Macitentan/ACT-064992

Pulmonary Arterial Hypertension

Protocol AC-055-303 OL

SERAPHIN-OL: Study with an ERA in Pulmonary arterial Hypertension to Improve cliNical outcome (Open Label)

Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT-064992 in patients with symptomatic pulmonary arterial hypertension

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Macitentan/ACT-064992

Disease

Pulmonary arterial hypertension.

Protocol number. acronym, title

AC-055-303/SERAPHIN OL:

Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT-064992 in patients with symptomatic pulmonary arterial hypertension

I approve the design of this study.

Title	Name	Date	Signature
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Drug name/number
Macitentan/ACT-064992

Disease
Pulmonary arterial hypertension.

Protocol number, acronym, title
AC-055-303 OL/SERAPHIN OL: Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT-064992 in patients with symptomatic pulmonary arterial hypertension

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Country Coordinating Investigator	Name Title	Country	Signature	Date
Center Principal Investigator	Name Title	Center number Town Country	Signature	Date

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BP	Blood pressure
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CRO	Contract research organization
CYP	Cytochrome
EC	Ethics committee
ECG	Electrocardiogram/graphy/graphic
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
ET_A	Endothelin receptor A
ET_B	Endothelin receptor B
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRT	Hormone replacement therapy
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IND	Investigational New Drug

IXRS	Interactive Voice/Web Recognition System
IRB	Institutional review board
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
OL	Open label
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamic
PH	Pulmonary hypertension
PK	Pharmacokinetic
PVR	Pulmonary vascular resistance
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
t.i.d.	Three times a day
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	17 Jul 2020
Amendment 5	10 June 2016
Amendment 4	27 Aug 2013
Amendment 3	22 Sep 2009
Amendment 2	18 Jul 2008
Amendment 1	15 Nov 2007
Original Protocol	01 Oct 2007

Amendment 6 (17 July 2020)

Overall Rationale for the Amendment: The purpose of this amendment is to update concomitant therapy section pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 and CYP2C9) from a pre-clinical study on implications of role of CYP2C9 in the metabolism of macitentan.

A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section Number and Name	**Description of Change**	**Brief Rationale**
3.1.4.1 Prohibited concomitant medications	Changes made to prohibited medications. • Current bullet point was modified as below: "Concomitant use of macitentan with strong inhibitors of CYP3A4 (ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) **or moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem,**	New DDI identified with implication on role of CYP2C9 in the metabolism of macitentan

Section Number and Name	Description of Change	Brief Rationale
	erythromycin, verapamil) should be avoided." • Following paragraph was added. "**If patients are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment."**	
3.1.4.1 Prohibited concomitant medications;6 References	A new reference was added to Section 3.1.4.1 and updated in the reference list.	To provide investigators with some examples of CYP3A4 and CYP2C9 inhibitors.

Abbreviations: CYP=cytochrome P450

PROTOCOL SYNOPSIS AC-055-303/SERAPHIN OL

TITLE	Long-term, single-arm, open label extension study of the SERAPHIN study to assess the safety and tolerability of macitentan/ACT-064992 in patients with symptomatic pulmonary arterial hypertension.					
ACRONYM	SERAPHIN OL: **S**tudy with an **ERA** in **P**ulmonary arterial **H**ypertension to **I**mprove cli**N**ical outcome (Open Label).					
OBJECTIVES	To assess the long-term safety and tolerability of macitentan in patients with symptomatic pulmonary arterial hypertension (PAH).					
DESIGN / PHASE	Multicenter, open-label (OL) extension, single-arm, Phase III study					
STUDY PLANNED DURATION	**First patient First visit**	Q4/07	**Last patient First visit**	Q1/12	**Last patient Last visit**	Open
CENTERS / COUNTRIES	118 centers in 34 countries.					
PATIENTS / GROUPS	550 patients in one group.					
INCLUSION CRITERIA	• Signed informed consent prior to initiation of any study-mandated procedure. • Patients with pulmonary arterial hypertension and having completed the event-driven study, AC-055-302/SERAPHIN, or Patients who have experienced a clinical worsening of PAH in AC-055-302/SERAPHIN and for whom a written approval to roll over into this study has been obtained from the Sponsor. • Women of childbearing potential must have a negative pre-treatment serum pregnancy test and must use a reliable method of contraception during study treatment and for at least 28 days after study treatment termination.					

EXCLUSION CRITERIA	• Any major violation of protocol AC-055-302/SERAPHIN. • Pregnancy or breast-feeding. • AST and/or ALT > 3 times the upper limit of the normal range. • Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. • Known hypersensitivity to macitentan or any of the excipients.
CONCOMITANT MEDICATIONS	**Prohibited** • Endothelin receptor antagonists (other than study drug). *Note: If the investigator considers a switch to commercial Opsumit®, treatment with commercial Opsumit® is allowed immediately after the EOT visit but the subject must still present for an EOS visit after the follow-up period.* *If the investigator considers a switch to another commercial ERA, treatment with that ERA must only begin after the follow-up period / EOS visit.* • Specific immune suppressants: cyclosporine A and tacrolimus, everolimus, sirolimus (calcineurin or mTOR inhibitors). • Concomitant use of macitentan with strong CYP3A4 inducers (carbamazepine, rifampin, rifabutin and St. John's wort) should be avoided. • Concomitant use of macitentan with strong inhibitors of CYP3A4 (ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) should be avoided. • Any investigational drug other than macitentan.

STUDY PERIODS	**Treatment period:** until the approval of macitentan for this indication is obtained or the sponsor decides to stop study AC-055-303/SERAPHIN OL. **Post-treatment safety follow-up:** up to 28 days after study drug discontinuation.
INVESTIGATIONAL DRUG	Macitentan tablet oral administration / dose 10 mg / once daily.
COMPARATIVE DRUG	Not applicable.
TOLERABILITY / SAFETY ENDPOINTS	• Treatment-emergent AEs up to 28 days after study drug discontinuation. • Treatment-emergent SAEs up to 28 days after study drug discontinuation. • AEs leading to premature discontinuation of study drug. • Occurrence of liver function test (ALT and/or AST) abnormality (> 3 and ≤ 5 × ULN; > 5 and ≤ 8 × ULN; > 8 × ULN) and hemoglobin abnormality (≤ 8 g/dL; > 8 and ≤ 10 g/dL) up to 28 days after study drug discontinuation.
STATISTICAL METHODOLOGY	This study will not be individually analyzed, but only in combination with data from the AC-055-302/SERAPHIN study. More precisely, the analysis set comprises (i) all patients in the AC-055-303/SERAPHIN OL study plus (ii) all patients who received macitentan during the AC-055-302/SERAPHIN study and did not participate in the AC-055-303/SERAPHIN OL study. In this set, the observation period for the individual patient starts at the time of the first administration of macitentan and ends with the permanent discontinuation of macitentan regardless of administration type (i.e., double blind or open label). The statistical evaluation of the safety and tolerability endpoints will be carried out descriptively.
STUDY COMMITTEES	A Steering Committee is involved in the study design and will provide guidance on the conduct of the study.

	An Independent Liver Safety Board is established to monitor the liver safety of macitentan including reviewing cases of confirmed elevations of aminotransferases > 3 × ULN.

Table 1 Visit and Assessment Schedule

PERIODS		**TREATMENT PERIOD**		**FOLLOW-UP PERIOD**
VISITS	**Enrollment (Visit 1)**	**Visit 2,3, etc.**	**End-of-Treatment (EOT)**	**End-of-Study (EOS)**
TIMEPOINTS / **ASSESSMENTS**	Day 1[1]	Month 6, and every 6 months thereafter ± 2 weeks		Up to 28 days after study drug discontinuation
Informed Consent	X			
Concomitant medication	X	X	X	X
Vital signs, Body weight Physical examination	Performed at each visit; Data will only be kept in patient's file			
Complete Laboratory Tests	X	X	X	
LFTs	X	Recommended monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Serum Pregnancy Test[2] (if applicable)	X	X	X	
Urine Pregnancy Test[2, 5] (if applicable)		Required monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Phone call for pregnancy test reminder and contraception counseling[2]		Required monthly (+/−1 week) up to at least 28 days after End-of-Treatment		
Study Drug Dispensing[4]	X	X		
Adverse Events[3]	X	X	X	X
Serious Adverse Events	X	X	X	X

[1]The tests are not to be repeated if measured during the End-of-Treatment visit of study AC-055-302/SERAPHIN that has been performed within 4 weeks of this visit. [2]Women of childbearing potential only; [3]AE reporting and follow-up: all AEs up to 28 days after study drug discontinuation. [4]Study drug may be dispensed on a monthly basis at each LFT visit. [5]Urine pregnancy test is required if no serum pregnancy test is performed.
AE = adverse event; LFT = liver function test.

PROTOCOL

1 BACKGROUND AND RATIONALE

1.1 Pulmonary hypertension

The most serious chronic disorder of the pulmonary circulation is pulmonary arterial hypertension (PAH), a syndrome of diverse etiology and pathogenesis characterized by the persistent increase in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death [Barst 2004, McLaughlin 2004, D'Alonzo 1991]. Pulmonary arterial hypertension is hemodynamically defined as a resting mean pulmonary arterial pressure greater than 25 mmHg with normal pulmonary capillary or left atrial pressure (< 15 mmHg) [McLaughlin 2004, Rubin 1997]. Numerous conditions are known to lead to or to be associated with the development of PAH. These conditions are classified into five groups based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach [Simonneau 2004]. Pulmonary arterial hypertension may occur in the absence of a demonstrable cause (idiopathic or familial) [Thomson 2003, McGoon 2004], or as a complication of congenital heart disease, systemic conditions such as connective tissue disease, particularly scleroderma [Battle 1996, Ungerer 1983, Tanaka 2002, Fagan 2004, Love 1990], HIV infection [Opravil 1997, Petitpretz 1994, Mehta 2000], sickle-cell disease [Gladwin 2004], chronic liver disease [Kuo 1997, Castro 1996], obstructive or restrictive lung disease [Weitzenblum 2005, Chaouat 2005, Thabut 2005], thromboembolic disease [Fedullo 2001, Pengo 2004], sarcoidosis [Shorr 2005], or as the result of the use of fenfluramine anorexigens [Gurther 1985, Fishman 1999, Abenhaim 1996, Delcroix 1998].

Pulmonary arterial hypertension is associated with structural changes in both the pulmonary vasculature and the right ventricle. The changes in vascular structure involve three combined elements: vasoconstriction, vascular-wall remodeling and thrombosis *in situ* [Humbert 2004a].

Recent advances [Farber 2004] in the understanding of the pathogenic factors leading to pulmonary vascular disease have led to the development of new therapies targeting specific pathways (the prostacyclin pathway, the endothelin pathway, and the nitric oxide pathway) [Humbert 2004b] that are believed to play pathogenic roles.

The available therapies have positive effects in PAH, but they do not provide a cure, and in many patients the disease will progress. Pure vasodilators, such as calcium channel blockers, are effective only in a minority of patients who have an acute response to vasodilator testing. Seven agents are currently approved for the treatment of PAH in the United States and Europe. Intravenous prostacyclin (epoprostenol), other prostanoid analogues (i.e., beraprost, treprostinil, and iloprost), a dual endothelin receptors antagonist (bosentan), and more recently, phosphodiesterase type 5 inhibitors (sildenafil) and

selective endothelin receptor antagonists (sitaxsentan and ambrisentan) have been shown to improve exercise capacity as assessed by the 6-minute walk test (6MWT) in short-term randomized placebo-controlled trials.

Despite these achievements, however, PAH remains a serious life-threatening condition [Humbert 2004b, Humbert 2004a]. Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

1.2 Endothelin-1 and pulmonary hypertension

Endothelin-1 (ET-1), a 21-amino-acid peptide, is one of the most potent vasoconstrictors and mitogens for smooth muscle and contributes to increased vascular tone and proliferation in pulmonary vasculopathy [Galie 2004].

There are two distinct receptors for ET-1: endothelin receptor A (ET_A) and endothelin receptor B (ET_B). The two receptors have unique binding locations and affinities for the endothelin peptide [Banigni 1995, Massaki 1998]. The ET_A receptors are expressed on pulmonary vascular smooth muscle cells, whereas ET_B receptors are present both on pulmonary vascular cells and on smooth muscle cells.

When activated, the ET_A receptor located in pulmonary vascular smooth muscle cells mediates a potent vasoconstrictive response and ET_B receptors on endothelial cells mediate vasodilatation via increased production of nitric oxide and prostacyclin [Hirata 1993, de Nucci 1988]. ET-1 is also known to be a potent mitogen, with the ability to induce cell proliferation in vascular smooth muscle cells. It has been shown that both the ET_A and ET_B mediate the mitogenic action of ET-1 [Clarke 1989, Chua 1992, Davie 2002, Sugawara 1996].

Laboratory and clinical investigations have clearly shown that ET-1 is overexpressed in several forms of pulmonary vascular disease. ET-1 is likely a major player in the vasodilator and vasoconstrictor imbalance, as well as in the abnormal pulmonary vascular remodeling present in the development and progression of PH of various etiologies [Stewart 1991, Giaid 1993].

1.3 Macitentan – Endothelin Receptor Antagonist

1.3.1 Macitentan – Preclinical information

Macitentan is a new, orally active, non-peptide, potent dual ET_A and ET_B receptor antagonist selected for clinical development in PAH and other indications associated with an activated ET-system. Macitentan shows dose-dependent efficacy similar to that observed with bosentan (Tracleer®, the first ERA registered for the treatment of patients with PAH) in preclinical models of hypertension and PAH, but macitentan is

approximately 10 times more potent than bosentan based on administered dose. In hypertensive rats, acute oral administration of macitentan dose-dependently decreases mean arterial blood pressure without affecting heart rate. Chronic oral administration of macitentan to hypertensive rats causes a sustained decrease in blood pressure that is not associated with accumulation, tachyphylaxis, rebound effect after cessation of treatment, or an increase in heart rate. In rats with monocrotaline-induced pulmonary hypertension, chronic oral administration of macitentan increases survival and dose-dependently reduces pulmonary pressure, pulmonary vascular hypertrophy, and right ventricular hypertrophy, without decreasing systemic blood pressure.

In preclinical safety studies, no effects on normal physiological functions or electrocardiographic (ECG) variables, including cardiac repolarization, were observed, with the exception of a decrease in arterial blood pressure observed in a cardiovascular study in dogs. Macitentan has no genotoxic potential. In the pivotal 26-week and 39-week toxicity studies, the exposures in animals found at the no-observed-adverse-effect-level are above the anticipated clinical exposures and provide a margin of safety for studies in man. A study conducted in hairless rats showed that macitentan is not phototoxic *in vivo*. Macitentan does not bind relevantly to melanin. Reproductive toxicity studies showed that macitentan is teratogenic without affecting male or female fertility. Teratogenicity is considered to be an ERA class effect.

Macitentan has been selected for further clinical development due to the following characteristics:

- Its potency and selectivity for endothelin receptors
- Its efficacy in preclinical models of hypertension and PAH
- The absence of significant inhibitory effects on bile salt transport, suggesting an improved liver safety profile compared to bosentan
- A pharmacokinetic profile consistent with once-daily dosing
- A good safety and tolerability profile

More detailed information on Macitentan can be found in the Macitentan Investigator's Brochure [Macitentan IB].

1.3.2 Macitentan – Clinical information

1.3.2.1 Phase I studies in healthy subjects

During the Phase I program about 150 healthy male subjects were treated with macitentan, administered as a capsule formulation. Macitentan was well tolerated in all studies. The most frequently reported adverse event (AE) was headache. No clear dose relationship could be discerned for any AE. However, in the single-ascending dose study, compared to

subjects receiving placebo, subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others). A dose of 300 mg was identified as the maximum tolerated dose.

Treatment with macitentan up to 600 mg as a single dose and 30 mg as multiple doses for 10 days (highest doses tested) was not associated with clinically relevant changes in systolic and diastolic blood pressures, heart rate, or ECG parameters and morphology.

Eight cases of asymptomatic increases in liver function tests (LFTs) were observed in the Phase I program. These increases in AST, ALT and/or GGT were below 2, 4, and 3 times the upper limit of normal (ULN), respectively. The increase in LFTs was not associated with any AE and resolved within 14 days of observation.

In healthy male subjects, the plasma concentration-time profile of macitentan, administered as a capsules formulation, can be described by slow absorption with maximum plasma concentrations achieved approximately 8 hours after dosing. The apparent elimination half-life was approximately 16 hours. After multiple dosing, the pharmacokinetics (PK) of macitentan were dose-proportional over the dose range tested. Steady-state conditions were reached by Day 3 and macitentan accumulated approximately 1.5-fold. In plasma, one metabolite was identified, ACT-132577. This metabolite was pharmacologically active, reached steady state by Day 7 and had an apparent elimination half-life of about 2 days. The accumulation factor was approximately 8.5. Also for the metabolite the PK after multiple dose administration were dose-proportional. Based on the PK of macitentan and its metabolite ACT-132577, as well as the observation that macitentan had no effect on the urinary 6β-hydroxycortisol/cortisol ratio, no signs of auto-induction were detected in this study.

Macitentan increased plasma ET-1 concentrations for all single doses from 5 mg upwards. When given as multiple doses, an increase in ET-1 levels was observed for all tested doses.

Results from the food interaction study showed that macitentan can be taken irrespective of food intake.

Macitentan did not influence the PK and pharmacodynamics (PD) of warfarin. Similarly, co-administration of warfarin with macitentan appeared not to have an impact on the exposure of macitentan.

There are no clinically relevant effects of sildenafil 20 mg t.i.d. on the PK of macitentan and its metabolite (ACT-132577). Also, no effect of macitentan was observed on the PK of sildenafil and its metabolite (N-desmethyl sildenafil).

In the presence of the strong CYP3A4 inhibitor ketoconazole, an increase of approximately 2-fold in area under the curve was observed for macitentan, while exposure to ACT-132577

was reduced by 26%. Therefore, concomitant use of macitentan with strong inhibitors of CYP3A4 should be avoided.

The results from the biocomparison study indicated a lower C_{max} of macitentan of the tablets when compared to the capsule formulation, which was deemed not to be clinically relevant as the total exposure of macitentan and ACT-132577 and C_{max} of ACT-132577 of the different formulations were found to be similar.

More detailed information on macitentan Phase I studies can be found in the Macitentan Investigator's Brochure [Macitentan IB].

1.3.2.2 Phase II study in patients with essential hypertension

A Phase II dose-finding study was conducted over 8 weeks in 379 patients with mild to moderate essential hypertension. Four doses of macitentan (0.3, 1, 3, and 10 mg) and enalapril (20 mg) once daily were evaluated versus placebo. The primary efficacy endpoint was the change from baseline to Week 8 in mean sitting diastolic blood pressure (BP) at trough (i.e., 24 hours post dose).

This study has demonstrated that macitentan is efficacious in reducing the blood pressure in subjects with mild to moderate essential hypertension. Treatment with the 10-mg dose showed a statistically significant reduction versus placebo in sitting diastolic and systolic BP at trough, and a dose-response for effect was indicated. The point estimates of the treatment effect at the two highest doses of macitentan tested were higher than that with enalapril 20 mg once a day (study was not powered to compare to enalapril). Most of the BP reduction with macitentan was reached within 4 weeks of treatment. The PK/PD analysis supported the clinical findings, and indicated that the 10 mg dose is close to the plateau of the pharmacological effect.

Macitentan was well tolerated across all four dose levels. The overall frequency of AEs was similar to that observed in the placebo group. The numbers of subjects with at least one serious adverse event (SAE) were equally distributed across groups. There were no deaths.

The study was terminated prematurely following the Sponsor's decision to break the blind for a safety evaluation of five cases of increased liver enzymes > 3 × ULN. These five cases occurred in the macitentan groups, without obvious dose relationship (one, two, one, and one in the 0.3-mg, 1-mg, 3-mg, and 10-mg dose groups, respectively). In three cases, there were other, plausible reasons for increased liver enzymes (pancreatic cancer, surgery with general anesthesia, and concomitant antibiotic therapy, respectively). All episodes of liver enzyme elevations resolved without sequelae within 14 days of observation. However, these data suggest that like other ERAs, macitentan may cause liver enzyme elevations in some patients.

More detailed information on macitentan Phase II studies can be found in the Macitentan Investigator's Brochure [Macitentan IB].

1.3.2.3 Phase III study in patients with pulmonary arterial hypertension

A Phase III study in patients with PAH (AC-055-302/ SERAPHIN) was conducted in 742 patients randomized to placebo or macitentan 3 or 10 mg in a 1:1:1 ratio. In this event driven study, macitentan or placebo was administered in a double-blind fashion for up to 3.6 years.

Mean exposure to study treatment was 85.3 weeks for placebo patients (n = 249), 99.5 weeks for patients on 3 mg (n = 250) and 103.9 weeks for patients on 10 mg (n = 242). Macitentan, at both the 3 mg and 10 mg dose, decreased the risk of a morbidity/mortality event over the treatment period versus placebo. This risk was reduced by 45% in the 10 mg dose group ($p < 0.0001$). At 3 mg, the observed risk reduction was 30% ($p = 0.0108$).

A dose-dependent effect ($p < 0.05$ for either dose) was also observed in all secondary efficacy variables including exercise capacity assessed with the 6MWT, PAH symptoms assessed by the WHO FC and hospitalization and mortality.

Additionally, in a hemodynamic sub-study, the observed treatment effect of reduction in PVR after 6 months of treatment with macitentan 3 mg and 10 mg was 30.0% (97.5% confidence limits 17.9, 44.0) and 36.5% (97.5% confidence limits 21.7, 49.2), respectively.

Treatment with macitentan was well tolerated. The number of AEs reported and patients discontinuing treatment due to AEs was similar across all groups. The overall incidence of elevations in liver aminotransferases was similar to placebo (4.5%, 3.6% and 3.4% incidence of ALT or AST > 3 × upper limit of the ULN in the placebo, macitentan 3 mg and macitentan 10 mg groups, respectively). In addition, no differences were observed between macitentan and placebo on fluid retention (edema). AEs associated with decreased hemoglobin was observed more frequently on macitentan 10 mg than placebo, with no difference in treatment discontinuation between groups.

More detailed information on macitentan Phase III studies can be found in the Macitentan Investigator's Brochure [Macitentan IB].

1.4 Study rationale

1.4.1 Medical background

Macitentan is a new orally active, non-peptide, dual ET_A and ET_B receptor antagonist selected for clinical development. In animal models of PAH and systemic hypertension, macitentan shows dose-dependent efficacy, similar to that observed with bosentan. In rats with monocrotaline-induced PH, oral chronic macitentan increased survival and dose-

dependently reduced pulmonary pressure, pulmonary vascular hypertrophy, and right ventricular hypertrophy, without decreasing blood pressure [Macitentan IB].

Macitentan was chosen for development in PAH because it is approximately 10 times more potent than bosentan, has shown a PK profile consistent with once-daily dosing, and a reduced potential to inhibit bile salt elimination and therefore a more attractive safety margin, especially in regard to liver enzyme injury [Macitentan IB].

The main objective of the AC-055-303/SERAPHIN OL study, which will follow the AC-055-302/SERAPHIN study, will be to assess the long-term safety and tolerability of macitentan in patients with symptomatic PAH.

1.4.2 Patient population

The patient population will consist of

- Patients who complete the event-driven treatment period of protocol AC-055-302/SERAPHIN as scheduled
- Patients experiencing a clinical worsening of PAH, as defined in the AC-055-302/SERAPHIN protocol, and leading to permanent study treatment discontinuation in the AC-055-302/SERAPHIN study. The enrollment of these patients can only be performed after a formal request from the site and after written approval from the Sponsor

1.4.3 Study design

An open-label, non-comparative, multicenter, extension study following the AC-055-302/SERAPHIN study to assess long-term safety and tolerability of macitentan in patients with symptomatic PAH.

The OL study design has been discussed and approved by the Steering Committee Members.

1.4.4 Dose selection

The proposed dose (10 mg once daily) is the higher dose used in the Phase III study (AC-055-302/SERAPHIN).

1.4.5 Treatment duration

Study treatment for each patient lasts from his/her enrollment date until the end of the trial i.e., until the earliest of: (i) the approval of macitentan in this indication is obtained in the patient's country, or (ii) the sponsor decides to stop study AC-055-303/SERAPHIN OL, or (iii) the patient's, investigator's or Sponsor's decision to discontinue study drug.

1.4.6 Primary endpoint

No primary efficacy endpoint is considered for this OL extension study.

1.4.7 Statistical hypotheses and sample size

No statistical hypothesis is considered for this OL extension study.

2 STUDY OBJECTIVES

To assess long-term safety and tolerability of macitentan in patients with symptomatic PAH.

3 INVESTIGATIONAL PLAN

This will be a multicenter, open-label, extension study to assess long-term safety and tolerability of macitentan in patients with symptomatic PAH.

550 patients (males or females aged 12 years or older) from the event-driven study AC-055-302/SERAPHIN are enrolled in this Phase III OL study (see Section 1.4.2). The study will be conducted in 118 centers in 34 countries. The patients are rolled over from the event-driven study to the OL study without knowledge of their previous study drug (macitentan or placebo).

Enrollment in the AC-055-303/SERAPHIN OL study (OL Visit 1) should correspond to the last visit in the AC-055-302/SERAPHIN study. If this is not possible, enrollment in the OL study must occur within 2 months of the AC-055-302/SERAPHIN End-of-Treatment (EOT) Visit.

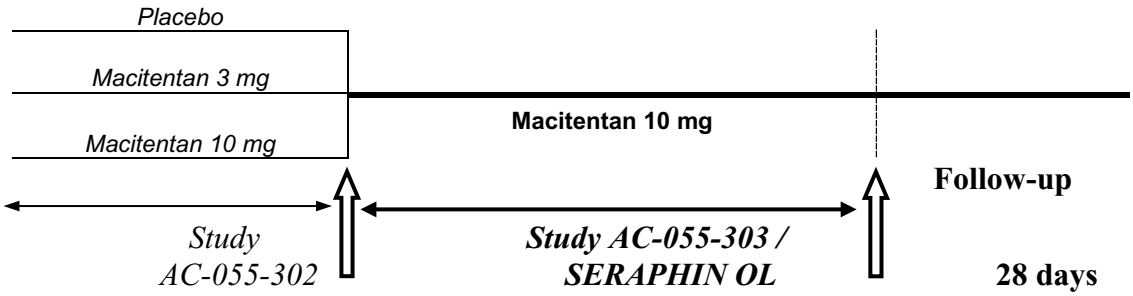
The target study drug tablet, 10 mg of macitentan, will be taken orally once daily, irrespective of food intake.

At the end of the open-treatment period/discontinuation of treatment, a post-treatment safety follow-up period (28 days) will follow.

A Steering Committee is involved in the study design and will provide guidance on the conduct of the study.

No interim analysis is planned.

Figure 1 Study design



3.1 Study population

3.1.1 Patient population

The patient population will consist of patients who complete the event-driven treatment period of protocol AC-055-302/SERAPHIN as scheduled, and patients who have experienced a clinical worsening of PAH in AC-055-302/SERAPHIN and for whom a written approval to roll over into this study has been obtained from the Sponsor.

3.1.2 Inclusion criteria

- Signed informed consent prior to initiation of any study-mandated procedure.
- Patients with pulmonary arterial hypertension and having completed the event-driven study, AC-055-302/SERAPHIN, or
- Patients who have experienced a morbidity event and for whom a written approval to roll over into this study has been obtained from the Sponsor.
- Pregnancy – Not allowed during the study:
  Women of childbearing potential* with a negative pre-treatment serum pregnancy test and who consistently and correctly use (from screening and up to 28 days after study treatment discontinuation) a reliable method of contraception with a Pearl index of < 1% (oral hormonal contraceptive, implant, vaginal hormone ring, intrauterine system, or tubal ligation only in combination with condom), are sexually abstinent or have a vasectomized partner are allowed in the study.

*A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy,
- premature ovarian failure confirmed by a specialist gynecologist,
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis,
- fulfilling the criteria of postmenopausal at the screening of AC-055-302/SERAPHIN,
- age > 50 years and not treated with any kind of hormone replacement therapy for at least 2 years prior to Visit 1 of the AC-055-303/SERAPHIN OL study with amenorrhea for at least 24 consecutive months prior to this visit and a serum follicle stimulating hormone level of > 40 IU/L if the investigator has insufficient evidence that the woman is postmenopausal.

3.1.3 Exclusion criteria

- Any major violation of protocol AC-055-302/SERAPHIN.
- Pregnancy or breast-feeding.
- AST and/or ALT > 3 times the upper limit of the normal range.
- Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence, or psychiatric disease.
- Known hypersensitivity to macitentan or any of the excipients.

3.1.4 Concomitant medications

All concomitant medications (ongoing, initiated, and discontinued) including PAH specific medications and diuretics, herbal drugs and implanted/vaginal hormonal contraceptives taken in the period between Visit 1 and up to End-of-Study (EOS) must be recorded on the Concomitant Medication pages of the CRF.

Any dose changes in PAH-specific medications only (e.g., endothelin receptor antagonists, prostanoids, and phosphodiesterase type 5 inhibitors, initiation of continuous chronic oxygen therapy), must be recorded in the CRF. Dose changes of other medications may be recorded in the CRF at the investigator's discretion.

3.1.4.1 Prohibited concomitant medications

- Endothelin receptor antagonists (other than study drug)
  Note: If the investigator considers a switch to commercial Opsumit®, treatment with commercial Opsumit® is allowed immediately after the EOT visit but the subject must still present for an EOS visit after the follow-up period.

If the investigator considers a switch to another commercial ERA, treatment with that ERA must only begin after the follow-up period / EOS visit.),

- Specific immune suppressants: cyclosporine A and tacrolimus, everolimus, sirolimus (calcineurin or mTOR inhibitors),
- Concomitant use of macitentan with strong CYP3A4 inducers (carbamazepine, rifampin, rifabutin and St. John's wort) should be avoided,
- Concomitant use of macitentan with strong inhibitors of CYP3A4 (ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) should be avoided, refer to the Food and Drug Administration website [FDA 2020],
- Any investigational drug other than the macitentan.

If patients are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment.

3.2 Study drug

3.2.1 Study drug packaging, labeling

Patients who meet all inclusion criteria and none of the exclusion criteria will receive macitentan, 10 mg, in addition to their usual treatment. Actelion will provide study drug as tablets in childproof bottles containing 36 tablets. The study drug will be provided in:

- One medication kit containing 6 bottles for a 6 month treatment period or
- 6 individual bottles covering a 6 month treatment period

The labeling and packaging of macitentan will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and any local or national regulatory requirements.

3.2.2 Study drug storage and dispensing

The investigator is responsible for the safe and proper handling and storage of the study drug at the investigational site, and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked room, which can be accessed only by the pharmacist, the investigator, or another duly designated person. The study drug must not be stored

above 30 °C and must be protected from moisture. The study centers will be supplied with study drug according to the centers' needs, depending on the enrolled number of patients. Each center will have an individual stock of study drug, which will be re-supplied in a timely manner as soon as a pre-defined minimum level of study drug has been reached as controlled by an Interactive Voice/Web Recognition System (IXRS).

At each visit the medication kit or bottle numbers will be allocated to the subject through IXRS.

Patients will receive study drug at enrollment (Visit 1) and at the 6-monthly visits thereafter up to EOT. The frequency of dispensing of study drug must be documented in the patient's file. The patients will either receive a medication kit containing 6 bottles or 6 individual bottles covering a 6 months' treatment period at scheduled visits (one bottle contains 36 tablets). Patients may receive study drug at monthly visits (if applicable) if deemed necessary due to logistical reasons.

Each medication kit or bottle will have a label with a tear-off part specifying the study protocol number and the batch number. At study drug dispensing, the investigator or pharmacist (if applicable) must remove the tear-off label from the medication kit or from the individual bottle (whatever applies) and attach the label to the Investigational Medicinal Product Label Dispensing Log.

3.2.3 Treatment dose and administration

One tablet must be taken orally once daily, irrespective of food intake.

3.3 Study drug discontinuation and study withdrawal

The permanent discontinuation of study drug corresponds to the EOT for an individual patient.

3.3.1 Study drug interruption or permanent discontinuation

The investigator must temporally interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.

The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., ECG or laboratory abnormalities), or for administrative reasons such as withdrawal of the patient's consent. The reason for study drug interruption or premature discontinuation must be documented in the case report form (CRF).

Interruptions should be for less than 4 weeks; longer interruptions should lead to permanent discontinuation of study drug.

A patient will be considered lost to follow up only after exhausting all means of contact.

3.3.2 Patient's follow-up after study drug discontinuation

If the patient is permanently withdrawn from the study, a complete EOT visit will be performed (see Section 3.8.2.2) and the patient will be followed for 28 days after the permanent study drug discontinuation and perform an EOS visit to collect information on serious adverse events related to macitentan. If withdrawal is considered study drug-related, the patient will remain under the supervision of the investigator until satisfactory health has returned.

3.3.3 Replacement policy

3.3.3.1 Patients

Patients prematurely discontinued from the study drug for any reason will not be replaced.

3.4 Treatment exposure, compliance and drug accountability

Adequate records of study drug received, dispensed, used, lost, and intervals between visits must be kept during the study. Study drug accountability is performed on an ongoing basis by the study staff and checked by the monitor during site visits and at completion of the study. Patients are asked to return all unused study drug (including empty bottles and cartons) at each visit. At the conclusion of each patient's participation in the study, all remaining drug supplies must be returned to the Sponsor for an accurate accounting of delivered and returned drugs.

All remaining drug supplies shall be collected and returned to the Sponsor for destruction by the Sponsor representative. Destruction must be documented.

3.5 Treatment assignment

3.5.1 Treatment assignment

Treatment is macitentan 10-mg tablets for all patients.

3.5.2 Blinding

Not applicable.

3.5.3 Emergency procedure for unblinding

Not applicable.

3.6 Study endpoints

3.6.1 Efficacy endpoints

Not applicable.

3.6.2 Safety and tolerability endpoints

- Treatment-emergent AEs up to 28 days after study drug discontinuation.
- Treatment-emergent SAEs up to 28 days after study drug discontinuation.
- AEs leading to premature discontinuation of study drug.
- Occurrence of treatment-emergent increase in ALT and/or AST up to 28 days after study drug discontinuation:
  - > 3 and $\leq 5 \times$ ULN
  - > 5 and $\leq 8 \times$ ULN
  - $> 8 \times$ ULN
- Occurrence of treatment-emergent hemoglobin abnormality up to 28 days after study drug discontinuation:
  - ≤ 8 g/dL
  - > 8 and ≤ 10 g/dL

3.7 Study assessments

The assessment performed at the EOT Visit for the event-driven study (AC-055-302/SERAPHIN) should not be repeated at enrollment (Visit 1) in the OL study if the EOT Visit was performed within 4 weeks of Visit 1. However, enrollment in the OL study must occur within 2 months of the AC-055-302/SERAPHIN EOT Visit.

3.7.1 Safety and tolerability assessments

The definitions, reporting and follow-up of AEs, SAEs and potential pregnancies are described in Section 4.

3.7.1.1 Vital signs and body weight

Vital signs (blood pressure and heart rate) and body weight will be assessed at the 6-monthly visits. The data will be kept in the patient's file (i.e., not recorded in the CRF).

3.7.1.2 Laboratory assessments

3.7.1.2.1 Type of laboratory

Both Central and Local Laboratories are used in the study.

Until approval of the Global Protocol version 5, blood sample analyses (hematology and biochemistry) were performed by local laboratories. For all the blood samples analyzed

from beginning of the study up to approval and implementation of the Global Protocol version 5, local laboratory reports present at the site were used to record protocol mandated laboratory results in the Actelion database. If re-test or unscheduled blood samples had been analyzed between regular visits for the purpose of monitoring an AE, the results of the analyses were also be recorded in the Actelion database.

After approval and implementation of Global Protocol version 5, the hematology and biochemistry blood samples are to be collected at site and sent to the Central Laboratory for analysis whenever possible (see contact details on page 2). The Central Laboratory reports will be sent to the Investigator. Any complete or partial re-test blood sample deemed necessary to follow-up an AE or to verify an unexpected abnormal value should also be sent to the Central Laboratory.

Under specific circumstances (e.g., patient lives far away from the site and cannot return every month), laboratory samples could be drawn in a local laboratory using Central Laboratory kits which will be sent to and analyzed by the Central Laboratory.

In the exceptional event (e.g., patient is admitted in a different hospital from the site) where a local laboratory is utilized for analysis of blood samples, data of these tests must be recorded in the Actelion database.

The results (whether obtained via Local or Central Laboratory) will be kept in the patient's file. Any clinically significant marked laboratory abnormalities must be reported by the investigator as an AE and/or SAE as appropriate (see Section 4). All Laboratory reports must be reviewed, signed and dated upon receipt.

Any pregnancy occurring during the treatment period and up to 28 days after study drug discontinuation must be reported immediately to the Actelion Drug Safety Department using the Actelion Pregnancy Form (see Section 4).

Details about collection and shipment of samples, and the reporting of results and abnormalities, can be found in the laboratory manual provided to the investigator.

3.7.1.2.2 Laboratory parameters

The laboratory tests from the last visit in AC-055-302/SERAPHIN can be used at the AC-055-303/SERAPHIN OL Enrollment Visit (OL Visit 1). The tests should not be repeated if enrollment in AC-055-303/SERAPHIN OL is within 4 weeks of the latest known results.

Hematology and blood chemistry

Hematology and blood chemistry tests will be performed at the Enrollment Visit (OL Visit 1), if it occurs more than 4 weeks after the last visit in AC-055-302/SERAPHIN, and then

every 6 months until EOT. They include hemoglobin, hematocrit, platelet, leukocyte and erythrocyte counts, liver aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, creatinine, urea, glucose, sodium, potassium, and albumin.

Pregnancy test

A serum pregnancy test for women of childbearing potential (WOCBP) must be performed at the Enrollment Visit (OL Visit 1), if it occurs more than 4 weeks after the last visit in AC-055-302/SERAPHIN, and then every 6 months until EOT.

At the 6-monthly visits, a serum pregnancy test will be obtained using the blood draw already scheduled at this visit.

For all other interim months, urine pregnancy tests will be performed by the patients at home. The urine pregnancy test kits provided to the patients by the site should be used.

In order to ensure proper pregnancy monitoring and contraception counseling, site staff must call each WOCBP once per month to:

- remind her to perform an urine pregnancy test and
- collect the outcome of the urine pregnancy test

During each visit at site / at each telephone call, it must be verified whether the method of contraception used previously is still valid, in accordance to the protocol and correctly used by the subject. For prepubescent women, childbearing potential must be assessed at each visit / telephone call and the women must be advised to use reliable methods of contraception as soon as childbearing potential has been established.

Urine pregnancy test kits will be provided by the central laboratory to the sites for dispensing to the patients.

Liver aminotransferase monitoring in all patients

Liver aminotransferase levels must be measured at the Enrollment Visit (OL Visit 1), if it occurs more than 4 weeks after the last visit in AC-055-302/SERAPHIN, and then every 6 months until EOT.

Monthly liver aminotransferase monitoring is recommended for up to at least 28 days after EOT but it is at the investigator's discretion to decide (taking into account the patient's medical history and AEs) if those additional monthly tests are required/justified.

Table 2 Study treatment adjustment in the event of ALT and/or AST elevations

ALT and/or AST	Treatment and monitoring recommendations
> 3 and ≤ 8 × ULN	Confirm by another test adding total and direct bilirubin and alkaline phosphatase measurements. If confirmed, interrupt treatment, monitor aminotransferase, bilirubin and alkaline phosphatase levels weekly until levels return to pre-treatment values. If the aminotransferase values return to pre-treatment levels re-introduction of study treatment can be considered. Interruptions should be for less than 4 weeks; longer interruptions should lead to permanent discontinuation of study drug. Re-introduction of study treatment after treatment interruption should only be considered if the potential benefits of treatment with macitentan outweigh the potential risks and when liver aminotransferase values are within pre-treatment levels. The advice of a hepatologist is recommended. Liver aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks and thereafter according to the recommendations above (i.e., at monthly intervals).

ULN = Upper Limit of Normal

In case of associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), and/or increases in total bilirubin ≥ 2 × ULN or aminotransferases > 8 × ULN, treatment must be stopped and re-introduction of study treatment is not to be considered. Aminotransferase, bilirubin and alkaline phosphatase levels must be monitored weekly after study drug discontinuation until values return to pre-treatment levels.

Other diagnoses should be considered and ruled out by performing the appropriate tests (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus, etc.). A "SERAPHIN LFT increase questionnaire" must be completed for confirmed elevations of aminotransferases > 3× ULN.

All LFT abnormalities leading to study drug discontinuation must be recorded as AEs (see Section 4).

3.8 Visit and assessment schedule

For a tabulated summary of all visits and assessments described in the following sections see Table 1.

3.8.1 Enrollment visit

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this OL study after adequate explanation of the aims, methods and objectives of the study.

The visit includes:

- Patient information and consent form signature
- Physical examination
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Complete laboratory tests including:
    - Hematology (including hemoglobin),
    - Blood chemistry (including LFTs),
  - Serum pregnancy test (for women of childbearing potential), NOTE: monthly monitoring from enrollment and up to at least 28 days after permanent discontinuation of the macitentan treatment,
- Concomitant medication
- Dispensing of study drug.

The tests are not to be repeated if they were measured during the EOT Visit in AC-055-302/SERAPHIN, and if that visit was performed within 4 weeks of this visit.

3.8.2 Treatment period

After approval and implementation of Global Protocol version 6, LFTs and pregnancy (for women of childbearing potential) will be assessed as outlined in Table 1.

During this period, AEs/SAEs and concomitant medication will be reported in the CRF.

3.8.2.1 Visits at 6-monthly intervals (Visit 2, 3, etc.)

After the OL Visit 1, all following visits are scheduled every 6 months ± 2 weeks. The morning dose of the study drug should be taken as usual.

These visits include:

- Physical examination
- Measurement of vital signs and body weight
- Laboratory tests including:

  - Complete laboratory tests including:
    - Hematology (including hemoglobin),
    - Blood chemistry (including LFTs),
  - Serum pregnancy test (for women of childbearing potential), NOTE: monthly monitoring from enrollment and for up to at least 28 days after permanent discontinuation of the macitentan treatment,
- AEs and SAEs since last visit will be reported in the CRF
- Concomitant medication will be reported in the CRF (for details see Section 3.1.4)
- Dispensing of study drug macitentan.

3.8.2.2 End-of-Treatment Visit (EOT) or Permanent discontinuation

Actelion will notify all sites when an EOT Visit should be planned. At the end of the OL study (see Section 1.4.5 for definition), the EOT Visit is scheduled for all patients. Any visit formerly scheduled within 2 weeks of the end of the study will not be performed.

Patient permanently discontinuing macitentan treatment must also undergo the EOT Visit as soon as the treatment is discontinued.

This visit includes:

- Physical examination
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Complete laboratory tests including:
    - Hematology (including hemoglobin),
    - Blood chemistry (including LFTs),
  - Serum pregnancy test (for women of childbearing potential),
- AEs and SAEs since last visit will be reported in the CRF
- Concomitant medication will be reported in the CRF (for details see Section 3.1.4)
- Return of unused medication including empty bottles and cartons.

All patients will have an EOS Visit (except for withdrawals and patients lost to follow-up).

3.8.3 End-of-Study (EOS) Visit or 28-day follow-up

Adverse events (serious or not) occurring up to 28 days after EOT should be reported in the CRF and in the SAE form, if applicable. Serious adverse events occurring thereafter, and ongoing SAEs, must be followed-up for 28 days after study drug discontinuation and reported in the SAE form.

Liver function tests, hemoglobin assessments and pregnancy tests (for women of childbearing potential) must also be performed up to at least 28 days after study drug discontinuation.

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

Periods	Treatment	Follow-up	After follow-up
Timeframe	During study drug administration	Up to 28 days after study drug discontinuation	After 28 days
AE/SAE reporting on CRF AE page	All AEs/SAEs	All AEs/SAEs	None
SAE reporting on SAE form	All SAEs	All SAEs	At investigator's discretion[2]
Reconciliation [1]	Yes	Yes	Not applicable
Final study report	Described	Described	Might be described

[1] Reconciliation between clinical and drug safety databases.
[2] Local laboratories must to be used to follow up on any laboratory abnormalities after the EOS visit.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the patient's baseline condition, i.e., any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.

- Abnormal assessments, e.g., ECG findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occurred, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

4.2.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale: mild, moderate, severe.

- **Mild**

Event may be noticeable to subject; does not influence daily activities; usually does not require intervention.

- **Moderate**

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

- **Severe**

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or intervention is usually needed.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day (see Section 4.3.1.2).

Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., LFT findings) considered as AEs. The investigator should tick non-applicable on the AE page of the CRF to qualify the intensity of the AE.

4.2.3 Relationship to study drug

Adverse events should be assessed by the investigators as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either related or unrelated.

- **Related to study drug**

This category applies to any AE (serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was interrupted, or discontinued.
- The event re-occurred when treatment was re-introduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

- **Unrelated to study drug**

This category applies to any AE (serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

4.2.4 Reporting of adverse events

All AEs occurring after study drug initiation and up to 28 days after study drug discontinuation must be recorded on specific AE pages of the CRF.

4.2.5 Follow-up of adverse events

Adverse events still ongoing after study drug discontinuation for a given patient must be followed up to 28 days after study drug discontinuation.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 Serious adverse events

A serious adverse event (SAE) is defined by the International Council for Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening.
- Requiring patient's hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above.

Life-threatening refers to an event in which the subject/patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it had been more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Macitentan Investigator's Brochure [Macitentan IB].

4.3.1.2 Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room due to an adverse event.

An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs/SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.

- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

4.3.1.3 Serious adverse events related to study-mandated procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

4.3.2 Reporting of serious adverse events

4.3.2.1 Enrollment period

Serious adverse events occurring from signature of the Informed Consent to study drug initiation must be reported only if they are considered by the investigator to be related to study-mandated procedures.

An SAE not temporally associated with the use of a study drug, should be considered by the investigator as study-related if it appears to have a reasonable possibility of relationship (i.e., a relationship cannot be ruled out) to protocol-mandated procedures (e.g., complication of a mandated invasive procedure or car accident on the way to the hospital for a study visit, etc.).

These SAEs are not reported in the CRF. Therefore, they are only collected on the SAE form and entered only into the drug safety database.

4.3.2.2 Treatment period

All SAEs regardless of causal relationship must be reported, including those related to study-mandated procedures. These SAEs occurring between study drug initiation and up to 28 days after study drug discontinuation must be reported, are defined as treatment-emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the CRF. Therefore, they are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 Reporting procedures

All SAEs must be reported by the investigator to the Actelion Drug Safety department within 24 hours of the investigator's knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, whether or not this event is considered by the investigator to be related to study drug.

These SAE forms must be faxed to Actelion Drug Safety (see SAE Form). The investigator must complete the SAE form in English (unless otherwise specified) and assess the relationship to study drug.

Such preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. Actelion Drug Safety department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) and unexpected (not previously described in the reference safety document), serious adverse reactions will be expedited by Actelion to Health Authorities, ECs/IRBs and investigators, as appropriate.

The AE/SAEs listed below are commonly seen with the underlying PAH disease. For reporting, these SAEs will be treated as "disease-related" and therefore will not be subject to regulatory expedited reporting to Health Authorities, IRBs/IECs, and investigators:

Signs and symptoms of PAH include worsening/exacerbation/progression, including fatal outcome, heart failure, worsening right heart failure, collapse, syncope, hemoptysis, anorexia, abdominal pain, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, hypoxia, fatigue, dyspnea, orthopnea, palpitations, systemic arterial hypotension, and tachycardia. These SAEs must be reported on an SAE form and also on AE pages in the eCRF.

4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the EOS Visit must be followed until resolution or stabilization or until the event is otherwise explained.

New SAEs occurring at any time after the 28-day follow-up period after study drug discontinuation may be reported on a SAE form to Actelion drug safety within 24 hours of the investigator's knowledge of the event, if felt appropriate by the investigators. Therefore, these SAEs are entered only into the drug safety database and hence will not affect study closure.

4.4 Pregnancy

4.4.1 Teratogenicity

Due to the potential teratogenicity of macitentan, women of childbearing potential must take appropriate precautions. Women must not become pregnant during the study and for up to 28 days after study drug discontinuation.

If a woman becomes pregnant or if pregnancy is suspected the study drug must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be discontinued from the study and the Sponsor must be notified within 24 hours. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Under certain circumstances, it will be acceptable for women who became pregnant during the study to remain in the study, if all of the following conditions are met:

- Study drug has been withdrawn immediately after confirmation of pregnancy and
- Absence of pregnancy is confirmed within the maximal drug interruption period, i.e., within 4 weeks, before study drug is re-started and
- Documentation of appropriate contraceptive counseling has taken place and
- The patient agrees to practice reliable and effective contraception as required by this protocol during the remaining study treatment and for at least 28 days after study treatment termination and
- The re-introduction of study drug has been approved by Actelion

4.4.2 Reporting of pregnancy

Any pregnancy occurring during study drug administration or up to 28 days following study drug discontinuation, must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to Actelion Drug Safety (see Pregnancy Form), and on an AE page of the CRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to Actelion Drug Safety.

Such follow-up information will only be entered into the drug safety database and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Statistical analysis plan

A statistical analysis plan (SAP) will be written and finalized before study closure, i.e., database closure. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations and the link of major protocol deviations to the analysis sets.

Before study closure, medically trained staff will identify major and minor protocol deviations.

5.2 Analysis sets

Two different analysis sets are defined.

5.2.1 All-treated set

This analysis set comprises (i) all patients in the AC-055-303/SERAPHIN OL study plus (ii) all patients who received macitentan during the AC-055-302/SERAPHIN study and did not participate in the AC-055-303/SERAPHIN OL study.

This analysis set is used for the patient disposition summary.

5.2.2 Safety set

This analysis set comprises all subjects included in the All-treated set, who had at least one post-baseline safety assessment. Baseline is defined as the Baseline of AC-055-302/SERAPHIN for the patients who received macitentan during AC-055-302/SERAPHIN and as macitentan initiation in AC-055-303/SERAPHIN OL for the patients who received placebo during AC-055-302/SERAPHIN. This analysis set is used as the denominator for the calculation of AE rates.

5.3 Primary efficacy endpoint

Not applicable.

5.4 Secondary efficacy endpoints

Not applicable.

5.5 Safety and tolerability endpoints

For a detailed description of the safety endpoints see Section 3.6.2.

The safety set is used to perform all safety analyses.

All AEs and all SAEs are coded using the MedDRA dictionary.

Treatment-emergent AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC. The incidence of patients who experienced AEs coded with the same preferred term is tabulated by treatment group (in descending order according to the incidence in the investigational study drug group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual patient listings broken down by treatment group and center.

Adverse events leading to premature discontinuation of study drug will be listed and summarized similarly to AEs.

Treatment-emergent SAEs will be listed and summarized similarly to AEs, separately for treatment-emergent SAEs and SAEs occurring before study drug initiation (only those related to study-mandated procedures) and after study drug discontinuation.

Reasons for death will be listed and summarized similarly to AEs, separately for treatment emergent deaths and deaths occurring before study drug initiation (only those related to study mandated procedures) and after study drug discontinuation.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency. Actelion internal guidelines will be used for the definition of marked laboratory abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory parameters are transformed to standard units. Absolute values and changes during the course of the study of laboratory parameters values converted to standardized units will be summarized by computing the usual location and scale statistics by period and treatment group.

5.6 Exposure to study drug(s)

Exposure to macitentan will be described in terms of duration and dose. The duration of exposure is defined as the time elapsing between study drug initiation and discontinuation, inclusive. The exposure time will be tabulated using the usual location and scale statistics by treatment group. The cumulative distribution of exposure time by different class intervals (e.g., at least 4 weeks, at least 8 weeks, etc.) will be tabulated to show the number and percentage of patients in each class interval. The mean daily dose per patient is defined as the ratio between the total dose administered during the treatment period and the total

exposure time. The mean daily dose is tabulated using the usual location and scale statistics by treatment group.

5.7 Baseline parameters

Continuous demographic variables (age, height, weight, others) and baseline disease characteristics will be summarized by the usual location and scale statistics (mean, median, standard deviation, Q1, Q3, minimum, and maximum).

Qualitative demographic characteristics (gender, race, others) and baseline disease characteristics will be summarized by counts and percentages.

5.8 Exploratory analyses

Not applicable.

5.9 Interim analyses

No interim efficacy analysis is planned.

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7 PROCEDURES AND GOOD CLINICAL PRACTICE

7.1 Procedures

7.1.1 Protocol amendments

Any change to a protocol has to be considered as an amendment as soon as these documents have been submitted to ECs/IRBs or Health Authorities. Therefore, an amendment could occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Actelion. It should be reviewed by the Principal Investigator(s) or Steering Committee, as appropriate.

Adaptations of the core Subject/Patient Information and Informed Consent requested by ECs/IRBs are not considered as amendments, as long as they do not significantly change the core document or affect the protocol.

- **Non-substantial amendment**

Administrative or logistical minor changes require a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., Actelion instead of CRO monitors) or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment could be done with or without (according to national regulations) notification to the appropriate ECs/IRBs and Health Authorities. It does not require their approval or to be signed by the investigators.

- **Substantial amendment**

Significant changes require a substantial amendment. Significant changes include but are not limited to: new data affecting the safety of subjects/patients, change of the objectives/endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, with or without the need to modify the core Subject/Patient Information and Informed Consent.

Substantial amendments are to be approved by the appropriate ECs/IRBs and in some countries by the Health Authorities. The implementation of a substantial amendment can only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities and must be signed by the investigators.

- **Urgent amendment**

An urgent amendment might become necessary to preserve the safety of the subjects/patients included in the study. The requirements for approval should in no way prevent any immediate action being taken by the investigators or Actelion in the best interests of the subjects/patients. Therefore, if deemed necessary, an investigator can

implement an immediate change to the protocol for safety reasons. This means that, exceptionally, the implementation of urgent amendments will occur before submission to and approval by ECs/IRBs and Health Authorities.

In such cases, the investigator must notify Actelion within 24 hours. A related substantial amendment will be written within 10 working days by Actelion and submitted to the appropriate ECs/IRBs and Health Authorities.

7.1.2 Monitoring

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents; provided that patient confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. Actelion monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

The identification of any data recorded directly on the CRFs and considered to be source data are specified in the following document: "*Site Guidelines".* The investigator must ensure that patients' anonymity will be maintained. On CRFs or other documents submitted to Actelion, patients should not be identified by their names, but by the patient number. The investigator must keep a subject/patient identification log showing the subject number, the subject/patient's name, date of birth and any other locally accepted identifiers. Documents identifying the patients (e.g., patients' signed informed consent forms) should not be sent to Actelion and must be kept by the investigator in strict confidence.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issue detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is in charge of contacting this hospital in order to document this SAE.

The investigator shall supply Actelion on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

7.1.3 Data management

7.1.3.1 Data collection

For each patient enrolled, regardless of study drug initiation, a CRF must be completed and signed by the principal investigator or co-investigator. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis. Completed CRFs will be collected by the monitor(s).

All forms should be completed using a digital pen (or in case it is not working a black ballpoint pen), and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator, co-investigator or study nurse.

7.1.3.2 Database management and quality control

All data from the CRF will be entered into the database twice, by two different individuals.

Subsequently, the entered data is systematically checked by Actelion staff, using error messages printed from validation programs and database listings. Errors with obvious corrections will be corrected and communicated to the site. Data clarification requests will be entered on Data Clarification Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Clarification Form is to be kept with the CRFs and, once received at Actelion, the resolutions will be entered into the clinical database.

A second review of the data will be performed by medically trained staff.

Quality control audits of the database will be made before study closure.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Global Trial Leader and the Head of Clinical Development.

7.1.4 Recording of data and retention of documents

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and patient clinical source documents.

The investigator's file will contain the protocol/amendments, FDA form 1572 for studies conducted under an US IND, financial disclosure form, CRFs and data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH / Good Clinical Practice (GCP) and local regulations.

Patient clinical source documents include, but are not limited to patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

When source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

7.1.5 Audit

The Actelion Global Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures to evaluate compliance with the principles of GCP and ICH related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the investigator must inform Actelion immediately that such request has been made.

The investigator will permit such audits by Actelion or Health Authorities and facilitate them by providing access to the relevant source documents.

7.1.6 Handling of study drug(s)

Actelion will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The responsible person must not destroy any drug labels, or unused drug supply. Upon termination of the study, the monitor will collect used and unused drug patient kits. They will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers can be destroyed at the site once drug accountability is final and checked by the sponsor or its deputy and written permission for destruction has been obtained from Actelion.

7.1.7 Publication and reporting of study results

Study results will be documented in a study report that will be signed by Actelion representatives and only one study coordinating investigator, for example the main investigator or the chairman of the Steering Committee.

In accordance with standard editorial and ethical practice, results of Actelion sponsored studies will be published. Results from multi-center studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies.

The main investigator(s) and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators should be submitted to Actelion for review at least 60 days prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of Actelion and will be determined by mutual agreement.

7.1.8 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Actelion in strict confidence and to request similar confidentiality from his/her staff and the EC/IRB. Study documents provided by Actelion (investigators' brochures, protocols, CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by Actelion to the investigator may not be disclosed to others without direct written authorization from Actelion, except to the extent necessary to obtain informed consent from subjects/patients who wish to participate in the trial.

7.1.9 Premature termination or suspension of the study

Both Actelion and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, Actelion will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reason(s) for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with Actelion should promptly inform the enrolled subjects/patients and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should promptly inform Actelion and the EC/IRB, and should provide the sponsor and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator should promptly notify Actelion and provide Actelion with a detailed written explanation of the termination or suspension.

Any premature termination or suspension of the study must be discussed with the Steering Committee as appropriate.

7.2 Good Clinical Practice

7.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided in the investigator site.

All studies must follow the ICH GCP Guidelines and, if applicable, the Code of Federal Regulations. In other countries in which GCP Guidelines exist, the investigators will strictly ensure adherence to the stated provisions.

7.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study, and should be documented in a dated letter to the investigator, clearly identifying the trial, the documents reviewed and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations (see Section 7.1.1).

7.2.3 Informed consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for documenting written informed consent will be provided to the sites prior to the study.

The Informed Consent and Patient Information will be provided in the local language.

7.2.4 Compensation to subjects and investigators

The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject/patient in the event of study-related injuries will comply with the applicable regulations.

8 APPENDIX

Appendix 1: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. Summary of previous amendments is provided below.

Amendment	Date	Main reason(s)
1	15-Nov-2007	*Non-substantial amendment*: As only macitentan is to be administered, the reference to placebo / treatment code break in affected sections has been removed. As local laboratories will be used for blood and urine tests, reference to central laboratory has been removed.
2	18-Jul-2008	*Substantial amendment*: Addition of CYP3A inducers to the list of prohibited concomitant medication. Definition of certain SAEs (expected in a PAH population) which will not require immediate reporting to Actelion Global Drug Safety on an SAE form unless the event is fatal.
3	22-Sep-2009	*Substantial amendment*: Increase in sample size from 525 to 699 subjects because the double-blind study AC-055-302 is expected to enroll more subjects than originally planned. Consequently, more subjects are expected to roll over into this open-label study. Request by the Data and Safety Monitoring Board for a weekly rather than bi-weekly follow-up of subjects with elevated liver transaminases.
4	27-Aug-2013	*Substantial amendment:* In order to facilitate the evaluation of the safety and tolerability data all concomitant treatments taken during the study will be collected. In accordance with the draft FDA "Guidance for Industry Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post-approval Clinical Investigations" (February 2012), to better characterize safety and tolerability of macitentan, a central laboratory

Amendment	Date	Main reason(s)
		will be used for prospective biochemistry and hematology analysis. An Independent Liver Safety Board is established to monitor the liver safety of macitentan including reviewing cases of confirmed elevations of aminotransferases > 3× ULN.
5	10 June 2016	The main reason for this amendment is to adjust the Liver Function Test (LFT) monitoring in SERAPHIN-OL considering safety data from available macitentan exposure data.

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
Long-term single-arm open-label extension study of the SERAPHIN study, to assess the safety and tolerability of macitentan/ACT 064992 in patients with symptomatic pulmonary arterial hypertension

SERAPHIN OL

Protocol AC-055-303; Phase 3

JNJ-67896062/ACT-064992 Macitentan

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).]

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Status: Approved
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Prepared by: Actelion Pharmaceuticals Ltd, a division of Janssen Research & Development
EDMS number: D-20.229

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement
The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

- **Scheduled Visits**

  In the event that a subject is unable to come to the site due to COVID-19-related restrictions for a protocol-required visit, the visit may be conducted by phone or using telemedicine, when permitted by local regulations and in line with local standard of care. The date of the phone call should be recorded as the visit date. If a visit is conducted by phone at a minimum data should be recorded for the following in the CRF:

  - Adverse event (AE)
  - Serious AE
  - Concomitant therapy
  - Pregnancy test results (as applicable for women of childbearing potential)

  In the event that a subject cannot come to the site for laboratory safety tests due to COVID-19-related restrictions, required tests may be conducted at a certified local laboratory. If samples are analyzed by a local laboratory, results, including units and normal ranges, must be recorded in the CRF. The investigator must review all safety assessments to confirm that the participant can pursue his/her study treatment. If the safety assessments cannot be performed and reviewed by the investigator in a timely manner, the investigator may decide to interrupt or permanently discontinue study intervention, if it is in the best interests of the participant.

  For women of childbearing potential, monthly pregnancy tests are required. Pregnancy test kits to be used at home were provided per protocol.

- **Missed visits and/or assessments**

  If a visit is missed entirely due to COVID-19-related restrictions (no site visit or phone visit performed), it will be captured as a protocol deviation in the clinical trial management system with the prefix “COVID-19-related”.

  Missed assessments will be captured in the clinical database as protocol deviations with the prefix “COVID-19 related”.

  In the exceptional situation that laboratory or pregnancy tests are missed or delayed due to the COVID-19 pandemic, they will be identified in the clinical database as protocol deviations with the prefix “COVID-19 related”.

- **Investigational Medical Product (IMP)**

  In the event that a subject cannot come to the site due to COVID-19-related restrictions to receive IMP, a caregiver or family member may pick up the IMP on behalf of the subject. This must first be discussed with the subject and the conversation must be documented in the subject source records. The subject must name the individual who will pick up the study drug on their behalf. Identification of the person who picks up the IMP must be confirmed and documented in the subject source record.

  If no other alternative is feasible, direct-to-patient (DTP) shipment of study drug from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the subject and record this in the subject source record for DTP shipments. DTP shipments must be done in accordance with local regulations.

Used, partially used, and unused study treatment bottles, including empty study treatment bottles, must be returned to the site for treatment accountability.

- **Informed Consent**

  An informed consent form (ICF) addendum will be prepared outlining the above mitigations. If allowed by local health authority / Institutional Review Board / Ethics Committee, verbal consent is acceptable and must be documented in the subject source notes. Documentation of verbal consent must include who consented, when they were consented, what they were told at the time, how they consented (eg, telephone, etc), who captured the oral/verbal consent (including signature of the investigator or staff member who captured the consent), and the identification of an impartial witness who was present at the time of consent, as well as how the impartial witness was selected.

- **Statistical Analysis**

  The sponsor will evaluate the totality of impact of COVID-19 on collection and missingness of key study data and the need for additional data analyses, which will be added to the clinical study report and statistical analysis plan.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Wassim Fares

Institution: Actelion Pharmaceuticals Ltd, a division of Janssen Research & Development

Signature: PPD Date: 01/07/2020
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.