178 , 1230	174 , 1090	178 , 1225
Min , Max	6 , 13267	1 , 11957	2 , 10199	1 , 13267
Etiology of PAH [n (%)]				
n	247	247	241	735
Idiopathic	126 51.0%	144 58.3%	134 55.6%	404 55.0%
Familial	3 1.2%	8 3.2%	2 0.8%	13 1.8%
Collagen vascular disease	81 32.8%	70 28.3%	73 30.3%	224 30.5%
Congenital shunts	26 10.5%	15 6.1%	21 8.7%	62 8.4%
HIV infection	3 1.2%	1 0.4%	6 2.5%	10 1.4%
Drugs and toxins	8 3.2%	9 3.6%	5 2.1%	22 3.0%
6mn Walk Test (m) (absolute)				
n	249	248	242	739
Mean	352.4	364.1	362.6	359.6
Standard deviation	110.62	95.52	93.21	100.15
Standard error	7.01	6.07	5.99	3.68
Median	360.0	378.0	378.0	372.0
Q1 , Q3	284.0 , 428.0	311.0 , 425.0	300.0 , 434.0	300.0 , 430.0
Min , Max	65.0 , 650.0	80.0 , 610.0	90.0 , 578.0	65.0 , 650.0
Signs of right heart failure [n (%)]				
n	249	248	242	739
Patients with at least one sign	78 31.3%	76 30.6%	76 31.4%	230 31.1%
Hepatomegaly	25 10.0%	29 11.7%	26 10.7%	80 10.8%
Ascites	6 2.4%	2 0.8%	3 1.2%	11 1.5%
Peripheral edema	34 13.7%	43 17.3%	43 17.8%	120 16.2%
S3 gallop	12 4.8%	7 2.8%	8 3.3%	27 3.7%
Hepato-jugular reflux	12 4.8%	16 6.5%	15 6.2%	43 5.8%
Central venous pressure >8 mmHg	23 9.2%	27 10.9%	23 9.5%	73 9.9%
Other	16 6.4%	14 5.6%	14 5.8%	44 6.0%
WHO functional class [n (%)]				
n	249	248	242	739
I	-	-	1 0.4%	1 0.1%
II	129 51.8%	138 55.6%	120 49.6%	387 52.4%
III	116 46.6%	105 42.3%	116 47.9%	337 45.6%
IV	4 1.6%	5 2.0%	5 2.1%	14 1.9%
Concomitant PAH therapy [n (%)]				
n	249	248	242	739
No	95 38.2%	85 34.3%	88 36.4%	268 36.3%
Yes	154 61.8%	163 65.7%	154 63.6%	471 63.7%
Sildenafil	140 56.2%	146 58.9%	140 57.9%	426 57.6%
Tadalafil	2 0.8%	3 1.2%	2 0.8%	7 0.9%
Vardenafil	8 3.2%	5 2.0%	8 3.3%	21 2.8%
Iloprost	3 1.2%	13 5.2%	10 4.1%	26 3.5%
Beraprost	4 1.6%	5 2.0%	6 2.5%	15 2.0%
Treprostinil	-	1 0.4%	-	1 0.1%

Source: Table 67

Baseline mean 6MWD was approximately 360 m. The mean Borg dyspnoea index at baseline was approximately 3.5 across the groups (Table E-03). At baseline, approximately 52% of patients were in WHO FC II and 46% of patients were in WHO FC III, with only 14 patients (2%) in WHO FC IV (Table O-E-03). During the procedure, patients in WHO FC IV were removed from the indication due to the very limited data available.

At least one sign of right heart failure was reported for approximately 31% of patients at baseline (Table E-03). Ancillary analyses of the primary and main secondary outcome in the population with heart failure were consistent with the results in the overall study population.

Results

All 742 patients were included in the 'All-randomized set'. One patient in the placebo group never received study treatment and therefore, a total of 741 patients were included in the 'All-treated set'. The 'Per-protocol set' included 675 of the randomized patients (91%) with a total of 67 patients (9%) excluded from this set.

Premature discontinuations from treatment

Of the 741 patients in the 'All-treated set', 373 (50.3%) discontinued study treatment prematurely (Table E-05). The proportion of patients who discontinued study treatment was 47.2% in the macitentan 3 mg group, 44.2% in the macitentan 10 mg group, and 59.4% in the

placebo group. Disease progression followed by enrolment in the SERAPHIN OL was the most frequent reason for discontinuation of study treatment in all three groups (22.8% macitentan 3 mg, 20.7% macitentan 10 mg, 32.1% placebo). An AE led to discontinuation of study treatment in 13.6% macitentan 3 mg, 10.7% macitentan 10 mg, and 12.4% placebo. These AEs included disease progression (without subsequent enrolment into the SERAPHIN OL study) in 6.8% of patients in the macitentan 3 mg group, 3.7% of patients in the macitentan 10 mg group, and 8.0% of patients in the placebo group. Other reasons included death, withdrawal from treatment (i.e., permanent discontinuation of study treatment, but with the patient's agreement to be contacted at EOS to check vital status), withdrawal of consent and administrative reasons.

Table O-E-04. Summary of reasons for discontinuation of treatment, All-treated set.

Preferred term *	Placebo N=249 No.	%	Macitentan 3 mg N=250 No.	%	Macitentan 10 mg N=242 No.	%
Total patients with at least one reason	148	59.4%	118	47.2%	107	44.2%
DISEASE PROGRESSION LEADING TO OL*	80	32.1%	57	22.8%	50	20.7%
ADVERSE EVENT	31	12.4%	34	13.6%	26	10.7%
DISEASE PROGRESSION NOT LEADING TO OL**[1]	20	8.0%	17	6.8%	9	3.7%
DEATH	12	4.8%	10	4.0%	10	4.1%
WITHDRAWAL FROM TREATMENT	11	4.4%	7	2.8%	12	5.0%
ADMINISTRATIVE/OTHER	5	2.0%	2	0.8%	5	2.1%
WITHDRAWAL OF CONSENT	1	0.4%	3	1.2%	4	1.7%
LOST TO FOLLOW-UP	3	1.2%	2	0.8%	-	
TREATMENT FAILURE	3	1.2%	2	0.8%	-	
ADMINISTRATION OF FORBIDDEN DRUG	2	0.8%	1	0.4%	-	

* Enrolment into the Open Label study following a morbidity event
**Patients who terminated the treatment due to a mortality/morbidity event
1 Disease progression not leading to OL is a component of adverse events leading to discontinuation
Table PWTS_T - Produced by sturlor on 26APR12 - Data dump of 26APR12
(Page 1/1)

Missing data for mortality after EoT

A total of 27 patients did not complete the study and therefore vital status was missing at EOS, i.e., lost to follow-up, etc.). Missing data were well balanced by treatment group. The results of the sensitivity analyses using the Best-case, Base-case and Worst-case scenarios were similar to that of the primary analysis for the time to death up to EOS, with risk reductions ranging from 33% to 16% across all analyses (none of them statistically significant). The primary analysis risk reduction of 23% falls within that range.

Protocol violations

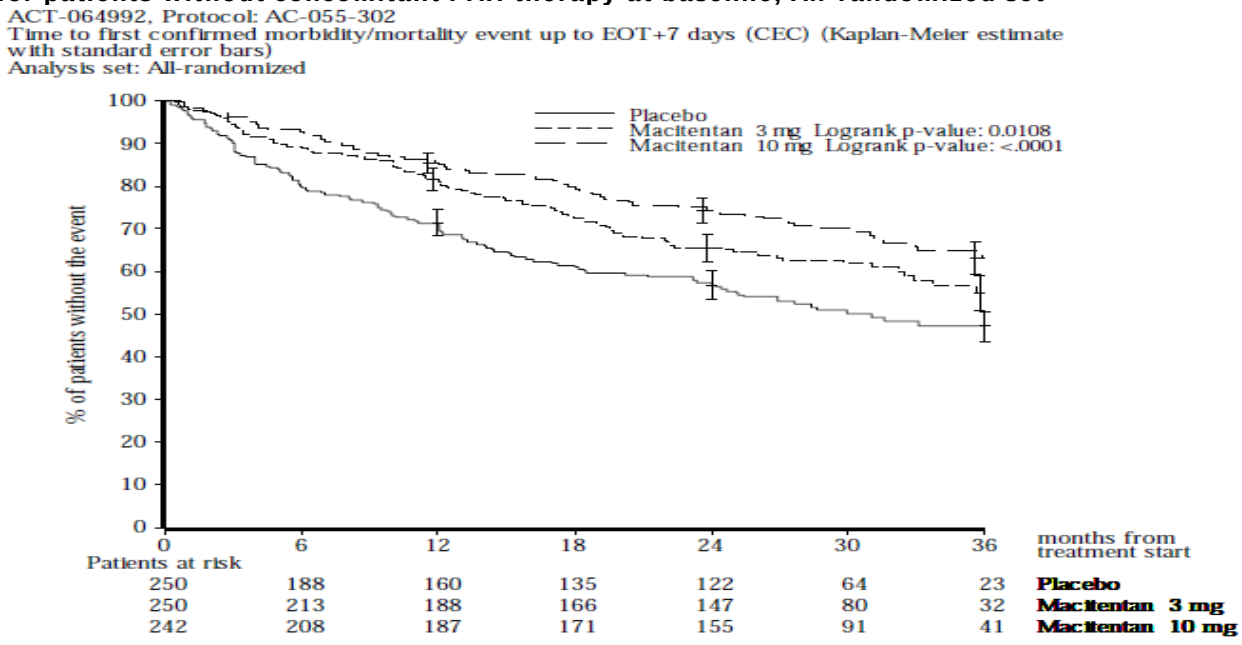
A total of 67 randomized patients (9%) were excluded from the 'per-protocol set' due to major protocol deviations. Overall, the proportion of patients with major protocol deviations was similar across the groups (9.2% macitentan 3 mg, 9.1% macitentan 10 mg, 8.8% placebo). Introduction of a new treatment for PAH or a change in treatment dose without documented disease worsening were the most common deviations in all groups (4.8% macitentan 3 mg, 4.5% macitentan 10 mg, 3.6% placebo).

Outcomes and estimation

Primary endpoint:

A confirmed primary endpoint event was recorded for 95 patients and 76 patients in the macitentan 3 mg and 10 mg groups, respectively, versus 116 patients in the placebo group (EOT + 7 days) (Figure E-05). In the time-to-event analysis, the hazard ratio versus placebo for the occurrence of the primary endpoint in the macitentan 3 mg group was 0.704 (97.5% CLs 0.516, 0.960, logrank p = 0.0108) (Figure E-05). In the macitentan 10 mg dose group, the effect versus placebo was highly statistically significant as measured by the hazard ratio of 0.547 (97.5% CLs 0.392, 0.762, logrank p < 0.0001). For the 10 mg dose it corresponded to an overall relative risk reduction of 45% and a number-needed-to-treat (NNT) of 6 patients (95% CLs 4.48, 10.80) to avoid one event at 2 years. The Kaplan-Meier curves of the first event in the 'All-randomized set' are shown in Figure 3. The separation between macitentan groups and placebo appeared early and was clearly established at 6 months (Kaplan-Meier estimates of primary endpoint event-free rate 89.3% macitentan 3 mg group, 92.7% macitentan 10 mg group, 80.1% placebo group). The treatment effect of macitentan was sustained for the duration of the study: at all time-points, the proportion of patients who had not experienced a morbidity or mortality event was greater in the macitentan 3 mg and 10 mg groups than in the placebo group.

Figure O-E-05. Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events for patients without concomitant PAH therapy at baseline, All-randomized set



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
Statistical tests are performed including all data available during the follow-up period.
Figure MMTBG_A - Produced by sturlor on 29MAY12 - Data dump of 26APR12

Treatment difference vs. placebo	Macitentan 3 mg	Macitentan 10 mg
Hazard ratio	0.704	0.547
97.5% CL of hazard ratio	0.516, 0.960	0.392, 0.762
Logrank p-value	0.0108	<.0001

Components of the primary endpoint events

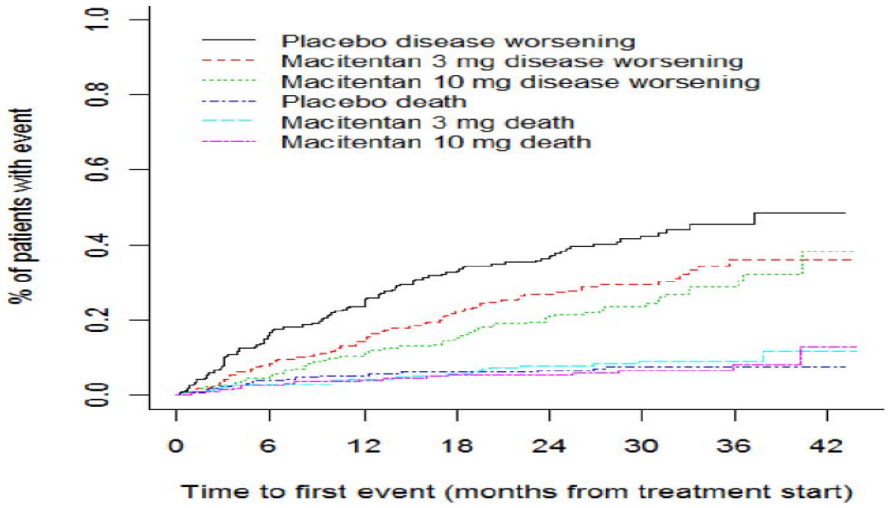
The most frequently first-reported CEC-confirmed event was "Other worsening of PAH" (Table OE-06). The proportion of patients with "Other worsening of PAH" was 28.8% in the macitentan 3 mg group and 24.4% in the macitentan 10 mg group, compared to 37.2% in the placebo group. The proportion of patients with death as the first event was 8.4% (21 patients) in the macitentan 3 mg group, 6.6% (16 patients) in the macitentan 10 mg group, and 6.8% (17 patients) in the placebo group, questioning any claim for a mortality benefit with macitentan. This is further confirmed in the competing risk analysis (fig OE-06).

Table O-E-06. Summary of components of primary endpoint events (CEC-confirmed), All-randomized set

	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total PATIENTS with at least one confirmed event	116	46.4%	95	38.0%	76	31.4%
First confirmed event						
WORSENING OF PAH*	93	37.2%	72	28.8%	59	24.4%
DEATH	17	6.8%	21	8.4%	16	6.6%
IV/SC PROSTANOID INITIATION	6	2.4%	1	0.4%	1	0.4%
LUNG TRANSPLANTATION	-		1	0.4%	-	

* Corresponds to 'Other worsening of PAH'
Events confirmed by Independent CEC.
CEC = Clinical Event Committee; EOT = End of treatment; IV = intravenous; PAH = pulmonary arterial hypertension; SC = subcutaneous.
Source: Appendix 2, table 8.

Figure OE-06. Cumulative incidence functions for the first confirmed morbidity or mortality event up to EOT+7 d (CEC), All-randomized set



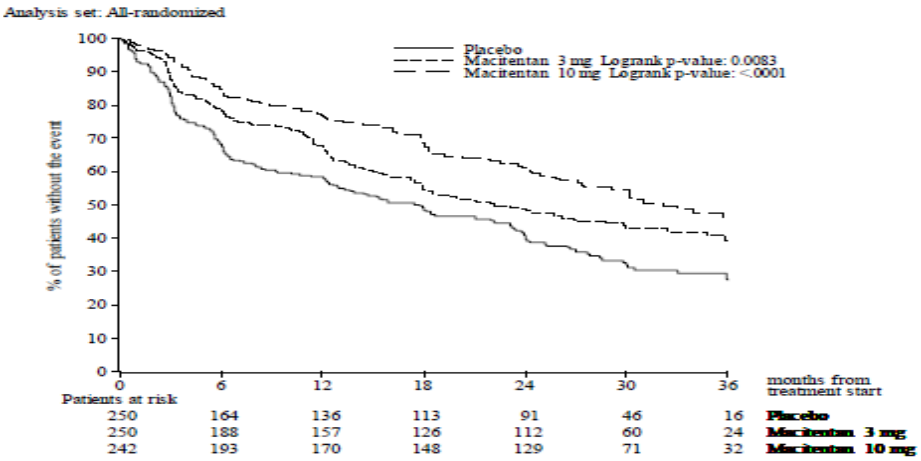
Results of sensitivity analyses for the primary endpoint, based on variation of the endpoint definition and/or population analyzed, supported those of the main analysis. In particular, results

of the analyses for time to first event and the risk reduction with macitentan, using the CHMP-defined morbidity/mortality event, were consistent with the results of the primary analysis of the SERAPHIN study. In the time-to-event analysis, the HR versus placebo for the occurrence of a CHMP-defined event in the macitentan 10 mg dose group was 0.550 (97.5%CI: 0.417, 0.725; logrank p<0.0001). In the macitentan 3 mg group was 0.737 (97.5% CI: 0.568, 0.956; p=0.0083). The corresponding relative risk reductions versus placebo were 45% and 26%, respectively.

Table OE-07. Summary of causes of CHMP defined events up to EOT+7 d, All-randomised set

	Placebo n = 250		Macitentan 3 mg n = 250		Macitentan 10 mg n = 242	
	n	%	n	%	n	%
Total PATIENTS with ≥ 1 CHMP defined event	163	65.2	137	54.8	113	46.7
First CHMP defined event						
PAH related hospitalisation	26	10.4	20	8.0	19	7.9
Death	13	5.2	14	5.6	9	3.7
Decrease of ≥ 15% in 6MWT from baseline	28	11.2	24	9.6	20	8.3
Worsening of WHO FC from baseline	21	8.4	12	4.8	13	5.4
Signs or symptoms of right-sided heart failure	75	30.0	67	26.8	52	21.5
Total NUMBER of CHMP defined events†	472		369		301	
PAH related hospitalisation	94	19.9	67	18.2	57	18.9
Death	19	4.0	21	5.7	14	4.7
Decrease of ≥ 15% in 6MWT from baseline	121	25.6	101	27.4	82	27.2
Worsening of WHO FC from baseline	112	23.7	79	21.4	68	22.6
Signs or symptoms of right-sided heart failure	126	26.7	101	27.4	80	26.6

Figure OE-07. K-M curves of the first CHMP defined event up to EOT+7 d, All-randomised set

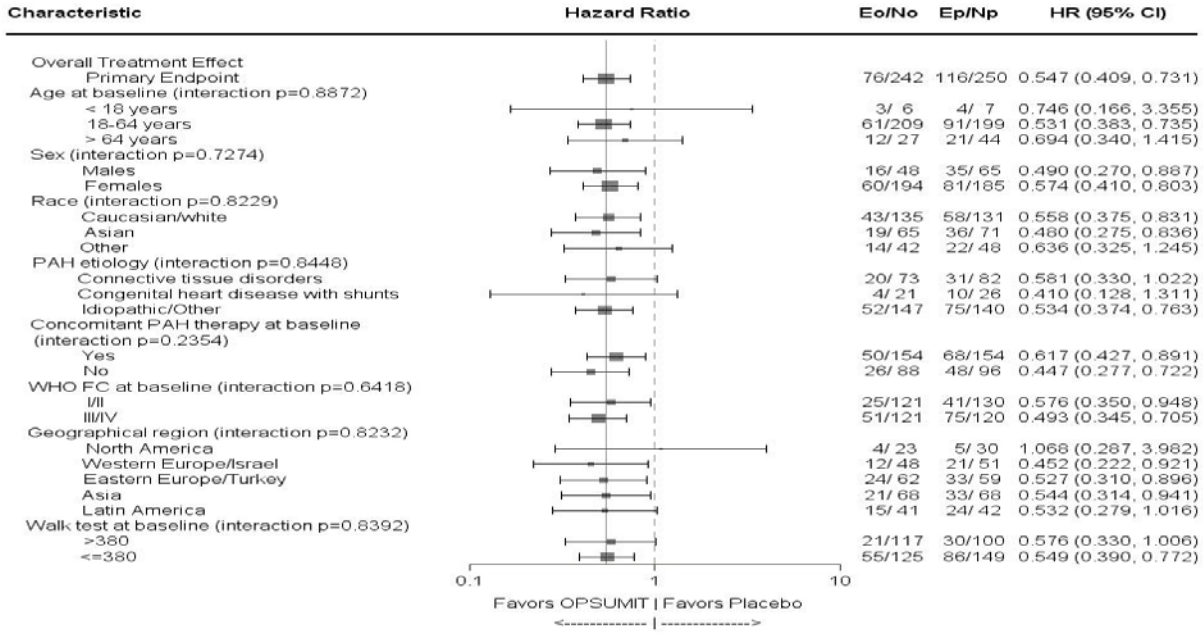


The treatment effects adjusted for covariates (sex, region, race, PAH therapy at baseline, PAH etiology and WHO FC at baseline) of both macitentan dose groups were consistent with the unadjusted results of the main analysis.

Subgroup analyses

The p-values for the statistical test of interaction did not formally show heterogeneity of the treatment effect (macitentan versus placebo) for any of the subgroup analyses. The point estimate was above 1 only in North-America, but the confidence limits were wide due to the low sample size in that region.

Figure O-E-08. Occurrence of the first morbidity or mortality event (CEC-confirmed) up to EOT + 7 days by subgroups (macitentan 10 mg versus placebo), All-randomized set



Paediatric patients

There was limited recruitment of paediatric patients in SERAPHIN (n=20), which could be expected in an orphan indication. However, unlike the adult population, 70% of the patients discontinued the medication because of disease progression. It is difficult to comment further on the efficacy data considering this high drop-out rate, but the results do not point to any benefit compared to the placebo. In line with the efficacy data, reported safety data concern worsening of PAH and right ventricular failure. The SmPC has been amended to acknowledge that the safety and efficacy of macitentan in children have not yet been established.

Right heart failure

A 43.7% of the patients enrolled in the SERAPHIN study met the criteria of right heart failure at baseline. Post-hoc analyses in this subgroup are consistent with those in the overall SERAPHIN population. The findings do not indicate that a potential increase in fluid retention would offset or impact negatively on the benefit of macitentan on morbidity/mortality in this population.

Main secondary endpoint: change in 6MWD from baseline to month 6.

The placebo-corrected median change in 6MWD from baseline to Month 6 showed similar treatment effects versus placebo in the macitentan 3 mg (14.0 m, 97.5% CLs 2.0, 27.0, Wilcoxon rank sum p = 0.0122) and macitentan 10 mg groups (15.0 m, 97.5% CLs 2.0, 28.0, Wilcoxon rank sum p = 0.0078) (Table OE-07). The corresponding mean (± standard deviation [SD]) treatment effect was 16.8 m (± 96.95) in the macitentan 3 mg group and 22.0 m (± 92.58) in the macitentan 10 mg group.

Table OE-08. Change from baseline in walk distance to Month 6, All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Use of supplemental oxygen during baseline walk test			
n	249	248	242
Yes	18 7.2%	21 8.5%	8 3.3%
No	231 92.8%	227 91.5%	234 96.7%
Baseline			
n	249	248	242
Mean	352	364	363
Standard deviation	110.6	95.5	93.2
Median	360	378	378
Q1 , Q3	284 , 428	311 , 425	300 , 434
Min , Max	65 , 650	80 , 610	90 , 578
Month 6			
n	249	248	242
Mean	343	371	375
Standard deviation	146.5	124.1	114.7
Median	365	394	390
Q1 , Q3	268 , 447	317 , 450	333 , 445
Min , Max	0 , 657	0 , 615	0 , 595
Imputations for missing values			
n	249	248	242
Total imputed at Month 6	52 20.9%	32 12.9%	30 12.4%
With an event (not death)			
Worst value	5 2.0%	2 0.8%	-
Carry-forward	23 9.2%	12 4.8%	10 4.1%
With an event (death only)			
Worst value	9 3.6%	6 2.4%	4 1.7%
Without an event			
Carry-forward (baseline)	7 2.8%	2 0.8%	10 4.1%
Carry-forward (not baseline)	8 3.2%	10 4.0%	6 2.5%
Change from baseline			
n	249	248	242
Mean	-9.4	7.4	12.5
Standard deviation	100.59	93.15	83.54
Median	1.0	17.0	15.5
Q1 , Q3	-42.0 , 44.0	-15.0 , 50.0	-14.0 , 51.0
Min , Max	-380.0 , 292.0	-465.0 , 258.0	-423.0 , 247.0
TREATMENT EFFECT			
Mean		16.8	22.0
Standard deviation		96.95	92.58
Standard error		8.70	8.36
97.5% CL of mean		-2.7 , 36.4	3.2 , 40.8
Median		14.0	15.0
97.5% CL of median		2.0 , 27.0	2.0 , 28.0
p-value Wilcoxon rank sum		0.0122	0.0078

Table WTS_A - Produced by sturlor on 26APR12 - Data dump of 26APR12, (Page 1/1)
CL = confidence limit.

Change in 6MWD across subgroups

Examination of 6MWD in WHO FC I/II and WHO FC III/IV patients shows that the treatment effects with macitentan were comparable to those observed in other studies with WHO FC II patient population [Galiè 2008] or a WHO FC III/IV patient population [Rubin 2002]. It also appears that macitentan provides symptomatic benefit when used concomitantly with PAH background medications. These findings differ from the experience gained from earlier clinical trials (PHIRST, EARLY, PACES and TRIUMPH), but are similar to those recently published PATENT-1 study (riociguat). Some imbalances in the geographic areas and aetiologies between the treatment naïve patients and patients on background PAH therapy could be the cause of such observation, but no definitive conclusions can be drawn.

Death-related secondary and exploratory analyses

Results of the secondary and exploratory analyses of SERAPHIN in which mortality was either a component of the endpoint or the endpoint itself are presented in Table O-E-08. With macitentan 10 mg, the risk reductions versus placebo in death or hospitalization due to PAH up to EOT + 7 days were up to 50% and statistically significant, while the reduction with macitentan 3 mg was 33%. A similar trend was seen for all cause death and death due to PAH for the 10 mg dose, but none of the comparisons was statistically significant. There was a neutral effect of the macitentan

3 mg dose versus placebo on mortality (Table O-E-09). The relative risk reduction in death-related endpoints was generally smaller for the entire study period compared to the period of analysis for the primary endpoint that covers the treatment phase only. This can be explained by the transition of the majority of placebo patients who experienced a non-fatal primary endpoint event in SERAPHIN to alternative therapies, including treatment with macitentan 10 mg in the SERAPHIN OL study. However, despite the small overall number of deaths irrespective of the length of the observation period, the observed positive effect of macitentan 10 mg on survival was consistent. These findings also illustrate the difficulties in conducting survival studies in PAH, as patients experiencing a worsening of PAH primary events cannot be left untreated. With a median post-event survival of over two years, an adequately powered survival study would require more than 3500 patients, which is not feasible in rare disease like PAH.

Table O-E-09. Results of the death-related endpoints of SERAPHIN, All-randomized set

Endpoint	Period of assessment	Placebo	Macitentan 3 mg	Macitentan 10 mg
Death due to PAH or hospitalization for PAH	**up to EOT + 7 days**	n = 84	n = 65	n = 50
Hazard ratio vs placebo (97.5% CLs),			0.669 (0.462, 0.970)	0.500 (0.335, 0.747)
logrank p-value			p = 0.0146	p < 0.0001
Relative risk reduction			33%	50%
Death due to PAH	**up to EOT + 7 days**	n = 14	n = 14	n = 7
Hazard ratio (97.5% CLs),			0.872 (0.373, 2.037)	0.441 (0.156, 1.248)
logrank p-value			p = 0.7180	p = 0.0699
Relative risk reduction			13%	56%
Death due to PAH	**up to EOS**	n = 28	n = 30	n = 26
Hazard ratio (97.5% CLs),			1.050 (0.583, 1.893)	0.901 (0.489, 1.660)
logrank p-value			p = 0.8514	p = 0.7027
Relative risk reduction			0%	10%
Death (all causes)	**up to EOT + 7 days**	n = 19	n = 21	n = 14
Hazard ratio (97.5% CLs),			0.971 (0.477, 1.976)	0.638 (0.287, 1.418)
logrank p-value			p = 0.9249	p = 0.2037
Relative risk reduction			3%	36%
Death (all causes)	**up to EOS**	n = 44	n = 47	n = 35
Hazard ratio (97.5% CLs),			1.046 (0.653, 1.673)	0.771 (0.464, 1.282)
logrank p-value			p = 0.8312	p = 0.2509
Relative risk reduction			0%	23%

Source: Appendix 2, table 15; Appendix 2, table 16; Appendix 2, figure 3; Appendix 2, table 17; Appendix 2, figure 4; Appendix 2, table 18; Appendix 2, table 19; Appendix 2, figure 5; Appendix 2, table 20; Appendix 2, table 21; Appendix 2, table 22; Appendix 2, figure 6; Appendix 2, table 23; and Figure 10.
CL = confidence limit; EOS = end of study; EOT = end of treatment; PAH = pulmonary arterial hypertension.

The applicant also conducted landmark analyses to show that in SERAPHIN, a morbidity event, as defined in the SERAPHIN study protocol, was a significant risk factor for subsequent death. Although the mortality results are not inconsistent with those of the main composite endpoint, the point estimate tends to be of a lesser magnitude than that of the composite endpoint (mainly driven by worsening of PAH), and statistical significance is not achieved for mortality.

Other endpoints of clinical relevance

Change in WHO FC

Improvements in WHO FC from baseline to Month 6 were reported for 19.8% of patients in the macitentan 3 mg group and 22.3% of patients in the macitentan 10 mg group, compared to

12.9% of patients in the placebo group. This translates into a 54% higher chance of WHO FC improvement relative to placebo for patients in the 3 mg dose group (relative risk 1.54, 97.5% CLs 0.96, 2.46, p = 0.0395) and a 74% higher chance of WHO FC improvement relative to placebo in patients in the 10 mg dose group (relative risk 1.74, 97.5% CLs 1.10, 2.74, p = 0.0063).

Borg dyspnoea index The estimated treatment effect over 12 months compared to placebo was – 0.47 (95% CLs – 0.72, – 0.22, p = 0.0002) for macitentan 3 mg and – 0.38 (95% CLs –0.63, – 0.13, p = 0.0029) for macitentan 10 mg (a negative difference favours macitentan).

Change in N-terminal pro-B type natriuretic peptide (NT-pro-BNP) from baseline to Month 6

The median change versus placebo in NT-pro-BNP (a biomarker predicting right ventricular overload) from baseline to Month 6 was –130 fmol/mL (97.5% CLs –202, –65) with macitentan 3 mg and –160 fmol/mL (97.5% CLs –235, –95) with macitentan 10 mg. The applicant compared NT-proBNP levels within the SERAPHIN study. Higher baseline and higher absolute values at Month 6 were associated with a higher risk of morbidity and mortality, however no prognostic value of change from baseline was observed.

Effect on quality of life

The normalized treatment effect (vs placebo) on the mean change from baseline to Month 6 was significantly in favour of macitentan (both doses) in the scores of the individual domains (norm-based) of physical functioning, role physical, pain index, vitality, social functioning, role emotional, mental health index, physical and mental component summary scores, with mean score improvements ranging between 2.6 to 3.8.

Effect of macitentan on hospitalizations

Treatment with macitentan reduces the number of hospitalizations and days in hospital by approximately 50%.

Effect of macitentan on hemodynamics: Hemodynamic endpoints (change in PVR and CI from baseline to Month 6) were analyzed in a sub-set of the SERAPHIN population who participated in the PK/PD sub-study (n = 187). Macitentan was associated with a treatment effect on pulmonary hemodynamics compared to placebo, which was of a magnitude similar to that observed with other ERAs treatments for PAH. There was no clear difference between the 3 mg and 10 mg doses on any of the hemodynamic variables collected in the overall population. The applicant explained that in treatment-naïve patients administered macitentan, a dose response can be demonstrated on PVR and to a lesser extent on CI. This is in line with observations made with ambrisentan and sildenafil. However such dose response is not observed in patients already on PAH therapy.

Summary of main efficacy results

The following table summarises 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 O-E-10. Summary of efficacy for SERAPHIN trial

Title: Study with **E**ndothelin **R**eceptor **A**ntagonist in **P**ulmonary arterial **Hy**pertension to improve cli**N**ical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, Phase III study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension.				
Study identifier	**AC-055-302 (SERAPHIN; Module 5.3.5.1)**			
Design	multicenter, double-blind, placebo-controlled, parallel-group, event-driven, Phase 3 study			
	Duration of main phase:		EOT: approximately 3.8 years*	
	Duration of Run-in phase:		Screening period up to 28 days	
	Duration of Extension phase:		28-day safety follow-up or inclusion in the open-label (OL) extension (SERAPHIN OL)	
Hypothesis	Superiority			
Treatments groups	Macitentan 10 mg, OD		N=242	
	Macitentan 3 mg, OD		N=250	
	Placebo		N=250	
Endpoints and definitions	Primary endpoint	the time to the first morbidity or mortality event up to EOT	- Death, or onset of a treatment-emergent adverse event (AE) with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or - Atrial septostomy or hospitalization for atrial septostomy, or - Lung transplantation or hospitalization for lung transplantation, or - Initiation of intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of intravenous or subcutaneous prostanoids, or - Other worsening of PAH	
	Main secondary endpoint	6MWD	Change in 6MWD from baseline to Month 6	
Database lock	26-April-2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (All-randomized set: all randomized patients irrespective of whether or not they received study drug)			
Descriptive statistics and estimate variability	Treatment group	Macitentan 10 mg	Macitentan 3 mg	Placebo
	Number of subject	N=242	N=250	N=250
	Patients with at least one confirmed event (PAH morbidity or mortality)	76 (31.4%)	95 (38%)	116 (46.4%)
	Number of subject	N=242	N=248	N=249
	Mean (±SD) change from baseline in 6MWD	12.5 ± 83.54 m	7.4 ± 93.15	-9.4 ± 100.59
Effect estimate per comparison	Primary endpoint	Comparison groups	Macitentan 10 mg vs placebo	
		Hazard ratio Kaplan-Meier - Logrank test	0.547	
		97.5% CL	0.392 to 0.762	
		P-value	<0.0001	

	Primary endpoint	Comparison groups	Macitentan 3 mg vs placebo
		Hazard ratio Kaplan-Meier - Logrank test	0.704
		97.5% CL	0.516 to 0.960
		P-value	0.0108
Effect estimate per comparison	Main secondary endpoint	Comparison groups	Macitentan 10 mg vs placebo
		Mean Wilcoxon rank sum	22.0 m
		97.5% CL of mean	3.2 to 40.8 m
		P-value	0.0078
	Main secondary endpoint	Comparison groups	Macitentan 3 mg vs placebo
		Mean Wilcoxon rank sum	16.8 m
		97.5% CL of mean	-2.7 to 36.4 m
		P-value	0.0122

CL = confidence limits; EoT = end of treatment (Patients could discontinue study treatment at any time following randomization. EOT coincided with end of study for patients who were still on study drug on the date of study completion: 30 January 2012, announced by Actelion); HR = hazard ratio;
*From first patient, first visit (25 May 2008) to last patient, last visit (15 March 2012)

Clinical studies in special populations

Not applicable (see previous section for subgroup analyses).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on the results of a single, long-term, double-blind pivotal Phase 3 study, AC-055-302/SERAPHIN. The pivotal study included a clinically relevant primary endpoint (time to clinical worsening or time to first morbidity or mortality event).

SERAPHIN is the largest study conducted so far in PAH (n=742) and included a wide population of PAH patients (n=742) with different ages, aetiologies, FC and background medications. However, some populations were under-represented. There was limited recruitment of paediatric patients in SERAPHIN (n=20). Unlike the adult population, 70% of the paediatric patients discontinued the medication because of disease progression, which do not support the use of macitentan in children.

Almost all patients were in WHO FC II-III, while only 1 patient was in FC I and only 14 patients were in FC IV. As a result, patients on FC I and IV have been removed from the indication due to the very limited data available. Idiopathic PAH was the most common aetiology (55%) followed by PAH due to connective tissue (30%) and PAH due to congenital shunts (8%). This latter subpopulation only included PAH associated to corrected simple congenital systemic-to-pulmonary shunts, since patients with PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and combined and complex systemic-to-pulmonary shunts were excluded. Therefore, “PAH due to congenital shunts” has been excluded from the indication initially applied for.

At baseline, the majority (approximately 64%) of patients were receiving at least one background PAH therapy at baseline. Sildenafil was the most common PAH therapy and was taken by approximately 58% of patients across the groups.

The patients were predominantly Caucasian (54.5%) or Asian (27.7%), reflecting the fact that the majority of patients were recruited at centres in Europe and Asia. Approximately 43.7% of the patients enrolled in the SERAPHIN study met the criteria of right heart failure at baseline. The analysis of the primary and main secondary outcome in the population with heart failure was consistent with the results in the overall study population. In addition, a planned sample size re-sizing was conducted during the study, resulting in an increase in the initially planned sample size. Additional analysis shows no influence of the sample size increase in the final study results.

The study was well designed and also well conducted.

Efficacy data and additional analyses

The primary endpoint analysis demonstrated a clinically relevant effect of macitentan 10 mg to reduce the risk of occurrence of a morbidity or mortality event in the study population, which was below the prespecified significance criteria ($p<0.001$) for a "conclusive study" [HR: 0.547 (97.5% CLs 0.392, 0.762, logrank $p < 0.0001$]. In contrast, the corresponding HR for the macitentan 3 mg group versus placebo was 0.704 [97.5% CI: 0.516 to 0.960; logrank $p = 0.0108$). The treatment effect with macitentan on the primary endpoint was established early and was sustained during treatment (median duration of more than 2 years). For the 10 mg dose it corresponded to an overall relative risk reduction of 45% and a number-needed-to-treat (NNT) of 6 patients (95% CLs 4.48, 10.80) to avoid one event at 2 years. Results of sensitivity analyses for the primary endpoint were consistent with those of the main analysis.

The Applicant was asked to perform a sensitivity analysis of the primary endpoint using the components recommended in the PAH guideline (EMEA/CHMP/EWP/356954/2008).

The most frequent first-reported morbidity or mortality event in all groups was 'other worsening of PAH' (28.8% macitentan 3 mg, 24.4% macitentan 10 mg, 37.2% placebo). The effect of macitentan 10 mg was generally consistent across subgroup and sensitivity analyses. In the time-to-event analysis, the HR versus placebo for the occurrence of a CHMP-defined event in the macitentan 10 mg dose group was 0.550 (97.5%CI: 0.417, 0.725; logrank $p<0.0001$). In the macitentan 3 mg group was 0.737 (97.5% CI: 0.568, 0.956; $p=0.0083$). The corresponding relative risk reductions versus placebo were 45% and 26%, respectively, which are broadly similar to the results of the main analysis.The applicant's reanalysis was consistent with the analysis of the main outcome as defined in SERAPHIN.

The secondary endpoints (change in 6MWD, separate components of the primary endpoint, hemodynamic endpoints, dyspnoea symptoms, NT-pro-BNP levels and QoL endpoints were considered exploratory and appropriate. The tested doses (3 mg and 10 mg) were well justified on the basis of PD data and the median exposure exceeded 2 years. Based on the PK/PD and efficacy data provided, the recommendation of the 10mg dose is appropriately justified.

Regarding mortality, the proportion of patients with death as the first event was 8.4% in the macitentan 3 mg group, 6.6% in the macitentan 10 mg group, and 6.8% in the placebo group, questioning any claim for a mortality benefit with macitentan. This is further confirmed in the competing risk analysis (fig OE-06). Although the mortality results are not inconsistent with those of the main composite endpoint, the point estimate tends to be of a lesser magnitude than that of the composite endpoint (mainly driven by worsening of PAH), and statistical significance is not achieved for mortality. According to the "Guideline on the clinical investigations of

medicinal products for the treatment of pulmonary arterial hypertension (Doc. Ref. EMEA/CHMP/EWP/356954/2008): "*Specific claims on mortality can only be supported by long-term controlled studies including death as a primary endpoint*". While acknowledging the big effort of the company to conduct the largest clinical trial so far in PAH, a mortality claim cannot be included in section 4.1 due to the above-mentioned reasons.

During the procedure, the CHMP requested the applicant to propose a wording of the indication in line with the PAH guideline, and the SERAPHIN results showing delay in "time to clinical worsening". The applicant did not accept, arguing that this is already stated in Section 5.1 for several PAH medicines (bosentan, ambrisentan, sildenafil) based on less stringent criteria than those implemented in SERAPHIN. The applicant also argued that delay in "time to clinical worsening" may not be an appropriate reflection of the SERAPHIN data and may not be an incentive to further improved drug development in PAH. The applicant then proposed a claim of "delay in progression of the disease", arguing that primary endpoint in SERAPHIN measured progression of the disease. However, this proposal was rejected by the CHMP as this would imply that macitentan is a disease-modifying agent,–whereas the main effect of ERAs is vasodilation.

Finally, the applicant proposed a new wording without including any specific claim in the indication but including a cross-reference to section 5.1. This proposal was deemed acceptable by the CHMP, and should be interpreted in light of the broader body of evidence with macitentan from SERAPHIN in comparison with other PAH studies where claims have been limited to the 6MWT and/or symptoms. However, as comparative studies are lacking, no final conclusions can be drawn on their relative benefit in patients with PAH.

A total of 27 patients did not complete the study and therefore vital status was missing at EOS, i.e., lost to follow-up, etc.). Missing data were well balanced by treatment group. The results of the sensitivity analyses using the Best-case, Base-case and Worst-case scenarios were similar to that of the primary analysis for the time to death up to EOS, with risk reductions ranging from 33% to 16% across all analyses (none of them statistically significant). The primary analysis risk reduction of 23% falls well within that range.

The secondary endpoint of placebo-corrected median change in 6MWD from baseline to Month 6 showed similar treatment effects versus placebo in the macitentan 3 mg (median 14.0 m, 97.5% CLs 2.0, 27.0 p=0.0122) and macitentan 10 mg groups (median 15.0 m, 97.5% CLs 2.0, 28.0, p = 0.0078). The p-value for improvement in 6MWD is above the 0.001 value prefixed in the protocol to consider the results as conclusive. In addition, the clinical relevance of a 15 m median improvement is questionable. Therefore, it is agreed the Applicant's proposal not to reflect the improvement in exercise capacity in the indication.

The composite of hospitalization or death due to PAH up to EOT + 7 days was reduced by 50% versus placebo with macitentan 10 mg [HR: 0.50 (97.5% CLs 0.34, 0.75, logrank p<0.0001)], thus providing consistent support for a benefit of macitentan 10 mg versus placebo.

Exploratory results in WHO FC, Borg dyspnoea index, Quality of life, hospitalizations, change versus placebo in NT-pro-BNP and hemodynamics were consistent with those of the primary endpoint.

A majority of patients (approximately 64%) of patients were receiving at least one background PAH therapy at baseline. Sildenafil was the most common PAH therapy and was taken by

approximately 58% of patients across the groups and the effect of macitentan was consistent in patients with or without background PAH therapy at baseline. These data are considered robust enough to support the indication of the use of macitentan alone or as combination therapy on top of the standard of care.

2.5.4. Conclusions on the clinical efficacy

Clinical data available supports the efficacy of macitentan 10 mg OD in the long-term treatment of PAH. The efficacy has been shown in adult patients with functional class II and III, as monotherapy or in combination with other PAH therapies (PDE-5 inhibitors and prostanoids), in a PAH population with idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

2.6. Clinical safety

The applicant has provided data of several pooled safety datasets comprising the pivotal study, the Phase 2 studies, data from the phase I studies and data from the Phase 3 trials in other indications (essential hypertension and IPF). No studies with an active comparator have been presented with this application.

The first pool (Pool 1) includes the Phase 2/3 completed controlled-trials (AC-055-201, AC-055B201, and AC-055-302 SERAPHIN). Nevertheless, results of this pool will likely be driven by SERAPHIN trial that recruited more than 700 patients. The second pool (Pool 2) includes the pivotal trial (AC-055-302/SERAPHIN) and its ongoing open-label extension (AC-055-303/SERAPHIN OL) with the aim of providing information on the long-term safety profile of macitentan. Only the SERAPHIN study and its open-label extension were conducted in the target population, as study AC-055-201 was performed in patients with essential hypertension, study AC-055B201 was conducted in patients with idiopathic pulmonary fibrosis (IPF) and clinical pharmacology studies were conducted in volunteers.

Patient exposure

A total of 1299 patients were enrolled in phase 2 and 3 studies. Of them, 863 patients were exposed to macitentan.

The safety dataset size seems adequate for the PAH indication.

Pool 1- Placebo-controlled trials (SERAPHIN PAH; MUSIC IPF; AC-055-201 in essential hypertension)

Of the 863 patients exposed to any dose of macitentan, 533 received treatment for at least 6 months (including 317 exposed to macitentan 10 mg); 447 patients received treatment for at least 12 months (including 258 exposed to macitentan 10 mg).

Pool 2 - PAH patients (SERAPHIN and SERAPHIN OL)

675 patients were treated with macitentan in the targeted indication, with a mean exposure of 126 weeks (up to 202 weeks). Around 60% were exposed for 96 weeks or more, corresponding to 1321 patient-years exposure.

Open-label extension trial

Of the 550 patients exposed to 10 mg macitentan during the ongoing open-label extension trial in PAH indication, 164 patients have been treated for at least 6 months, and 127 patients have been treated for at least 12 months (excluding previous exposure time during the double-blind phase).

Table S-01. Overall exposure to macitentan in Phase 2 and Phase 3 studies

	Total number of patients enrolled	Patients exposed to macitentan (any dose)	Patients exposed to the proposed dose (10 mg)	Patients with long-term safety data (any dose)[a]	
				≥ 6 months	≥ 12 months
Placebo-controlled (AC-055-201, AC-055B201, AC-055-302)	1299	863	423	533[b]	447[c]
Open-label PAH extension trial (AC-055-303)[d]	550	550	550	164[e]	127[e]
Post marketing	0	0	0	0	0
Compassionate use	0	0	0	0	0

[a]Patients exposed to any dose of macitentan for at least 6 or 12 months; note that in study AC-055-201, all patients were exposed for less than 6 months, and are therefore not included in this column.
[b]Of these, 317 patients were exposed to the proposed dose of 10 mg for ≥ 6 months.
[c]Of these, 258 patients were exposed to the proposed dose of 10 mg for ≥ 12 months.
[d]Ongoing open-label extension study; all patients are treated with macitentan 10 mg.
[e]Exposure to macitentan (10 mg) during the open-label extension to SERAPHIN; excludes time of exposure to previous treatment in the double-blind PAH study (AC-055-302).
No active comparators were used in trials in PAH or IPF indications.
Source: Integrated Safety Analysis, Appendix 5, Table 4 and Appendix 6, Table 2 [D-12.601]; refers to exposure in Phase 2 and 3 studies, up to the cut-off date of 26 April 2012.
PAH = pulmonary arterial hypertension

It is also important to highlight the additional exposure from the following 2 indications:

Ischaemic digital ulcers associated with systemic sclerosis

245 and 193 patients, respectively, were receiving double-blind study treatment with macitentan 3 or 10 mg or placebo in the ongoing studies AC-055C301 and AC-055C302 in patients with ischaemic digital ulcers associated with systemic sclerosis. Up to the 29 March 2013 cut-off date, the duration of exposure to double-blind treatment was up to 63.7 weeks (median 24.1 weeks) and 59.3 weeks (median 22.7 weeks), respectively.

Recurrent gliobastoma

As of 7 February 2013, 13 patients were enrolled and exposed to daily macitentan doses of 30 mg up to 120 mg in the ongoing study in recurrent glioblastoma (AC-055-115). Maximum exposure to macitentan 30 mg was 391 days, to macitentan 60 mg was 59 days, to macitentan 90 mg was 147 days and to macitentan 120 mg was 107 days.

Adverse events

In the double-blind PAH population, the overall incidence of AEs in the macitentan groups was similar to that in the placebo group. PAH (i.e., worsening of PAH) was the most frequently reported (30 %, 21 % and 34.9 % for macitentan 3mg, 10mg and placebo). Right ventricular failure (14.8%, 13.2 % and 22.5 % for macitentan 3mg, 10mg and placebo), which is the most clinically relevant long-term complication of PAH was also reported at a lower incidence in the macitentan treatment groups than in the placebo group.

Table 31 Adverse events in the double-blind PAH population by preferred term (at least 3.0% in the total macitentan group)

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients with AEs	240 (96.0)	229 (94.6)	469 (95.3)	240 (96.4)
PULMONARY ARTERIAL HYPERTENSION	75 (30.0)	53 (21.9)	128 (26.0)	87 (34.9)
UPPER RESPIRATORY TRACT INFECTION	50 (20.0)	37 (15.3)	87 (17.7)	33 (13.3)
OEDEMA PERIPHERAL	40 (16.0)	44 (18.2)	84 (17.1)	45 (18.1)
NASOPHARYNGITIS	37 (14.8)	34 (14.0)	71 (14.4)	26 (10.4)
RIGHT VENTRICULAR FAILURE	37 (14.8)	32 (13.2)	69 (14.0)	56 (22.5)
HEADACHE	33 (13.2)	33 (13.6)	66 (13.4)	22 (8.8)
ANAEMIA	22 (8.8)	32 (13.2)	54 (11.0)	8 (3.2)
DIZZINESS	24 (9.6)	26 (10.7)	50 (10.2)	27 (10.8)
BRONCHITIS	20 (8.0)	28 (11.6)	48 (9.8)	14 (5.6)
DYSPNOEA	26 (10.4)	18 (7.4)	44 (8.9)	22 (8.8)
COUGH	20 (8.0)	21 (8.7)	41 (8.3)	30 (12.0)
CHEST PAIN	20 (8.0)	19 (7.9)	39 (7.9)	20 (8.0)
URINARY TRACT INFECTION	16 (6.4)	21 (8.7)	37 (7.5)	14 (5.6)
DIARRHOEA	14 (5.6)	22 (9.1)	36 (7.3)	17 (6.8)
INSOMNIA	17 (6.8)	17 (7.0)	34 (6.9)	10 (4.0)
SYNCOPE	21 (8.4)	11 (4.5)	32 (6.5)	21 (8.4)
HYPOTENSION	14 (5.6)	15 (6.2)	29 (5.9)	11 (4.4)
HYPOKALAEMIA	13 (5.2)	14 (5.8)	27 (5.5)	14 (5.6)
ARTHRALGIA	15 (6.0)	11 (4.5)	26 (5.3)	10 (4.0)
PALPITATIONS	14 (5.6)	12 (5.0)	26 (5.3)	13 (5.2)
PHARYNGITIS	11 (4.4)	15 (6.2)	26 (5.3)	7 (2.8)
BACK PAIN	16 (6.4)	9 (3.7)	25 (5.1)	21 (8.4)
INFLUENZA	11 (4.4)	14 (5.8)	25 (5.1)	4 (1.6)
NAUSEA	13 (5.2)	12 (5.0)	25 (5.1)	13 (5.2)
RESPIRATORY TRACT INFECTION VIRAL	9 (3.6)	15 (6.2)	24 (4.9)	9 (3.6)
SINUSITIS	11 (4.4)	11 (4.5)	22 (4.5)	6 (2.4)
FATIGUE	11 (4.4)	9 (3.7)	20 (4.1)	15 (6.0)
GASTROENTERITIS	12 (4.8)	8 (3.3)	20 (4.1)	3 (1.2)
PNEUMONIA	10 (4.0)	10 (4.1)	20 (4.1)	13 (5.2)
EPISTAXIS	11 (4.4)	8 (3.3)	19 (3.9)	9 (3.6)
PYREXIA	9 (3.6)	9 (3.7)	18 (3.7)	9 (3.6)
RESPIRATORY TRACT INFECTION	9 (3.6)	9 (3.7)	18 (3.7)	10 (4.0)
THROMBOCYTOPENIA	6 (2.4)	12 (5.0)	18 (3.7)	7 (2.8)
VOMITING	8 (3.2)	10 (4.1)	18 (3.7)	17 (6.8)
DYSPEPSIA	10 (4.0)	7 (2.9)	17 (3.5)	14 (5.6)
PAIN IN EXTREMITY	10 (4.0)	7 (2.9)	17 (3.5)	15 (6.0)
ABDOMINAL PAIN UPPER	5 (2.0)	11 (4.5)	16 (3.3)	11 (4.4)
CONSTIPATION	9 (3.6)	7 (2.9)	16 (3.3)	6 (2.4)
GASTRITIS	10 (4.0)	6 (2.5)	16 (3.3)	7 (2.8)
ABDOMINAL PAIN	8 (3.2)	7 (2.9)	15 (3.0)	4 (1.6)
MYALGIA	7 (2.8)	8 (3.3)	15 (3.0)	4 (1.6)
SKIN ULCER	7 (2.8)	8 (3.3)	15 (3.0)	3 (1.2)

AE = adverse event
Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.
Denominators for percentages are based on number of patients in Safety Population for each treatment group.
Preferred terms are sorted in descending order of the Total Macitentan frequency count.
Study AC-055-302
Source: Appendix 5, Table 31 and Table 36

Other AEs reported were: upper respiratory tract infection (20%, 15.3 % and 13,3% for macitentan 3mg, 10mg and placebo), anaemia (8.8 %, 13.2 % and 3.2 %, respectively), thrombocytopenia (2.4 %, 5.0 % and 2.8 %), oedema peripheral (16%, 18.2 % and 18,1%), hypotension (5.6% and 6.2%, and 4.4 %), headache (13.2% and 13.6%, 8.8%), insomnia (6.8 %, 7.0 % and 4.0%), urinary tract infection (6.4%, 8.7 % and 5.6 %), gastroenteritis (4.8 %, 3.3 % and 1, 2%), skin ulcers (2.8%, 3.3 % and 1.2%), abdominal pain (3.2 %, 2.9 % and 1,6 %), and drug hypersensitivity (1.2%, 0.8 % and 0%). Around 95% of patients of the pooled double-blind PAH population had at least one AE (96%, 94.6% and 96.4% for macitentan 3mg, 10mg and placebo). Similar distribution of AEs was observed in other groups of patients.

In the pool 1, the majority of patients experienced at least one AE (more than 80% in the three treatment groups). The most common AEs were similar to double blind PAH population. These AEs would be reflecting disease progression in the placebo group (and in the 3mg treatment group). In the pool 2, while the proportion of patients with any AEs increased from 63.3% at 0–6 months of macitentan exposure to 75.2% at 6–12 months and slightly increased up to 30 months of macitentan exposure (85.4%), indicating that the longer the exposure, the higher percentage of AEs. The percentage of patients with any SAE was constant (around 15-20%) over time. With respect to AEs, the incidence liver abnormalities, oedema and anaemia increased up

to 30 months of exposure while the incidence decreased or was maintained for hypotension, renal impairment, respiratory infections, malignancies or MACE. In none of the analyses was there evidence of dose-response relationship.

Hypotension: In the double-blind PAH trial, there was also a higher incidence of hypotension relative to placebo (6.0%, 7.0% and 4.4% for macitentan 3 mg, 10 mg, and placebo, respectively). However, hypotension as an SAE was reported less frequently for macitentan (0.4% and 0.8% for macitentan 3mg and 10mg) than for placebo (1.2%), and only 1 patient on macitentan 10 mg discontinued due to this AE. Hypotension cases were predominantly reported in female patients and there was no indication of an increased incidence in other potentially vulnerable subgroups, such as the elderly. Hypotension cases were not associated to a higher incidence of dizziness or syncope in the macitentan group. No data have been provided for the Pool 1 as it includes patients coming from the essential hypertension study.

Table 73 Hypotension by subgroup in the double-blind PAH population

	Macitentan 3 mg	Macitentan 10 mg	Placebo
Sub-group by sex			
Male	0	2.1% (1/48)	3.1% (2/65)
Female	7.4% (14/189)	7.2% (14/194)	4.9% (9/184)
Sub-group by age			
Elderly	3.0% (1/33)	3.7% (1/27)	6.8% (3/44)
Adults	5.7% (12/210)	6.7% (14/209)	3.5% (7/198)
Adolescents	14.3% (1/7)	0	14.3% (1/7)
Sub-group by WHO FC at baseline			
WHO FC I/II	3.6% (5/138)	4.1% (5/121)	1.5% (2/130)
WHO FC III/IV	8.0% (9/112)	8.3% (10/121)	7.6% (9/119)
Sub-group by PAH etiology			
Idiopathic / other PAH	4.9% (8/164)	6.1% (9/147)	3.6% (5/140)
PAH due to congenital shunts	13.3% (2/15)	4.8% (1/21)	3.8% (1/26)
PAH due to CVD	5.7% (4/70)	6.8% (5/73)	6.1% (5/82)
Sub-group by clinical signs and symptoms of RHF at baseline (yes/no)			
Yes	9.2% (7/76)	7.9% (6/76)	7.7% (6/78)
No	4.0% (7/174)	5.4% (9/166)	2.9% (5/171)
Sub-group by PAH therapy at baseline (yes/no)			
Yes	6.1% (10/164)	4.5% (7/154)	3.3% (5/153)
No	4.7% (4/86)	9.1% (8/88)	6.3% (6/96)
Sub-group by race			
White	6.6% (9/137)	8.1% (11/135)	6.9% (9/130)
Asian	1.4% (1/70)	4.6% (3/65)	1.4% (1/71)
Other	9.3% (4/43)	2.4% (1/42)	2.1% (1/48)
Sub-group by location			
North America (including Canada)	3.3% (1/30)	4.3% (1/23)	6.7% (2/30)
Western Europe (including S. Africa and Israel)	2.4% (1/42)	4.2% (2/48)	8.0% (4/50)
Eastern Europe (including Turkey)	9.5% (6/63)	12.9% (8/62)	6.8% (4/59)
Asia (including Australia)	2.8% (2/71)	4.4% (3/68)	1.5% (1/68)
Latin America	9.1% (4/44)	2.4% (1/41)	0
Baseline renal impairment[a]			
No	4.9% (5/102)	4.0% (4/100)	0
Mild	5.7% (6/105)	7.4% (7/94)	9.5% (9/95)
Moderate severe	7.5% (3/40)	6.8% (3/44)	4.3% (2/46)

CVD = collagen vascular disease, FC = functional class, PAH = pulmonary arterial hypertension, RHF = right heart failure.

[a] baseline renal impairment status was unknown for 2 patients in the macitentan 10 mg group.

Study AC-055-302

Source: Appendix 5, Table 128, Table 129, Table 130, Table 131, Table 132, Table 133, Table 134, Table 135 and Listing 6

In Pool 2, the incidence of hypotension was slightly more frequent at the start of treatment (2.7%) compared to patients treated longer than 30 months (0.7%). In the IPF population, similar percentages were observed for macitentan 10mg and placebo (5.9% and 5.1% respectively). Incidence was also higher for the macitentan group when it was presented as per 100 patient-years (5.4% versus 4.3% respectively). In the clinical pharmacology DDI study with macitentan and sildenafil, a decrease in systolic pressure by a maximum of 8 mmHg from a baseline of 120mmHg was observed.

Considering that patients on macitentan are likely to be treated concomitantly with sildenafil, cases of hypotension (decrease in systolic pressure from baseline and concomitant symptoms like dizziness or syncope) were reviewed. After review, despite the fact that hypotension does

not seem particularly worrisome in PAH patients even in combination with other PAH therapy, it is considered a class effect of ERAs and data on hypotension from SERAPHIN have been included in section 4.8 of the Opsumit SmPC.

Infections: The incidence of respiratory infection AEs in patients on macitentan 3 mg and 10 mg was higher than in placebo, both in Pool 1 (36%, 33.1% and 24.6%, respectively) and in the double-blind PAH population (43.6%, 40.9% and 28.5%). Nevertheless, the majority of respiratory infections occurred in the upper respiratory tract and few resulted in discontinuation of the study (none in pool 1 and 0.8% in macitentan 3mg in the double-blind PAH population). The applicant states that this higher incidence may be due to a reporting bias, as nasal congestion symptoms are observed in relation to the effect of vasodilation of the drug which seems reasonable. It is reassuring that when incidence is adjusted by exposure results are similar for macitentan a placebo (23.1, 22.6 and 18.8 events per 100 patient-years for the two doses of macitentan and placebo) for Pool 1. In case of double-blind PAH population similar results are found (22.8, 20.5 and 17.4 events/100 patient-years). Regarding Pool 2, around 20% of patients presented respiratory infections over the treatment, with no clear exposure-time-dependent pattern.

Table 80 Respiratory infection AEs in the double-blind PAH safety population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients with any SMQ Respiratory Infection AE	140 (56.0)	126 (52.1)	266 (54.1)	108 (43.4)
Upper respiratory infection	109 (43.6)	99 (40.9)	208 (42.3)	71 (28.5)
Lower respiratory infection	38 (15.2)	41 (16.9)	79 (16.1)	34 (13.7)
Respiratory infection AEs per 100 patient-years	29.3	26.1	27.7	26.5
Upper respiratory infection	22.8	20.5	21.7	17.4
Lower respiratory infection	8.0	8.5	8.2	8.3
Number of AEs	287	276	563	207
Crude incidence				
UPPER RESPIRATORY TRACT INFECTION	50 (20.0)	37 (15.3)	87 (17.7)	33 (13.3)
NASOPHARYNGITIS	37 (14.8)	34 (14.0)	71 (14.4)	26 (10.4)
BRONCHITIS	20 (8.0)	28 (11.6)	48 (9.8)	14 (5.6)
PHARYNGITIS	11 (4.4)	15 (6.2)	26 (5.3)	7 (2.8)
INFLUENZA	11 (4.4)	14 (5.8)	25 (5.1)	4 (1.6)
RESPIRATORY TRACT INFECTION VIRAL	9 (3.6)	15 (6.2)	24 (4.9)	9 (3.6)
SINUSITIS	11 (4.4)	11 (4.5)	22 (4.5)	6 (2.4)
PNEUMONIA	10 (4.0)	10 (4.1)	20 (4.1)	13 (5.2)
RESPIRATORY TRACT INFECTION	9 (3.6)	9 (3.7)	18 (3.7)	10 (4.0)
LOWER RESPIRATORY TRACT INFECTION	6 (2.4)	7 (2.9)	13 (2.6)	4 (1.6)
RHINITIS	3 (1.2)	8 (3.3)	11 (2.2)	2 (0.8)
LARYNGITIS	6 (2.4)	1 (0.4)	7 (1.4)	2 (0.8)
TRACHEOBRONCHITIS	5 (2.0)	2 (0.8)	7 (1.4)	2 (0.8)
TRACHEITIS	2 (0.8)	4 (1.7)	6 (1.2)	0
PHARYNGOTONSILLITIS	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.4)
TONSILLITIS	0	3 (1.2)	3 (0.6)	0
ACUTE SINUSITIS	2 (0.8)	0	2 (0.4)	0
LOBAR PNEUMONIA	2 (0.8)	0	2 (0.4)	0
VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (0.8)	0	2 (0.4)	0
BRONCHITIS BACTERIAL	0	1 (0.4)	1 (0.2)	0
BRONCHITIS VIRAL	0	1 (0.4)	1 (0.2)	2 (0.8)
CHRONIC SINUSITIS	1 (0.4)	0	1 (0.2)	0
H1N1 INFLUENZA	1 (0.4)	0	1 (0.2)	0
LARYNGITIS VIRAL	0	1 (0.4)	1 (0.2)	0
LUNG INFECTION	1 (0.4)	0	1 (0.2)	2 (0.8)
LUNG INFECTION PSEUDOMONAL	0	1 (0.4)	1 (0.2)	0
PNEUMONIA INFLUENZAL	1 (0.4)	0	1 (0.2)	0
PNEUMONIA MORAXELLA	1 (0.4)	0	1 (0.2)	0
PNEUMONIA NECROTISING	0	1 (0.4)	1 (0.2)	0
PNEUMONIA PNEUMOCOCCAL	1 (0.4)	0	1 (0.2)	0
ACUTE TONSILLITIS	0	0	0	2 (0.8)
BRONCHOPNEUMONIA	0	0	0	1 (0.4)

AE = adverse event, PAH = pulmonary arterial hypertension, PT = preferred term, SMQ = standardized MedDRA query
Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.
Denominators for percentages are based on number of patients in Safety Population for each treatment group.
AEs per 100 patient-years Exposure derived as (%) = 100(incidence/[total treatment duration days/365].
Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.
PTs are sorted in descending order of the Total Macitentan frequency count.
Study AC-055-302
Source: Appendix 5, Table 79, Table 89, Table 91, Table 105, Table 115, and Table 117

Other infections: In the double-blind PAH population there was certain a imbalance in the incidence of AEs of urinary tract infections and gastroenteritis in patients who received macitentan compared to those who received placebo (6.4%, 8.7% and 5.7% for macitentan 3 mg, 10 mg and placebo respectively). However, such infections were not associated with an excess of SAEs or AEs leading to discontinuation, or an increase in reporting rate over time.

Oedemas: In the double-blind PAH population the incidence of oedemas was similar in the total macitentan group (20.9%) and the placebo group (20.5%). In the 10 mg group the incidence was marginally higher than in placebo. However, when adjusted on the basis of patients years of exposure, the incidence in the macitentan group (11 events /100 patients years) was actually lower than in placebo (12. 5 events/100 patients years). Similar incidences of oedemas were also observed for macitentan and placebo in the Pool 1 population.

Table 53 Edema AEs in the double-blind PAH population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients with any SMQ Oedema AE	50 (20.0)	53 (21.9)	103 (20.9)	51 (20.5)
Oedema AEs per 100 patient-years	10.5	11.0	10.7	12.5
Number of AEs	72	69	141	63
Crude incidence				
OEDEMA PERIPHERAL	40 (16.0)	44 (18.2)	84 (17.1)	45 (18.1)
PULMONARY OEDEMA	4 (1.6)	1 (0.4)	5 (1.0)	0
FLUID OVERLOAD	3 (1.2)	1 (0.4)	4 (0.8)	1 (0.4)
FLUID RETENTION	4 (1.6)	0	4 (0.8)	1 (0.4)
PERICARDIAL EFFUSION	1 (0.4)	3 (1.2)	4 (0.8)	1 (0.4)
PLEURAL EFFUSION	2 (0.8)	2 (0.8)	4 (0.8)	2 (0.8)
HYDROTHORAX	0	2 (0.8)	2 (0.4)	0
HYPERVOLAEMIA	2 (0.8)	0	2 (0.4)	0
ASCITES	1 (0.4)	0	1 (0.2)	1 (0.4)
GENERALISED OEDEMA	0	1 (0.4)	1 (0.2)	1 (0.4)
LOCALISED OEDEMA	0	1 (0.4)	1 (0.2)	0
LYMPHOEDEMA	1 (0.4)	0	1 (0.2)	0
PELVIC FLUID COLLECTION	0	1 (0.4)	1 (0.2)	0
JOINT SWELLING	0	0	0	1 (0.4)

AE = adverse event, PAH = pulmonary arterial hypertension, PT = preferred term
Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.
Denominators for percentages are based on number of patients in Safety Population for each treatment group.
AEs per 100 patient-years Exposure derived as (%) = 100(incidence/[total treatment duration days/365].
Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.
PTs are sorted in descending order of the Total Macitentan frequency count.
Study AC-055-302
Source: Appendix 5, Table 71 and Table 97

Oedema as SAE in the Pool 1 was uncommon with macitentan treatment (0.6%, 0.7% and 1.1% for the macitentan groups and placebo) and no patients discontinued treatment due to this AE.

In the double-blind PAH population, the incidence of peripheral oedemas was higher in the elderly (30.3%, 25.9% and 18.2% for macitentan 3mg, 10mg and placebo) compared to adults (14.3%, 17.7% and 18.6%, respectively). Nevertheless in the Pool 1 a clearly higher incidence of oedema was not seen in the elderly for the proposed dose (22.2%, 13.0% and 9.1% for macitentan 3mg and 10mg and placebo) compared to the adult population (11.6%, 14.2% and 14.9%). Higher incidence was only observed with the lowest dose (3mg). This is surprising considering that there is a known dose-dependent effect of ERAs.

For the Pool 2, the longer periods of time receiving macitentan were associated with a higher incidence of oedema (from 8.9% for 0-6 months of exposure to 12% for patients treated for more than 30 months).

A higher rate of oedema with macitentan 3 mg than with macitentan 10 mg was found in elderly patients. No relationship with diuretic use was found in a post-hoc analysis and therefore it might correspond to a chance finding.

Data on oedema/fluid retention during SERAPHIN have been included in section 4.8 of the Opsumit SmPC.

Table 55 Peripheral edema AEs by subgroup in the double-blind PAH population

	Macitentan 3 mg	Macitentan 10 mg	Placebo
Sub-group by sex			
Male	14.8% (9/61)	18.8% (9/48)	13.8% (9/65)
Female	16.4% (31/189)	18.0% (35/194)	19.6% (36/184)
Sub-group by age			
Elderly	30.3% (10/33)	25.9% (7/27)	18.2% (8/44)
Adults	14.3% (30/210)	17.7% (37/209)	18.7% (37/198)
Sub-group by WHO FC at baseline			
WHO FC I/II	11.6% (16/138)	22.3% (27/121)	14.6% (19/130)
WHO FC III/IV	21.4% (24/112)	14.0% (17/121)	21.8% (26/119)
Sub-group by PAH etiology			
Idiopathic / other PAH	15.2% (25/164)	16.3% (24/147)	15.7% (22/140)
PAH due to congenital shunts	20.0% (3/15)	28.6% (6/21)	15.4% (4/26)
PAH due to CVD	17.1% (12/70)	19.2% (14/73)	23.2% (19/82)
Sub-group by clinical signs and symptoms of RHF at baseline (yes/no)			
Yes	22.4% (17/76)	17.1% (13/76)	26.9% (21/78)
No	13.2% (23/174)	18.7% (31/166)	14.0% (24/171)
Sub-group by PAH therapy at baseline (yes/no)			
Yes	17.7% (29/164)	19.5% (30/154)	23.5% (36/153)
No	12.8% (11/86)	15.9% (14/88)	9.4% (9/96)
Sub-group by race			
White	15.3% (21/137)	17.8% (24/135)	16.2% (21/130)
Asian	22.9% (16/70)	23.1% (15/65)	18.3% (13/71)
Other	7.0% (3/43)	11.9% (5/42)	22.9% (11/48)
Sub-group by location			
North America (including Canada)	33.3% (10/30)	39.1% (9/23)	33.3% (10/30)
Western Europe (including S. Africa and Israel)	16.7% (7/42)	20.8% (10/48)	18.0% (9/50)
Eastern Europe (including Turkey)	7.9% (5/63)	8.1% (5/62)	10.2% (6/59)
Asia (including Australia)	21.1% (15/71)	22.1% (15/68)	20.6% (14/68)
Latin America	6.8% (3/44)	12.2% (5/41)	14.3% (6/42)

AE = adverse event, CVD = collagen vascular disease, FC = functional class, PAH = pulmonary arterial hypertension, RHF = right heart failure.
Study AC-055-302
Source: Appendix 5, Table 128, Table 129, Table 130, Table 131, Table 132, Table 133, Table 134, and Table 135.

Malignancies: In the double-blind PAH population lower incidence adjusted by exposure was seen in the macitentan 10 mg group compared to the placebo group. In addition, there was no increase over time in the reporting rate of malignancies. In some cases, short latency or confounding factors such as medical history of malignancy were documented, and in a few cases malignancy was not confirmed. In Pool 1 there was a slight excess of malignancies in patients treated with the macitentan 3 mg compared to placebo (1.7 versus 1.4 per patient/year). Similar figures were seen for patients on the macitentan 10 mg (1.8 per patient/year). The small numbers do not allow drawing sound conclusions although malignancies have not been described as a safety concern with other ERAs.

Menstrual disorders and ovarian cyst: In the double-blind PAH SERAPHIN study, an imbalance was recorded in the reporting of menstrual disorders (6.9% for macitentan 3 mg, 5.1% for 10 mg and 1.1% in the placebo group). No consistent drug-exposure pattern could be identified as latency varied from 1 to 35 months. There were confounding factors in most patients (concomitant anticoagulants, hormonal contraception, medical history or concomitant events). These events have not been described as AEs with other ERAs. The data available are insufficient to establish a causal relationship between macitentan and menstrual disorders or ovarian cysts. However, due to the numerical imbalance observed, menstrual disorders and ovarian cysts have been considered important potential risks for macitentan.

Other AEs: The most frequently reported AE for macitentan in other clinical studies was headache. Other AEs were: nasopharyngitis, rhinitis, hypotension; upper respiratory tract infection and syncope, dysmenorrhoea, peripheral oedema. Those are in line with the AEs reported in PAH studies. No deaths, SAEs, or severe intensity AEs were reported in the macitentan-treated healthy subjects. AEs leading to discontinuation of study treatment were reported in two studies. In the drug-drug interaction (DDI) study with ketoconazole, one subject discontinued study treatment due to AEs of increased AST, ALT, and gammaglutamyltransferase (GGT) during treatment with ketoconazole (18 days) and 13 days after a single dose of macitentan 10 mg.

IPF study: The overall incidence of treatment-emergent AEs was 97.5% in the macitentan group and 98.3% in the placebo groups. Worsening of IPF was the most frequently reported AE (21.0% macitentan, 25.4% placebo). Dyspnea (20.2% macitentan,15.3% placebo), peripheral oedema (11.8% macitentan, 6.8% placebo), anaemia (10.9% macitentan only), pneumonia (9.2% macitentan, 6.8% placebo) and nausea (7.6% macitentan, 3.4% placebo), occurred at a higher incidence in patients on macitentan than on placebo. The incidences of cough and pulmonary hypertension were lower on macitentan (18.5% and 0.8%, respectively) than on placebo (35.6% and 5.1%, respectively). The majority of AEs were of mild or moderate intensity. Only 7 out of 178 enrolled patients had pulmonary hypertension (PH) or pulmonary arterial hypertension (PAH) reported in their medical history: 4 in the placebo arm and 3 in the macitentan 10 mg group. None of these 7 patients had a fatal outcome. Considering the very low number of patients with PH/PAH at baseline, no meaningful, comparative analysis could be conducted based on the presence or absence of concomitant PH/PAH.

Serious adverse event / deaths / other significant events

Overall SAEs: For PAH patients a higher incidence of SAEs was observed on placebo than on macitentan (52%, 45% and 55% for macitentan 3 mg, 10 mg and placebo, respectively) (Table 36). The most frequent were pulmonary arterial hypertension and right ventricular failure both related to progression of the disease. In Pool 1, as expected, the percentage of patients reporting SAEs was higher for macitentan 3mg (42.4%) and placebo (42, 7%) compared to macitentan 10mg (35.0%). The most frequent were pulmonary arterial hypertension and right ventricular failure both related to progression of the disease. Pneumonia was reported as SAE in around 2% of patients in all treatment groups. Anaemia was more frequent in both macitentan groups (1.6% and 1.4%) than in placebo (0.3%).

MACE: The overall incidence of major adverse cardiovascular events (MACE) was comparable between the macitentan and placebo groups. Cardiovascular deaths were less frequent in macitentan groups than in placebo (Table 91).

Table 91 Deaths due to cardiac AEs up to 28 days after end of treatment in the double-blind PAH population by preferred term

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients who died	3 (1.2)	6 (2.5)	9(1.8)	8 (3.2)
SUDDEN DEATH	1 (0.4)	2 (0.8)	3 (0.6)	0
SUDDEN CARDIAC DEATH	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)
DEATH	0	1 (0.4)	1 (0.2)	1 (0.4)
CARDIOGENIC SHOCK	0	0	0	2 (0.8)
ACUTE MYOCARDIAL INFARCTION	0	1 (0.4)	1 (0.2)	0
ARRHYTHMIA	0	1 (0.4)	1 (0.2)	0
CARDIAC ARREST	1 (0.4)	0	1 (0.2)	0
CARDIO-RESPIRATORY ARREST	0	1 (0.4)	1 (0.2)	0
ACUTE LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (0.4)
CARDIOPULMONARY FAILURE	0	0	0	1 (0.4)
LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)

AE = adverse event, PAH = pulmonary arterial hypertension
Note: there may be more than one AE with outcome death for any 1 patient.
Death = unspecified death
Study AC-055-302
Source: Appendix 5, Listing 13

Deaths:

Deaths occurred in a similar percentage in patients on macitentan and placebo both in the double blind PAH study (8,8% for macitentan 3 mg, 6,6% for macitentan 10 mg and 8,4% for placebo) and in the pool 1 (7,1% for macitentan 3mg, 5,9% for macitentan 10mg and 6,8% for placebo) (Table 34). Most of the deaths were considered as related to underlying condition (progressing right heart or respiratory failure).

Table 34 Deaths up to 28 days after end of treatment in the double-blind PAH population by preferred term

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients who died	22 (8.8)	16 (6.6)	38 (7.7)	21 (8.4)
RIGHT VENTRICULAR FAILURE	4 (1.6)	6 (2.5)	10 (2.0)	6 (2.4)
PULMONARY ARTERIAL HYPERTENSION	6 (2.4)	2 (0.8)	8 (1.6)	3 (1.2)
SUDDEN DEATH	1 (0.4)	2 (0.8)	3 (0.6)	0
RESPIRATORY FAILURE	2 (0.8)	0	2 (0.4)	1 (0.4)
SUDDEN CARDIAC DEATH	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)
ACUTE MYOCARDIAL INFARCTION	0	1 (0.4)	1 (0.2)	0
ACUTE RESPIRATORY FAILURE	1 (0.4)	0	1 (0.2)	1 (0.4)
ANGIOSARCOMA	1 (0.4)	0	1 (0.2)	0
ARRHYTHMIA	0	1 (0.4)	1 (0.2)	0
BACTERIAL SEPSIS	0	1 (0.4)	1 (0.2)	0
CARDIAC ARREST	1 (0.4)	0	1 (0.2)	0
CARDIO-RESPIRATORY ARREST	0	1 (0.4)	1 (0.2)	0
DEATH	0	1 (0.4)	1 (0.2)	1 (0.4)
DIARRHOEA INFECTIOUS	1 (0.4)	0	1 (0.2)	0
GASTROINTESTINAL HAEMORRHAGE	1 (0.4)	0	1 (0.2)	0
HAEMATEMESIS	0	1 (0.4)	1 (0.2)	0
HYPOVOLAEMIC SHOCK	1 (0.4)	0	1 (0.2)	0
METABOLIC ACIDOSIS	1 (0.4)	0	1 (0.2)	0
METASTATIC NEOPLASM	1 (0.4)	0	1 (0.2)	0
MULTI-ORGAN DISORDER	1 (0.4)	0	1 (0.2)	0
MULTI-ORGAN FAILURE	0	1 (0.4)	1 (0.2)	0
OESOPHAGEAL VARICES HAEMORRHAGE	1 (0.4)	0	1 (0.2)	0
PNEUMONIA INFLUENZAL	1 (0.4)	0	1 (0.2)	0
PULMONARY EMBOLISM	0	1 (0.4)	1 (0.2)	1 (0.4)
ROAD TRAFFIC ACCIDENT	1 (0.4)	0	1 (0.2)	0
SEPTIC SHOCK	1 (0.4)	0	1 (0.2)	0
SYSTEMIC SCLEROSIS	0	1 (0.4)	1 (0.2)	0
ACUTE LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (0.4)
CARDIOGENIC SHOCK	0	0	0	2 (0.8)
CARDIOPULMONARY FAILURE	0	0	0	1 (0.4)
LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
PANCREATIC MASS	0	0	0	1 (0.4)
RENAL FAILURE	0	0	0	1 (0.4)
SEPSIS	0	0	0	1 (0.4)
SYSTEMIC LUPUS ERYTHEMATOSUS	0	0	0	1 (0.4)

Note: Denominators for percentages are based on number of patients in Safety Population for each treatment group.
Preferred terms are sorted in descending order of the Total Macitentan frequency count.
Cause of Death is from the Disposition CRF, where coded
Preferred terms may have more than one cause of death for any 1 patient. A patient is counted once if the patient had one or more events in that category.
Study AC-055-302
Source: Appendix 5, Table 149

Two deaths were considered as related to macitentan treatment. One was due to right ventricular failure associated to jaundice within the context of right ventricular failure progression (SERAPHIN study in PAH). The other was due to pulmonary embolism (MUSIC study in IPF). The 2 deaths are unlikely to be related to the drug. In the first case hepatic enzyme alterations increased over time despite the drug was discontinued and the patient died 100 days after withdrawal. In the second case, pulmonary thromboembolism is a common cause of death in IPF patients.

Laboratory findings

Liver abnormalities:

Other ERAs have shown dose-dependent LFT abnormalities, specifically increases in serum aminotransferases that can be associated to hepatotoxicity. The mechanism is not fully understood but is considered to be related in part to inhibition of bile acid export.

In the SERAPHIN study, ALT and AST were measured at screening and at monthly intervals after initiation of study treatment until at least 28 days after the EOT. In Pool 1 10.3%, 9% and 11.9% in the macitentan 3mg, 10mg and placebo groups, respectively, had liver abnormalities compared to placebo. A higher proportion of patients, however, discontinued treatment in the macitentan groups (2.3% and 2.6%) versus placebo (1.1%). Similarly a higher incidence was observed for the placebo group in the double-blind PAH population, but, again, the percentage of patients who discontinued was higher for the macitentan groups. In addition, both in the Pool 1 and in the double-blind PAH populations, more SAEs and more AEs leading to discontinuations

were reported in patients on macitentan than on placebo. In relation to the clinically relevant serum aminotransferase abnormalities observed both in the Pool 1 and double-blind PAH populations, there does not seem to be relevant differences between the macitentan groups and placebo, except for patients with AST or ALT > 8xULN where higher percentages were seen for patients on macitentan in both safety populations.

Table 46 **Incidence of liver function abnormalities occurring from treatment start up to 28 days after EOT in the pooled double-blind safety set (Pool 1)**

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
ALT or AST > 3 x ULN					
n	125	307	414	846	360
n (%)	3 (2.4)	11 (3.6)	13 (3.1)	27 (3.2)	14 (3.9)
ALT or AST > 5 x ULN					
n	125	307	414	846	360
n (%)	1 (0.8)	4 (1.3)	8 (1.9)	13 (1.5)	7 (1.9)
ALT or AST > 8 x ULN					
n	125	307	414	846	360
n (%)	1 (0.8)	4 (1.3)	6 (1.4)	11 (1.3)	2 (0.6)
ALT or AST > 3 x ULN and TBIL > 2 x ULN at any time					
n	125	301	398	824	349
n (%)	0	5 (1.7)	5 (1.3)	10 (1.2)	5 (1.4)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = end of treatment, TBIL = total bilirubin, ULN = upper limit of the normal range
Note: Denominator for percentages based on number of non-missing observations for each treatment group and total.
Incidence based on the number of patients with at least one post-baseline abnormality for each category.
Patient 1406/11104 (placebo) is not counted in source table since TBIL > 2 × ULN as reported by a local laboratory was not included in the clinical database. Patient 9103/12093 (macitentan 3 mg) was incorrectly included in source table, despite TBIL < 2 × ULN. Patient 204-1011 (3 mg group) was not classified in the ALT/AST > 3 × ULN and TBIL > 2 × ULN in source table, since TBIL > 2 × ULN was observed more than 28 days after treatment discontinuation.
Studies AC-055-201, AC-055B201, AC-055-302
Source: Appendix 5, Table 167, and, D-12.559: Annex 1, narratives

Table 47 **Incidence of liver function abnormalities occurring from treatment start up to 28 days after EOT in the double-blind PAH safety population**

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
ALT or AST > 3 x ULN				
n	247	236	483	244
n (%)	10 (4.0)	8 (3.4)	18 (3.7)	11 (4.5)
ALT or AST > 5 x ULN				
n	247	236	483	244
n (%)	4 (1.6)	6 (2.5)	10 (2.1)	5 (2.0)
ALT or AST > 8 x ULN				
n	247	236	483	244
n (%)	4 (1.6)	5 (2.1)	9 (1.9)	1 (0.4)
ALT or AST > 3 x ULN and TBIL > 2 x ULN at any time				
n	241	230	471	237
n (%)	4 (1.7)	4 (1.7)	8 (1.7)	5 (2.1)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = end of treatment, TBIL = total bilirubin, ULN = upper limit of the normal range
Note: Denominator for percentages based on number of non-missing observations for each treatment group and total.
Incidence based on the number of patients with at least one post-baseline abnormality for each category.
Patient 1406/11104 (placebo) was not included in source table since TBIL > 2 × ULN as reported by a local laboratory was not included in the clinical database. Patient 9103/12093 (macitentan 3 mg) was incorrectly included in source table, despite TBIL < 2 × ULN.
Study AC-055-302
Source: Appendix 5, Table 168, and D-12.559, Annex 1: narratives

Table 48 Kaplan-Meier estimates of the percentage of patients with aminotransferase elevations > 3 × ULN at different time points in the double-blind PAH population

Study treatment		6 months %	12 months %	24 months %	36 months %
3 mg	ALT and/or AST > 3 ×ULN	1.2	2.2	3.9	4.5
	ALT > 3 x ULN	0.4	1.4	3.7	4.4
10 mg	ALT and/or AST > 3 × ULN	1.3	2.8	3.3	4.1
	ALT > 3 x ULN	1.3	2.8	3.3	4.1
Placebo	ALT and/or AST > 3 × ULN	1.7	1.7	5.9	8.0
	ALT > 3 × ULN	0.9	0.9	1.5	3.7

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of the normal range
Study AC-055-302
Source: Appendix 5, Table 170; D-12.425, Table 183

Based on the review of all the data, the ILSB concluded that there is no definite hepatotoxicity signal from macitentan. However, as stated before, hepatotoxicity is a well-known AE associated to ERAs. While a lack of hepatotoxic potential is not excluded, macitentan should be contraindicated in patients with baseline values of transaminases > 3xUL, in line with the exclusion criteria applied in the SERAPHIN trial after 5 cases of liver transaminases >3xULN were reported in the dose-finding study in mild-to-moderate essential hypertension (AC-055-201), which led to the Sponsor's decision to end the dose-finding study earlier than planned.

Nine of the 10 Hy's law cases (ALT>3xULN and total bilirubin >2xULN) were reported in the double-blind PAH population (4 on macitentan 10 mg, 3 on macitentan 3 mg and 2 on placebo). In addition, 5 cases with ALT>8xULN and total bilirubin<2xULN were also identified. Most cases finally recovered but there were 5 cases in all with a result of death. Although in all cases there seems to be confounding factors and they could be related to worsening of PAH or IPF a cautious approach seems appropriate including monitoring of patients, changes in the SmPC and RMP measures.

A post-hoc analysis of hepatic events has been conducted in patients at high risk (those who had a history of liver disease at screening) (n=114). The analysis does show an increase in hepatic events between patients at high risk and those without risk factors, but without differences between macitentan and placebo in both strata. Summarized information on hepatic events from ongoing or recently completed studies with macitentan (e.g. MUSIC IPF, ischaemic digital ulcers, glioblastoma) has been provided by the Applicant (cut-off date: 30 June 2013).

The pattern of hepatic events (AEs related to hepatobiliary disorders as well as the incidence of liver test elevation) is different across indications. In the PAH population, the lower incidence of hepatic events in macitentan-treated patients versus placebo is likely to be related to an efficacy of macitentan versus placebo in preventing right sided heart failure and associated hepatic congestion, which is the main cause of transaminase elevations in patients with PAH.

The incidence of ALT and/or AST > 3xULN (3.4% in the SERAPHIN study in the 10 mg group with a median exposure of 116 weeks) is well within the range observed with ambrisentan (3.6% from Kaplan-Meier estimate at 1 year in 483 patients) and below that which had been observed with bosentan in PAH (11%-14% at the target dose of 250 mg/day). However, there are no head-to-head clinical studies to conclude that macitentan provides an improved safety profile in comparison with other ERAs (i.e.: bosentan, ambrisentan).

Although no hepatic signal was observed in the SERAPHIN study in PAH, an imbalance in adverse hepatobiliary events was found in IPF and in patients with essential hypertension. In conclusion, with the data available, a potential association between macitentan and risk of liver toxicity cannot be definitively ruled out.

The SmPC information on liver safety with macitentan, regarding posology, contraindications and warnings, has been revised and is aligned with the SmPC of ambrisentan, as the hepatotoxicity risk seems similar.

Renal function: No clinical data is available for patients with severe renal impairment. In addition, patients administered macitentan 10 mg with mild to moderate renal impairment had a higher reported rate of anaemia and/or hypotension (Table 90.2), which has been included in the revised SPC.

Table 90.2 AEs related to renal impairment, categorised by baseline renal function status; number of patients with AEs (PAH double-blind population; AC-055-302)

	Renal function impairment at baseline								
	None			Mild			Moderate–severe		
Treatment group	3 mg N=102 n (%)	10 mg N=100 n (%)	Placebo N=103 n (%)	3 mg N=105 n (%)	10 mg N=94 n (%)	Placebo N=95 n (%)	3 mg N=40 n (%)	10 mg N=44 n (%)	Placebo N=46 n (%)
Number of patients who experienced:									
at least 1 AE	96 (94.1)	93 (93.0)	100 (97.1)	101 (96.2)	89 (94.7)	90 (94.7)	40 (100)	43 (97.7)	46 (100)
at least 1 AE leading to discontinuation	12 (11.8)	11 (11.0)	11 (10.7)	11 (10.5)	10 (10.6)	10 (10.5)	9 (22.5)	4 (9.1)	10 (21.7)
at least 1 SAE	50 (49.0)	40 (40.0)	56 (54.4)	53 (50.5)	42 (44.7)	50 (52.6)	25 (62.5)	26 (59.1)	30 (65.2)
any AE of special interest[a]	43 (42.2)	51 (51.0)	58 (56.3)	60 (57.1)	45 (47.9)	60 (63.2)	30 (75.0)	31 (70.5)	35 (76.1)
Specified AEs related to renal impairment:									
PAH	22 (21.6)	22 (22.0)	30 (29.1)	35 (33.3)	16 (17.0)	40 (42.1)	17 (42.5)	15 (34.1)	17 (37.0)
Oedema peripheral	10 (9.8)	20 (20.0)	20 (19.4)	20 (19.0)	13 (13.8)	14 (14.7)	10 (25.0)	10 (22.7)	11 (23.9)
Anaemia	8 (7.8)	7 (7.0)	3 (2.9)	7 (6.7)	16 (17.0)	4 (4.2)	7 (17.5)	9 (20.5)	1 (2.2)
RVF	12 (11.8)	11 (11.0)	22 (21.4)	15 (14.3)	12 (12.8)	19 (20.0)	8 (20.0)	8 (18.2)	13 (28.3)
Hypotension	5 (4.9)	4 (4.0)	0	6 (5.7)	7 (7.4)	9 (9.5)	3 (7.5)	3 (6.8)	2 (4.3)
Renal failure	0	0	2 (1.9)	0	2 (2.1)	0	3 (7.5)	0	0
Renal failure acute	1 (1.0)	0	0	2 (1.9)	1 (1.1)	0	2 (5.0)	0	0
Blood uric acid increased	–	–	–	1 (1.0)	0	1 (1.1)	–	–	–
Renal impairment	–	–	–	1 (1.0)	0	0	–	–	–

Anaemia (AEs and laboratory data): Like with other ERAs, decrease in haemoglobin concentrations was a laboratory abnormality observed with macitentan that was associated to a dose-dependent increase in the incidence of anaemia compared to placebo (Figure 1). In the double-blind PAH population, the mean maximum reduction from baseline in haemoglobin was 0.73 g/dL in the macitentan 3 mg group (baseline 15.5 g/dL) and 1.1 g/dL in the macitentan 10 mg group at month 3 (baseline 15.6 g/dL). This effect was apparent at 3 months and it was stable thereafter. In the PAH population, haemoglobin < 10 g/dL was recorded in 5.8% and 8.7% of patients on macitentan 3 mg and 10 mg, respectively, compared with 3.4% on placebo. In most cases the decreases were associated to a medical history of anaemia or were reported in the setting of concurrent clinical events including, in some cases, bleeding. Importantly, the incidence of SAEs of anaemia in macitentan-treated patients was relatively low (2.4 % macitentan 3 mg, 2.9 % macitentan 10 mg) and it was the cause of discontinuation only in a single patient at each macitentan dose. Blood transfusions were given more frequently to patients treated with macitentan than to those treated with placebo.

In general, these data indicate that macitentan exhibits a moderate, non progressive and dose-related haemoglobin reduction. As for other ERA, the initiation of treatment is not recommended in patients with clinically significant anemia as stated in the proposed SmPC.

Leukocyte and platelets counts: In the double-blind PAH population, macitentan was associated with modest and non dose-dependent decreases in mean leukocyte count from baseline to EOT (macitentan 3 mg: 0.9×109/mL, macitentan 10 mg: 0.7×109/mL, placebo: 0.0×109/mL) (Table 94), corresponding to a 9% decrease from baseline (7.5×109/mL) with the 10 mg dose. Two patients (2/218, 0.9%), both on macitentan 10 mg, had shifts from baseline to CTC grade 3 (1.0 to < 2.0×109/L). No infections were observed in either of these patients.

A small proportion of PAH patients, in both placebo and macitentan groups, showed markedly reduced platelet counts (to < 50.0 × 109/L), with or without bleeding complications, at some time during the study. Resolution occurred during continued macitentan treatment and there was an absence of recurrence after treatment reinitiating.

Coagulation tests: Macitentan prolonged the values of some coagulation tests (e.g.: prothrombin time) in preclinical studies.

Bleeding events: There is a slightly higher incidence of bleeding events reported in the macitentan groups (19.6% and 18.6% in the macitentan 3 mg and 10 mg respectively) compared to placebo (14.5%). This was mainly driven by the higher incidence of gynaecological bleedings (6.9% and 5.1% in the macitentan 3 mg and 10 mg respectively) compared to placebo (1.1%). Importantly, there is no dose response observed in all these reported bleedings. In general, concomitant administration of antithrombotics or PDE5 inhibitors was associated with a higher bleeding rate, which is expected. No direct causal relationship can be found between macitentan administration and the increased bleeding events. There are no known PK interactions between macitentan and warfarin or sildenafil.

Vital signs

Heart rate: No effect of macitentan on heart rate was apparent in the overall pooled double-blind safety set.

Electrocardiography: See “Secondary pharmacology" section.

Safety in special populations

Intrinsic factors:

Age: The table below provides a summary of adverse events per age group for patients in Pool 1, comparing events occurring in patients treated with 10 mg macitentan with those receiving placebo.

Table 68. Summary of adverse events displayed by age group (Pool 1)

Age (years)	< 65				65–74				75–84				85+			
Treatment group	10 mg N = 308 n (%)		placebo N = 282 n (%)		10 mg N = 97 n (%)		placebo N = 69 n (%)		10 mg N = 18 n (%)		placebo N = 18 n (%)		10 mg N = 0 n (%)		placebo N = 1 n (%)	
Adverse events																
Total	263	(85.4)	241	(85.5)	84	(86.6)	59	(85.5)	16	(88.9)	16	(88.9)	0		1	(100.0)
Fatal	19	(6.2)	18	(6.4)	6	(6.2)	4	(5.8)	3	(16.7)	2	(11.1)	0		0	
Serious	109	(35.4)	119	(42.2)	33	(34.0)	29	(42.0)	6	(33.3)	9	(50.0)	0		1	(100.0)
Withdrawal[a]	26	(8.4)	29	(10.3)	11	(11.3)	10	(14.5)	4	(22.2)	6	(33.3)	0		1	(100.0)
CNS (confusion/ extrapyramidal)	10	(3.2)	8	(2.8)	3	(3.1)	2	(2.9)	0		0		0		0	
AE related to falling	10	(3.2)	21	(7.4)	2	(2.1)	3	(4.3)	2	(11.1)	0		0		0	
CV events	1	(0.3)	2	(0.7)	3	(3.1)	2	(2.9)	0		1	(5.6)	0		0	
Cerebrovascular events	2	(0.6)	1	(0.4)	2	(2.1)	1	(1.4)	1	(5.6)	0		0		0	
Infections	163	(52.9)	134	(47.5)	48	(49.5)	30	(43.5)	11	(61.1)	10	(55.6)	0		0	

[a]Withdrawal = adverse events leading to permanent discontinuation of study medication
Source: Table 5, Appendix 5
AE = adverse event; CNS = central nervous system; CV = cardiovascular.

With respect to specific adverse events, in the elderly PAH-patient population (> 65 years), there was a higher incidence of dyspnoea in the macitentan 3 mg group (18.2%) and 10 mg group (14.8%) compared to the placebo group (11.4). Oedema AEs were reported at a higher incidence in elderly PAH patients treated with macitentan compared to placebo (there were no oedema AEs in adolescents). The incidences were 30.3%, 25.9% and 18.2% in the macitentan 10 mg, 3 mg and placebo groups, respectively. There was no dose-dependency and in a logistic regression analysis, no statistically significant interaction between age and treatment was observed.

There was no obvious effect of PAH disease severity at baseline (WHO FC I/II vs III/IV) on the pattern of AEs across the age groups.

The pattern of AEs was generally similar for males and females both for Pool 1 and the double-blind PAH population. Evaluation by subgroup in the double-blind PAH population showed that most hypotension AEs were reported in female patients. In the macitentan 10 mg group, 16 of the 17 patients with hypotension AEs were female (incidence of 8.2% vs 2.1% in males). The AE urinary tract infection was reported at a higher incidence in females than in males.

Race/ethnicity is only described for the double-blind PAH population, as the IPF study (AC-055B201) and essential hypertension study (AC-055-201) comprised almost exclusively White patients. Subgroup differences on the basis of race/ethnicity and geographical region were unremarkable.

The analysis of AEs for Pool 1 did not reveal any clear or consistent differences in the pattern of AEs on the basis of no, mild or moderate–severe baseline renal impairment. No correlation between the severity (mild, moderate, or severe) of hepatic impairment and the mean plasma exposure to macitentan and its metabolites, ACT-132577 and ACT-373898, was apparent in a study in subjects with hepatic impairment. Other than infections and oedema, subgroup differences on the basis of baseline PAH therapy were unremarkable.

Pregnancy and lactation

In the clinical development program, there were a total of 7 pregnancies (5 on macitentan 3 mg and 2 on placebo). All occurred in the double-blind PAH population. Of the 5 patients in the macitentan 3 mg group, one had a therapeutic abortion, one had a spontaneous abortion. Both patients subsequently restarted macitentan treatment. The spontaneous abortion was assessed by the investigator as unrelated to study treatment. One patient had an abortion scheduled, but died due to worsening of PAH before the scheduled date. For the other 2 macitentan-treated patients, both permanently discontinued treatment and continued the pregnancy. Both women gave birth prematurely. In one case the baby had hyaline membrane disease complicated by sepsis, a grade 4 intracranial haemorrhages and poor skin condition. Three days after birth, the baby died from persistent hypotension, due to extreme prematurity. No obvious dysmorphism was noted and the prenatal screening at Week 18 had shown no anomaly. The death was reported as unrelated to study treatment. In the second case, the baby had no neonatal abnormalities and survived. Both placebo-treated patients had therapeutic abortions, one of whom subsequently restarted study treatment, while the other permanently discontinued treatment. It is not known whether macitentan is excreted into human breast milk. In rats, macitentan and its metabolites were excreted into milk during lactation. Breast-feeding is not recommended during treatment with macitentan.

Overdose

There is no experience with accidental overdose of macitentan. Single doses of up to and including 600 mg were administered in healthy subjects. This dose was associated with headache, nausea and vomiting. In the case of overdose, general supportive treatment is recommended. Considering the high degree of protein binding, macitentan is not likely to be removed by dialysis.

Rebound effect

Available data do not indicate that the discontinuation of macitentan 10 mg is associated with any AE suggestive of a rebound effect.

Ability to drive and use machines

No studies on the effect of macitentan on the ability to drive and use machines have been performed, as an effect is not anticipated.

Potential for abuse

There is no indication of any potential for abuse from clinical studies or from current knowledge of ERAs in general.

Testicular safety: see "pharmacodynamic" section.

Immunological events

All cases of hypersensitivity appear to be associated with concomitant medications and seasonal allergy, not with macitentan. Only one case was considered by the investigator to be related to treatment.

Safety related to drug-drug interactions and other interactions

See "pharmacodynamics" section for safety related to drug-drug interaction with sildenafil (increase in headache and hypotension). No other information is available.

Discontinuation due to AES

Around 10% of patients discontinued due to AEs both in the pool 1 and the double blind PAH population. Pulmonary arterial hypertension and right ventricular failure, both related to the underlying condition, were more frequent in the placebo group in these populations. As expected, anaemia and increase in aminotransferases were more frequency in the macitentan groups.

2.6.1. Discussion on clinical safety

The applicant has provided data of several pooled safety datasets comprising the pivotal study, the phase II studies, data from the phase I studies data from the phase III trials in other indications (essential Hypertension and IPF). No studies with an active comparator have been presented with this application. According to the applicant, 675 patients were treated with macitentan in the targeted indication, with a mean exposure of 126 weeks (up to 202 weeks). Around 60% were exposed for 96 weeks or more, corresponding to 1321 patient-years exposure. The safety dataset size seems adequate for the PAH indication.

There is clinical information on specific serious AE or serious AE that could represent an alert that have been identified with other ERAs. Therefore, a focus was done on hepatotoxicity, vasodilatation, decrease in haemoglobin and teratogenicity among others.

Adverse events:

Overall AEs:

Double-blind PAH population (SERAPHIN study):

The overall incidence of AEs in the macitentan groups was similar to that in the placebo group. PAH (i.e., worsening of PAH) was the most frequently reported.

Right ventricular failure, which is the most clinically relevant long-term complication of PAH was also reported at a lower incidence in the macitentan treatment groups than in the placebo group.

Other AEs reported were: upper respiratory tract infection, anaemia, thrombocytopenia, oedema peripheral, hypotension, headache, insomnia, urinary tract infection, gastroenteritis, skin ulcers, abdominal pain and drug hypersensitivity.

Around 95% of patients of the pooled double-blind PAH population had at least one AE. Similar distribution of AEs was observed in other groups of patients.

In the pool 1, the majority of patients experienced at least one AE (more than 80% in the three treatment groups). The most common AEs were similar to double blind PAH population. These

AEs would be reflecting disease progression in the placebo group (and in the 3mg treatment group).

In the pool 2, the proportion of patients with any AEs increased from 63.3% at 0–6 months of macitentan exposure to 75.2% at 6–12 months and slightly increased up to 30 months of macitentan exposure (85.4%), indicating that the longer exposure the higher percentage of AEs. The percentage of patients with any SAE was quite constant (around 15-20%) over time.

With respect to AEs, the incidence liver abnormalities, oedema and anaemia increased up to 30 months of exposure while the incidence decreased or was maintained for hypotension, renal impairment, respiratory infections, malignancies or MACE.

A dose-response relationship was found for anaemia but not for other AEs.

In summary, the applicant has analysed some safety topics considered of special interest based on the experience with other ERAs, the nonclinical safety data, and findings in the studies. These topics refer to AEs and laboratory findings denoting hypotension, respiratory and other infections, oedema/fluid retention, liver abnormalities, anaemia/haemoglobin decrease, renal impairment, malignant neoplasms, menstrual disorders and ovarian cysts myocardial infarction and cerebrovascular events, as well as effects of macitentan on QTc and other ECG variables.

Hypotension:

Double-blind PAH population (SERAPHIN study):

There was a higher incidence of hypotension relative to placebo for macitentan 3 mg and 10 mg. Hypotension cases were not associated to a higher incidence of dizziness or syncope in the macitentan group.

Despite hypotension does not seem particularly worrisome in PAH patients it is considered a class effect of ERAs and data on hypotension from SERAPHIN has been reflected in section 4.8 of the Opsumit SmPC.

Infections:

Respiratory infections:

The incidence of respiratory infection AEs in patients on macitentan 3 mg and 10 mg was higher than in placebo, both in the double-blind PAH population and in Pool 1. Nevertheless, the majority of respiratory infections occurred in the upper respiratory tract and few resulted in discontinuation of the study. The applicant states that this higher incidence may be due to a reporting bias, as nasal congestion symptoms are observed in relation to the effect of vasodilator of the drug which seems reasonable.

It is reassuring that when incidence is adjusted by exposure results are similar for macitentan a placebo for the two doses of macitentan and placebo for the Pool 1. In case of double-blind PAH population also similar results are found. Regarding Pool 2, around 20% of patients presented respiratory infections over the treatment, with no clear exposure time-dependent pattern. In conclusion, nasopharyngitis, bronchitis pharyngitis have been included in section 4.8 of the SmPC.

Other infections:

In the double-blind PAH population there was certain imbalance in the incidence of AEs of urinary tract infections and gastroenteritis in patients who received macitentan compared to those who received placebo. However, such infections were not associated with an excess of SAEs or AEs leading to discontinuation, or an increase in reporting rate over time. The information is appropriately reflected in the SmPC.

Oedemas:

In the double-blind PAH population, the incidence of oedemas was similar in the total macitentan group and the placebo group. In the 10 mg group the incidence was marginally higher than in placebo. However, when adjusted on the basis of patient years of exposure, the incidence in the macitentan group was actually lower than in placebo.

Similar incidences of oedemas were observed also for macitentan and placebo in the Pool 1 population. In the double-blind PAH population, the incidence of peripheral oedemas was more common in the elderly compared to adults. Nevertheless in the Pool 1 a clearly higher incidence of oedema was not seen in the elderly for the proposed dose compared to the adult population.

A higher rate of oedema with macitentan 3 mg than with macitentan 10 mg was found in elderly patients. No relationship with diuretic use was found in a post-hoc analysis and therefore it might correspond to a chance finding.

In conclusion, a specific description on oedema/fluid retention during SERAPHIN has been included in section 4.8 of the Opsumit SmPC.

Malignancies:

In the double-blind PAH population lower incidence adjusted by exposure was seen in the macitentan 10 mg group compared to the placebo group. In addition, there was no increase over time in the reporting rate of malignancies. In the Pool 1 there was a slight excess of malignancies in patients treated with the macitentan 3 mg compared to placebo. Similar figures were seen for patients on the macitentan 10 mg.

In conclusion, the small numbers do not allow drawing sound conclusions although malignancies have not been described as a safety concern with other ERAs. Therefore, no information is included in the SmPC.

Menstrual disorders and ovarian cyst:

In the double-blind PAH SERAPHIN study, an imbalance was recorded in the reported menstrual disorders and there were confounding factors in most patients. These events have not been described as AEs with other ERAs.

At present, the data available are insufficient to establish a causal relationship between macitentan and menstrual disorders or ovarian cysts. However, due to the numerical imbalance observed, menstrual disorders and ovarian cysts have been considered important potential risks for macitentan.

Other AEs:

The most frequently reported AE for macitentan in other clinical studies was headache. Other AEs were: nasopharyngitis, rhinitis, hypotension; upper respiratory tract infection and syncope dysmenorrhoea, peripheral oedema. Those are in line with the AEs reported in PAH studies.

IPF study:

The overall incidence of treatment-emergent AEs was 97.5% in the macitentan group and 98.3% in the placebo groups. Worsening of IPF was the most frequently reported AE. Dyspnea, peripheral edema, anemia, pneumonia and nausea, occurred at a higher incidence in patients on macitentan than on placebo.

The incidences of cough and pulmonary hypertension were lower on macitentan than on placebo. The majority of AEs were of mild or moderate intensity on placebo. Only 7 out of 178 enrolled patients had pulmonary hypertension (PH) or pulmonary arterial hypertension (PAH) reported in their medical history. None of these 7 patients had a fatal outcome. Considering the very low number of patients with PH/PAH at baseline, no meaningful, comparative analysis could be conducted based on the presence or absence of concomitant PH/PAH.

SAEs:

For PAH patients a higher incidence of SAEs was observed for macitentan 3 mg, 10 mg and placebo, respectively PAH and right ventricular failure both related to progression of the diseases. In Pool 1, as expected, the percentage of patients reporting SAEs was higher for macitentan 3mg and placebo compared to macitentan 10mg. The most frequent were pulmonary arterial hypertension and right ventricular failure both related to progression of the disease. Pneumonia was also reported as SAE in around 2% of patients in all treatment groups. Anaemia was more frequent in both macitentan groups than in placebo.

MACE: The overall incidence of major adverse cardiovascular events (MACE) was comparable between the macitentan and placebo groups. However, the incidence of cerebrovascular events was a bit higher in patients on both macitentan groups versus placebo. On the other hand, cardiovascular deaths were less frequent in macitentan groups than in placebo.

Deaths:

Deaths occurred in a similar percentage in patients on macitentan and placebo both in the double blind PAH study and in the pool 1. Most of deaths were considered as related to underlying condition (progressing right heart or respiratory failure). Two deaths were considered as related to macitentan treatment, one was due to right ventricular failure associated to jaundice within the context of right ventricular failure progression in a PAH study. The other was due to pulmonary embolism in an IPF patient. However, they are unlikely to be related to the drug.

Laboratory findings:

Liver abnormalities (AEs and laboratory data):

Other ERAs have shown dose-dependent liver abnormalities, specifically increases in serum aminotransferases that can be associated to hepatotoxicity. The mechanism for this is not fully understood but is considered to be related in part to inhibition of bile acid export.

In the double-blind PAH safety population the incidence of liver abnormality AEs was 10.8% in the total macitentan group and 16.1% in the placebo group.

The incidences in the macitentan 3 mg and 10 mg groups were 12.0% and 9.5%, respectively, indicating a dose-related reduction. The AE incidence findings are supported by laboratory data indicating liver abnormalities compared to placebo.

In relation to clinically relevant serum aminotransferase abnormalities observed both in the Pool 1 and double-blind PAH populations, no relevant differences between the macitentan groups and placebo were observed, except for patients with AST or ALT > 8xULN where higher percentages were seen for patients on macitentan in both safety populations.

A post-hoc analysis of hepatic events does show an increase in hepatic events between patients at high risk and those without risk factors, but without differences between macitentan and placebo in both strata.

The pattern of hepatic events is different across indications.

In the PAH population, the lower incidence of hepatic events in macitentan-treated patients versus placebo is likely to be related to a better efficacy of macitentan versus placebo in preventing right sided heart failure and associated hepatic congestion, which is the main cause of transaminase elevations in patients with PAH. The incidence of ALT and/or AST > 3xULN (3.4% in the SERAPHIN study in the 10 mg group with a median exposure of 116 weeks) is well within the range observed with ambrisentan (3.6% from Kaplan-Meier estimate at 1 year in 483 patients) and below that which had been observed with bosentan in PAH (11%-14% at the target dose of 250 mg/day). However, there are no head-to-head clinical studies to conclude that macitentan provides an improved safety profile in comparison with other ERAs (i.e.: bosentan, ambrisentan). Although no hepatic signal was observed in the SERAPHIN study in PAH, an imbalance in hepatobiliary adverse events was found in IPF and in patients with essential hypertension. In conclusion, with the data available, a potential association between macitentan and risk of liver toxicity cannot be definitely ruled out.

While a lack of hepatotoxic potential is not excluded, macitentan should be contraindicated in patients with baseline values of transaminases > 3xULN and in patients with severe hepatic impairment.

Although in all cases confounding factors can be identified related to worsening of PAH or IPF, a cautious approach is considered appropriate including monitoring of patients, appropriate measures and warnings in the SmPC. In the RMP , appropriate risk minimisation measures have been put in place. (patient card, HCP prescriber kit..)

Renal function:

No clinical data is available for patients with severe renal impairment. In addition, patients administered macitentan 10 mg with mild to moderate renal impairment had a higher reported rate of anaemia and/or hypotension> This is appropriately reflected in the SmPC.

Anaemia (AEs and laboratory data):

Like with other ERAS, decrease in haemoglobin concentrations was a laboratory abnormality observed with macitentan that was associated to a dose-dependent increase in the incidence of anaemia compared to placebo. In the double-blind PAH population, the mean maximum

reduction from baseline in haemoglobin was 0.73 g/dL in the macitentan 3 mg group and 1.1 g/dL in the macitentan 10 mg group at month 3.

In the PAH population, haemoglobin < 10 g/dL was recorded in 5.8% and 8.7% of patients on macitentan 3 mg and 10 mg, respectively, compared with 3.4% on placebo.

In general, these data indicate that macitentan exhibits a moderate, non progressive and dose-related haemoglobin reduction.

As for other drugs of the same group, the initiation of treatment is not recommended in patients with clinically significant anemia as stated in the SmPC. In addition the applicant provided further information discussing the appropriateness of making dose reduction recommendations in the event of reductions in haemoglobin or hematocrit. After review of the available data, the CHMP considered that no dose reduction is required.

Leukocyte counts:
In the double-blind PAH population, macitentan was associated with modest and non dose-dependent decreases in mean leukocyte count from baseline to EOT, corresponding to a 9% decrease from baseline with the 10 mg dose. No infections were observed in either of these patients.

Platelet counts:
A small proportion of PAH patients, in both placebo and macitentan groups, showed markedly reduced platelet counts, with or without bleeding complications during the study. Resolution occurred during continued macitentan treatment and there was an absence of recurrence after treatment re-initiation.

Bleeding events:
There is a slightly higher incidence of bleeding events reported in the macitentan groups compared to placebo. This was mainly driven by the higher incidence of gynaecological bleedings compared to placebo. In general, concomitant administration of antithrombotics or PDE5 inhibitors was associated with a higher bleeding rate, which is expected. No direct causal relationship can be found between macitentan administration and the increased occurrence of bleeding events. There are no known PK interactions between macitentan and warfarin or sildenafil.

Vital signs:

No effect of macitentan on heart rate was apparent in the overall pooled double-blind safety set.

Safety in special populations:

Intrinsic factors:

In the elderly PAH-patient population (> 65 years), there was a higher incidence of dyspnoea in the macitentan 3 mg group and 10 mg group compared to the placebo group, respect the rest of populations.

Oedema AEs were reported at a higher incidence in elderly PAH patients treated with macitentan compared to placebo. There was no dose-dependency and no statistically significant interaction between age and treatment was observed. There was no obvious effect of PAH disease severity at baseline (WHO FC I/II vs III/IV) on the pattern of AEs across the age groups.

The pattern of AEs was generally similar for males and females both for Pool 1 and the double-blind PAH population.

Evaluation by subgroup in the double-blind PAH population showed that most hypotension AEs were reported in female patients. The AE urinary tract infection was reported at a higher incidence in females than in males.

Race/ethnicity is only described for the double-blind PAH population, as the IPF study (AC-055B201) and essential hypertension study (AC-055-201) comprised almost exclusively Caucasian patients.

Subgroup differences on the basis of race/ethnicity and geographical region were unremarkable

Pregnancy and lactation:

In the clinical development program, there were a total of 7 pregnancies all in the double-blind PAH population. Based on review of the cases, no specific conclusion can be drawn in relation to macitentan.

In view of the teratogenicity observed in non-clinical studies, macitentan is contraindicated during pregnancy. Furthermore, if appropriate, the need for reliable contraception and monthly pregnancy tests during treatment is mentioned in section 4.6 of the SmPC with corresponding warnings in section 4.4.

It is not known whether macitentan is excreted into human breast milk. However, in rats, macitentan and its metabolites were excreted into milk during lactation. Thus, breast-feeding is not recommended during treatment with macitentan.

Overdose:

There is no experience with accidental overdose of macitentan. In the case of overdose, general supportive treatment is recommended. Considering the high degree of protein binding, macitentan is not likely to be removed by dialysis.

Rebound effect:

The results did not indicate that the discontinuation of macitentan 10 mg was associated with any AE suggestive of a rebound effect.

Ability to drive and use machines:

No studies on the effect of macitentan on the ability to drive and use machines have been performed, as an effect is not anticipated.

There is no indication of any potential for abuse from clinical studies or from current knowledge of ERAs in general.

Hypersensitivity:
All of the cases of hypersensitivity appear to be associated with concomitant medications and seasonal allergy, not with macitentan. Only one case was considered by the investigator to be related to treatment.

Discontinuation to AEs:
Around 10 % of patients discontinued due to AEs both in the pool 1 and the double blind PAH population. Pulmonary arterial hypertension and right ventricular failure, both related to the underlying condition, were more frequent in the placebo group in these populations. As expected, anaemia and increase in aminotransferases were more frequency in the macitentan groups.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, macitentan seems to have a safety profile similar to that of other ERAs. The adverse events most frequently reported were right heart failure, pulmonary arterial hypertension (both in principle related to the underlying condition), oedemas, upper tract infection, anaemia and liver abnormalities.

Although there are no major safety concerns related to macitentan, a potential association between macitentan and risk of liver toxicity cannot be definitively ruled out. The SmPC of Opsumit has been 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 is contraindicated during pregnancy. Furthermore, the need for reliable contraception and monthly pregnancy tests during treatment is reflected in section 4.6 of the SmPC with corresponding warnings in section 4.4 of the SmPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 5, the PRAC considers by consensus that the risk management system for macitentan (Opsumit) in the treatment of pulmonary arterial hypertension is acceptable.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

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

PVOD = pulmonary oedema associated with veno-occlusive disease

The PRAC agrees that the safety concerns listed by the MAH are appropriate.

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

3. Proposal for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Anaemia, decrease in haemoglobin concentration	SmPC Warning in section 4.4 Inclusion in ADR table in section 4.8 Inclusion in the PIL	Controlled distribution Risk minimisation tools (HCP brochure, prescribing checklist)

Hepatotoxicity	SmPC Contraindication in section 4.3 Warning in section 4.4 Inclusion in section 4.8 under laboratory abnormalities Inclusion in the PIL	Controlled distribution Risk minimisation tools (HCP brochure, prescribing checklist
Teratogenicity	SmPC Contraindication for pregnancy, women of child-bearing potential not using contraception and lactation in section 4.3. Warning for women of child bearing potential in section 4.4. Recommendations in section 4.6. Inclusion in the PIL	Controlled distribution Risk minimisation tools (HCP brochure, prescribing checklist and patient card)
Symptomatic hypotension	SmPC Warning in section 4.4 for patients with severe renal impairment Inclusion in section 4.8	None
Thrombocytopenia	SmPC Inclusion in section 4.8 under laboratory abnormalities	None
Leukopenia	SmPC Inclusion in section 4.8 under laboratory abnormalities	None
Menstrual disorders (primarily bleeding)	None	None
Ovarian cysts	None	None
Pulmonary oedema associated with PVOD	SmPC Warning in section 4.4	None
Testicular disorders and male infertility	SmPC Statement in section 4.6	None
Off-label use (including in paediatric patients)	SmPC Definition of target patient population in section 4.1 Information about lack of data in paediatric patients in section 4.2 Inclusion in the PIL	None
Missing information in paediatric Patients	SmPC Statement in sections 4.2 Inclusion in the PIL	None

Missing information in elderly patients above 75 years	SmPC Statement in section 4.2 Warning in section 4.4 Inclusion in PIL	None
Missing information in patients with moderate to severe hepatic impairment	SmPC Statement in section 4.2 Contraindication in section 4.3 for patients with severe hepatic impairment Warning in section 4.4 Inclusion in PIL	None
Missing information in patients with severe renal impairment and/or undergoing dialysis	SmPC Statement in section 4.2 Warning in section 4.4	None

The PRAC is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.
The CHMP endorsed this advice without changes.

Of note, an updated RMP version 6 was submitted as the final version for the opinion incorporating minor changes related to the finalisation of SmPC wording after the PRAC discussion.

3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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. Benefit-Risk Balance

Benefits

Beneficial effects

This application is based on the results of a single, long-term, double-blind pivotal Phase 3 study, AC-055-302/SERAPHIN. The pivotal study included a clinically relevant primary endpoint (the time to first morbidity-mortality event). The secondary endpoints (change in 6MWD, separate components of the primary endpoint, change in WHO FC, haemodynamic endpoints, dyspnoea symptoms, NT-pro-BNP levels and QoL endpoints) were considered exploratory and appropriate. The tested doses (3 mg and 10 mg) were well justified on the basis of PD data and the median exposure exceeded 2 years.

SERAPHIN is the largest study conducted to date in PAH (n=742) and included a wide population of PAH patients with different aetiologies, Function Class and background medications. One of the

positive contribution of the current application is that it addresses combination therapy, which is an unmet need in PAH.

The primary endpoint analysis demonstrated a clinically relevant effect of macitentan 10 mg to reduce the risk of occurrence of the primary endpoint in the study population, which was below the pre-specified significance criteria ($p<0.001$) for a "conclusive study" [HR: 0.547 (97.5% CLs 0.392, 0.762, logrank $p < 0.0001$]. The treatment effect with macitentan on the primary endpoint was established early and was sustained during treatment (median duration of more than 2 years).The 10mg dose was considered the appropriate dose on the basis of efficacy and safety results. For the 10 mg dose the treatment effect corresponded to an overall relative risk reduction of 45% and a number-needed-to-treat (NNT) of 6 patients (95% CLs 4.48, 10.80) to avoid one event at 2 years. Results of sensitivity analyses for the primary endpoint were consistent with those of the main analysis. In a reanalysis of the primary endpoint using the components recommended in the PAH guideline (EMEA/CHMP/EWP/356954/2008), the HR versus placebo for the occurrence of a CHMP-defined event in the macitentan 10 mg dose group was 0.550 (97.5%CI: 0.417, 0.725; logrank $p<0.0001$). In the macitentan 3 mg group, the HR was 0.737 (97.5% CI: 0.568, 0.956; $p=0.0083$). The corresponding relative risk reductions versus placebo were 45% and 26%, respectively, which are broadly similar to the results of the main analysis. In addition, the effect of macitentan 10 mg on the primary outcome was generally consistent across subgroup analyses. At baseline, the majority (approximately 64%) of patients were receiving at least one background PAH therapy. Sildenafil was the most common PAH therapy and was taken by approximately 58% of patients across the groups. Macitentan administered on top of sildenafil or inhaled prostanoids showed benefits, with minimal PK interactions.

The majority of secondary and exploratory endpoints (e.g.: the composite of hospitalization or death due to PAH, deaths related to PAH, all cause death, improvement in WHO FC, Borg dyspnoea index, Quality of life, reduced hospitalizations, change versus placebo in NT-pro-BNP and hemodynamic parameters), provided consistent support for a benefit of macitentan 10 mg versus placebo.

Uncertainty in the knowledge about the beneficial effects

Not all the components of the chosen primary composite in SERAPHIN are equally robust. In the main analysis, the rate of death was comparable between the placebo (6.8%) and the macitentan 10 mg arms (6.6%), while there is a numerical increase in the reported deaths in the macitentan 3 mg arm (8.4%) compared to the other 2 arms. In addition, no robust statistical effect was found in the time to death analyses. Although the mortality results for macitentan 10 mg are not inconsistent with those of the main composite endpoint, the point estimate tends to be of a lesser magnitude than that of the composite endpoint (mainly driven by worsening of PAH), and statistical significance is not achieved for mortality. In addition, beyond statistical significance, the conclusions about a benefit in survival with the 10 mg dose were based on a limited number of deaths within a single pivotal trial. Furthermore, according to the PAH Guideline (EMEA/CHMP/EWP/356954/2008): "*Specific claims on mortality can only be supported by long-term controlled studies including death as a primary endpoint*". A mortality claim cannot be included in section 4.1 due to the above-mentioned reasons. A description of the effect observed on deaths in section 5.1 of the SmPC is considered sufficient.

The most frequent first-reported component of the primary endpoint in all groups was 'other worsening of PAH' (28.8% macitentan 3 mg, 24.4% macitentan 10 mg, 37.2% placebo), driving the positive results of the study. This implies that the main benefit was in delaying clinical worsening events (worsening of PAH).

During the procedure, the applicant proposed a new wording without including any specific claim in the indication but including a cross-reference to section 5.1. This proposal was deemed acceptable by the CHMP, and should be interpreted in light of the more robust evidence with macitentan from SERAPHIN regarding delay in clinical worsening of PAH in comparison to other PAH therapies where claims have been limited to the change in 6MWT and/or symptoms. However, as comparative studies are lacking, no final conclusions can be drawn on their relative benefit in patients with PAH.

With respect to missing data, a total of 27 patients did not complete the study and therefore vital status was missing at EOS, i.e., lost to follow-up, etc.). Additional data provided by the Company shows that missing data were well balanced by treatment groups. In addition, the results of the sensitivity analyses using the Best-case, Base-case and Worst-case scenarios were similar to that of the primary analysis for the time to death up to EOS, with risk reductions ranging from 33% to 16% across all analyses (none of them statistically significant). The primary analysis risk reduction of 23% falls well within that range.

Some subpopulations were under-represented in the pivotal study. Almost all patients were in WHO FC II-III, while only 1 patient was in FC I and only 14 patients were in FC IV. Therefore, the indication has been restricted to patients on FC II and III. Idiopathic PAH was the most common aetiology (55%) followed by PAH due to connective tissue (30%) and PAH due to congenital shunts (8%). This latter subpopulation only included PAH associated to corrected simple congenital systemic-to-pulmonary shunts, since patients with PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and combined and complex systemic-to-pulmonary shunts were excluded. Therefore, "PAH due to congenital shunts" has not been included in the approved indication.

Regarding paediatric population (12-18), their actual representation in the clinical study and the scarce efficacy and safety data available does not support a recommendation of use for macitentan in children. Therefore, the safety and efficacy of Opsumit in children have not yet been established, as included in the product information. Further data is awaited upon completion of planned studies in paediatric patients.

Only about 20 patients were in the age range between 75-84 years in the pivotal trial. Therefore, macitentan should be used with caution in that population, as included in the product information

The p-value for improvement in 6MWD (one of the secondary outcomes) was above the 0.001 value predefined in the protocol to consider the results as conclusive. In addition, the clinical relevance of the 15 m median improvement obtained with macitentan 10 mg versus placebo is questionable. Therefore, the Applicant's proposal of not including the improvement in exercise capacity in the indication is endorsed. Results of the 6MWT showed no difference between treatment naïve patients and patients administered macitentan in combination with other PAH therapies (median=13 m; 95%CI: -5 to 31 and median =15 m; 95%CI: 2 to 30). No plausible explanation is available at present.

Results showed some improvement in PVR and CI with dose response in treatment naïve patients, but not in patients already on PAH-specific therapies. Within SERAPHIN, higher baseline NT-proBNP levels and higher absolute values at Month 6 were associated with a higher risk of morbidity and mortality, however no prognostic value of change from baseline was observed. Finally, no head-to-head comparisons are available with other ERAs. Therefore, it is unknown if macitentan would provide some benefit in efficacy compared with bosentan or ambrisentan.

Risks

Unfavourable effects

Overall, macitentan seems to have a safety profile similar to that of other ERAs. The adverse events most frequently reported were right heart failure, pulmonary arterial hypertension (both in principle related to the underlying condition), liver abnormalities, anaemia, oedemas and upper tract infection.

Elevations of liver aminotransferases (AST, ALT) have been associated with the treatment with ERAs, including macitentan. This toxic effect on the liver seems to be time-dependent, with higher incidence with longer exposition to macitentan. In relation to the clinically relevant serum aminotransferase abnormalities observed the safety pool, there does not seem to be relevant differences between macitentan and placebo in elevated aminotransferases >3×ULN (3.2% vs. 3.9%) or Hy's law cases (1.2% vs. 1.4%), but the rate of AST/ALT elevations >8xULN where higher in patients on macitentan versus placebo (1,3% vs 0,6%). In addition, the phase II study in mild-to-moderate essential hypertension was ended earlier than planned after 5 cases of liver transaminases >3xULN were reported (study AC-055-201).

Because a lack of hepatotoxic potential cannot be excluded, Opsumit is not to be initiated in patients with elevated aminotransferases (>3×ULN) at baseline or in patients with severe hepatic impairment, in line with the exclusion criteria applied in the SERAPHIN study. Liver enzyme tests should be obtained prior to initiation of Opsumit. Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended.

As with other ERAs, treatment with macitentan has been associated with a decrease in haemoglobin concentration, including some cases that may blood cell transfusion. Therefore, Opsumit is not recommended in patients with severe anaemia and haemoglobin concentrations should be measured prior to initiation of treatment and tests repeated during treatment as clinically indicated.

Hypotension is considered a class effect of ERAs and some SmPC amendments, in particular in patient at risk of hypotension (e.g.: elderly, renal insufficiency, concomitant treatment with other vasodilators, may be necessary.

Although the product has a low potential for drug-drug interactions, some of them (PK interactions with strong inducers/inhibitors of CYP3A4 and PD interactions with vasodilators) may be of clinical relevance.

Macitentan was teratogenic in animal studies and therefore it is contraindicated during pregnancy and in women of child-bearing potential who are not using reliable contraception. There is a need for reliable contraception and monthly pregnancy tests during treatment. The contraindication

has been extended to breastfeeding, as there is preclinical evidence of excretion into milk during lactation and a risk to the newborns/infants cannot be excluded.

These unfavourable effects may be manageable in standard clinical practise.

Uncertainty in the knowledge about the unfavourable effects

The incidence of oedemas seems to be lower with the high macitentan dose (10 mg) than with the low macitentan dose in the elderly as compared to the adult population.

A causal relationship between macitentan and menstrual disorders or ovarian cyst is difficult to establish at the present time due to the overall low incidence of events, the confounding factors identified in patients with an event, and also due to the absence of dose-dependency or the presence of a specific temporal pattern. These events have been considered as potential risks in the RMP.

There are very limited data of macitentan in patients with IPF and associated PH/PAH (7 patients from the MUSIC-IPF study). However, the overall data with macitentan in IPF do not show any safety signal.

The SmPC (sections 4.2 and 4.4) reflects the limited clinical experience in patients over the age of 75 years, and therefore macitentan should be used with caution in this population.

There is also a higher rate of discontinuation due to liver related AEs in the macitentan groups, showing a dose response of 2.4% and 3.3% in the macitentan 3 mg and 10 mg respectively compared to the rate of 1.6% on the placebo group. These results can not totally negate the concern of hepatotoxicity. A post-hoc analysis of hepatic events has been conducted in patients at high risk (those who had a history of liver disease at screening; n=114). The analysis does show an increase in hepatic events between patients at high risk and those without risk factors, but without differences between macitentan and placebo in both strata. After review of summarized information on hepatic events from ongoing or recently completed studies with macitentan (e.g. MUSIC IPF, ischaemic digital ulcers, glioblastoma), it can be concluded that the pattern of hepatic events (AEs related to hepatobiliary disorders as well as the incidence of liver test elevation) is different across indications.

In the PAH population, the lower incidence of hepatic events in macitentan-treated patients versus placebo is likely to be related to the efficacy of macitentan versus placebo in preventing right sided heart failure and associated hepatic congestion, which is the main cause of transaminase elevations in patients with PAH. The incidence of ALT and/or AST > 3xULN (3.4% in the SERAPHIN study in the 10 mg group with a median exposure of 116 weeks) is well within the range observed with ambrisentan (3.6% from Kaplan-Meier estimate at 1 year in 483 patients) and below that which had been observed with bosentan in PAH (11%-14% at the target dose of 250 mg/day). However, there are no head-to-head clinical studies to conclude that macitentan provides an improved safety profile in comparison with other ERAs (i.e.: bosentan, ambrisentan). Although no hepatic signal was observed in the SERAPHIN study in PAH, an imbalance in hepatobiliary adverse events was found in IPF and in patients with essential hypertension. In conclusion, with the data available, a potential association between macitentan and risk of liver toxicity cannot be definitively ruled out.

Macitentan prolonged the values of some coagulation tests (e.g.: prothrombin time) in preclinical studies. There are no clinical data suggesting a potential interference of macitentan with coagulation tests in humans.

There is a slightly higher incidence of bleeding events reported in the macitentan groups (19.6% and 18.6% in the macitentan 3 mg and 10 mg respectively) compared to placebo (14.5%). This was mainly driven by the higher incidence of gynaecological bleedings (6.9% and 5.1% in the macitentan 3 mg and 10 mg respectively) compared to placebo (1.1%). Importantly, there is no dose response observed in all these reported bleedings. In general, concomitant administration of antithrombotics or PDE5 inhibitors was associated with a higher bleeding rate, which is expected. No direct causal relationship can be found between macitentan administration and the increased bleeding events. There are no known PK interactions between macitentan and warfarin or sildenafil.

Benefit-risk balance

Importance of favourable and unfavourable effects

Prevention of PAH-related morbidity/mortality is the most important target in PAH. This is the first application in PAH that provides a pivotal study appropriately designed and powered to show an outcome benefit of a specific therapy in patients with PAH. The benefit of macitentan 10 mg versus placebo in the chosen primary endpoint was highly clinically relevant, corresponding to an overall relative risk reduction of 45% and a number-needed-to-treat (NNT) of approximately 6 patients needed to prevent an event at 2 years, and was accompanied by consistent favourable effects in other clinically relevant endpoints (e.g.: improvement in WHO FC, dyspnoea symptoms, quality of life, reduced hospitalizations, and hemodynamic parameters). However, the positive results were mainly driven by events signifying clinical worsening rather hospitalisation. In addition, SERAPHIN study had some drawbacks related to mortality data that preclude including a mortality claim (see section about “uncertainty in the knowledge about the beneficial effects”).

The unfavourable effects were mainly class effects seen with other ERAs (e.g.: oedemas, anaemia transaminase increase) that are manageable in standard practice.

Benefit-risk balance

The importance and magnitude of the clinically relevant favourable effects of macitentan on the clinical course of PAH exceeds the importance and magnitude of the unfavourable effects.

Discussion on the benefit-risk balance

Clinical data available supports the efficacy of macitentan 10 mg OD in the long-term treatment of PAH in adults. The efficacy has been shown in adult patients with functional class II and III, as monotherapy or in combination with other PAH therapies (PDE-5 inhibitors and prostanoids), in a PAH population with idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. The agreed indication does not include any specific claim and should be interpreted in light of the more robust evidence with macitentan from SERAPHIN regarding delay in clinical worsening of PAH in comparison with other PAH therapies where claims have been limited to the 6MWT and/or symptoms. However, as comparative studies are lacking, no final conclusions can be drawn on their relative benefit in patients with PAH.

The overall Benefit Risk of Opsumit is positive.

5. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Opsumit/macitentan is not similar to sildenafil, iloprost, bosentan and ambrisentan within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Opsumit for the following indication:

Opsumit, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in patients of WHO Functional Class II to III.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease (see section 5.1).

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Healthcare Professional brochure addressing the important identified risks of anaemia, hepatotoxicity and teratogenicity as well as the need for patient communication regarding these risks.

Prescribing checklist for healthcare professionals to address the risk(s) of anaemia, hepatotoxicity, and teratogenicity

Educational material for patients and/or carers to address the risk(s) of anaemia, hepatotoxicity and teratogenicity

Patient alert card

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall agree the details of the Prescriber kit and a controlled distribution system with the National Competent Authority and implement it prior to launch in that Member State. The MAH shall ensure that prior to prescribing all healthcare professionals who intend to prescribe and/or dispense Opsumit are provided with a Prescriber Kit containing the following:

• The Summary of Product Characteristics for Opsumit
• Prescribing checklists
• Healthcare Professional brochure containing information about Opsumit
• Patient reminder cards

The prescribing checklist should remind prescribers of the contraindications, warnings and precautions as well as the following key elements:

- to provide patients with appropriate information regarding the safe use of the product
- To ensure females of childbearing potential are not pregnant and are on reliable contraception prior to starting Opsumit
- to provide patients with the patient card
- the need for baseline and monthly pregnancy tests and monitoring of haemoglobin levels and liver function.

The Healthcare Professionals brochure should contain the following key elements:

- That patients should be capable of complying with the requirements for the safe use of Opsumit

- the risk of anaemia, hepatotoxicity and teratogenicity and the need for reliable contraception
- the need for baseline and:
  - monthly pregnancy tests
  - regular monitoring of haemoglobin levels
  - regular monitoring of liver function.
- The importance of telling patients to report immediately any possible pregnancy that occurs during Opsumit use.

The patient reminder card for patients prescribed Opsumit should include the following key elements:
• That Opsumit is teratogenic in animals
• That pregnant women must not take Opsumit
• That women of childbearing potential must use reliable contraception
• The need monthly pregnancy tests for
• The need for regular blood tests because Opsumit causes a decrease in haemoglobin
• The need for regular monitoring of liver function because Opsumit has hepatotoxic potential

- **Obligation to complete post-authorisation measures**

Not applicable.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member State shall agree the details of the Prescriber kit and a controlled distribution system with the Marketing Authorisation Holder (MAH) and must implement such programme nationally prior to launch to ensure that:

- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) are provided with a prescriber kit containing the following:
  - Educational Health Care Professional's kit
  - Educational brochures for Patients
  - Patient cards

- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

These conditions reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that macitentan is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan [P/0087/2012] and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.