# Macitentan / ACT-064992

# Eisenmenger Syndrome

# Protocol AC-055-308

**MAESTRO-OL: MAcitentan in Eisenmenger Syndrome To RestOre exercise capacity (Open-Label)**

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

| | |
|---|---|
| Study Phase: | 3 |
| **Identifier:** | **NCT02382016** |
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| MEDICAL HOTLINE | Toll-free Hotline telephone numbers for participating countries can be found in the Investigator Site File binder.<br>For countries where no toll-free number is available, a toll telephone number will be used.<br>The medical hotline is intended for the use by health care professionals. Subjects should be asked to contact the investigator in case of any medical emergency or any other health problem. |

# SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

**Drug name / number**

Macitentan / ACT-064992

**Indication**

Eisenmenger Syndrome

**Protocol number, acronym, title**

AC-055-308, MAESTRO-OL, Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome

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# INVESTIGATOR SIGNATURE PAGE

## Drug name / number

Macitentan / ACT-064992

## Indication

Eisenmenger Syndrome

## Protocol number, acronym, title

AC-055-308, MAESTRO-OL, Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome

I agree to the terms and conditions relating to this study as defined in this protocol, the Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent from all subjects included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

| | Country | Center number | Town | Date | Signature |
|---|---|---|---|---|---|
| **Country Coordinating Investigator** | | | | | |
| **Center Principal Investigator** | | | | | |

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# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 6MWD | 6-minute walk distance |
| 6MWT | 6-minute walk test |
| AE | Adverse event |
| ALT | Alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT) |
| ASD | Atrial septal defect |
| AST | Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT) |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CHD | Congenital heart disease |
| CL | Confidence limit(s) |
| CV | Curriculum Vitae |
| CYP | Cytochrome P-450 |
| DB | Double-blind |
| DBP | Diastolic blood pressure |
| DCF | Data Clarification Form |
| DMC | Data Monitoring Committee |
| DoA | Delegation of Authority |
| DS | Down Syndrome |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EOS | End-of-Study |
| EOT | End-of-Treatment |
| ERA | Endothelin receptor antagonist |

| | |
|---|---|
| ES | Eisenmenger Syndrome |
| ET-1 | Endothelin 1 |
| $ET_A$ | Endothelin receptor A |
| $ET_B$ | Endothelin receptor B |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| IXRS | Interactive Voice or Web Response System |
| LDH | Lactate dehydrogenase |
| LT | Liver test |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MLA | Marked laboratory abnormality(ies) |
| OL | Open-label |
| PAH | Pulmonary arterial hypertension |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| SAE | Serious adverse event |

| | |
|---|---|
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SDV | Source Data Verification |
| SiDBP | Sitting diastolic blood pressure |
| SiSBP | Sitting systolic blood pressure |
| SOC | System organ class |
| $SpO_2$ | Saturation of peripheral oxygen |
| SUSAR | Suspected unexpected serious adverse reaction |
| TIBC | Total iron binding capacity |
| ULN | Upper limit of normal |
| VSD | Ventricular septal defect |
| WHO | World Health Organization |

# PROTOCOL SYNOPSIS AC-055-308

| | | | | | | |
|---|---|---|---|---|---|---|
| TITLE | Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome | | | | | |
| ACRONYM | **MAESTRO-OL: MA**citentan in **E**isenmenger **S**yndrome **T**o **R**est**O**re exercise capacity (**O**pen-**L**abel) | | | | | |
| OBJECTIVES | To assess the long-term safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome (ES). | | | | | |
| DESIGN / PHASE | Multi-center, open-label (OL) extension, single-arm, Phase 3 study. | | | | | |
| STUDY PLANNED DURATION | **First subject First visit** | Q2 2013 | **Last subject First visit** | Q1 2016 | **Last subject Last visit** | Open |
| CENTERS/COUNTRIES | Approximately 90 centers in approximately 30 countries. | | | | | |
| SUBJECTS / GROUPS | Up to 220 subjects in one group*.<br>* Sample size may be increased up to 330 subjects based on the interim blind sample size review during the double-blind AC-055-305 / MAESTRO study. | | | | | |
| INCLUSION CRITERIA | **1.** Written informed consent/assent to participate in the study must be obtained from the subject or a parent / legal representative, and from the caregiver, where applicable, according to local regulations, prior to initiation of any study-mandated procedure.<br>**2.** Subjects with ES (including those with DS) having completed the double-blind AC-055-305 / MAESTRO study as scheduled, i.e., who remained in the double-blind study up to Week 16 (whether or not they were still taking study drug at the end of this period).<br>**3.** Females of childbearing potential must have a negative serum pregnancy test prior to first intake of OL study drug, and must use 2 reliable methods of contraception at the same time from enrollment up to at least 30 days after study treatment discontinuation. True abstinence is permissible under specific circumstances [see Section 3.2.2 of the protocol for more details]. | | | | | |
| EXCLUSION CRITERIA | **1.** Subjects who prematurely discontinue double-blind study drug during the AC-055-305 / MAESTRO study due to:<br>• an adverse event (AE) assessed as related to the use of study | | | | | |

| | |
|---|---|
| | drug, or<br>• elevated liver tests (LTs; related or unrelated to study drug).<br>**2.** Subjects with Down Syndrome (DS) who are not fully independent and need help to perform daily activities, and who do not have a caregiver or family member who agrees to accompany them to all visits, provide information about the participant as required by the protocol, and ensure compliance with study medication schedule.<br>**3.** Systolic blood pressure (SBP) < 85 mmHg.<br>**4.** Hemoglobin or hematocrit < 75% of the lower limit of normal.<br>**5.** Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN).<br>**6.** Severe hepatic impairment according to National Cancer Institute organ dysfunction working group criteria defined as total bilirubin > 3 × ULN accompanied by any AST elevation above the ULN.<br>**7.** Any known factor or disease that may interfere with treatment compliance or interpretation of the results, or that may influence the ability to comply with any of the study requirements.<br>**8.** Known hypersensitivity to drugs of the same class as macitentan, or any of the excipients.<br>**9.** Females who are pregnant or plan to become pregnant during the study or are lactating. |
| CONCOMITANT MEDICATIONS | **Prohibited**<br>• Any endothelin receptor antagonist (ERA) or any investigational drug other than macitentan.<br>• Cytochrome P-450 (CYP) 3A inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifapentin, rifabutin, St. John's wort). |
| STUDY PERIODS | **Treatment period**: for each subject, the OL treatment duration will last from his/her enrollment (Visit 1) up to the End-of-Treatment (EOT), i.e., until whichever of the following occurs first:<br>• Commercial availability of macitentan in this indication in the subject's country,<br>• The sponsor decides to stop this AC-055-308 OL study, |

| | |
|---|---|
| | • The subject or the investigator decides to discontinue the study drug.<br>**Post-treatment safety follow-up / End-of-Study (EOS)**: for an individual subject, the end of this OL study corresponds to the 30-day safety follow-up / EOS visit, which should be performed 30 days after the permanent discontinuation of study drug. |
| TRIAL DRUG | Macitentan 10 mg tablet, once daily. |
| REFERENCE DRUG | Not applicable. |
| EFFICACY ENDPOINTS | **Exploratory endpoints:**<br>Change from baseline of the OL* to Month 6 and Month 12 in:<br>• Exercise capacity, as measured by the 6-minute walk distance (6MWD),<br>• World Health Organization (WHO) functional class,<br>• Dyspnea (assessed by the Borg dyspnea index),<br>• Oxygen saturation, assessed by pulse oximetry: saturation of peripheral oxygen ($SpO_2$) at rest before the 6-minute walk test (6MWT).<br>* Baseline is defined as the last value obtained prior to or on the day of first administration of macitentan during this AC-055-308 OL study.<br>For subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study:<br>Change from baseline** of AC-055-305 / MAESTRO to Month 6 and Month 12 in:<br>• Exercise capacity, as measured by the 6MWD,<br>• WHO functional class,<br>• Dyspnea (assessed by the Borg dyspnea index),<br>• Oxygen saturation, assessed by pulse oximetry: $SpO_2$ at rest before the 6MWT.<br>** Baseline is defined as the last value obtained prior to or on the day of first administration of macitentan during the double-blind AC-055-305 / MAESTRO study. |
| TOLERABILITY / SAFETY ENDPOINTS | • Treatment-emergent AEs up to 30 days after study drug discontinuation.<br>• AEs leading to premature discontinuation of study drug. |

| | |
|---|---|
| | • Treatment-emergent serious adverse events (SAEs) up to 30 days after study drug discontinuation.<br>• Treatment-emergent marked laboratory abnormalities (MLA) up to EOT.<br>• Proportion of subjects with treatment-emergent ALT and/or AST abnormality (> 3 and ≤ 5 × ULN; > 5 and ≤ 8 × ULN; > 8 × ULN) associated or not with total bilirubin > 2 × ULN, up to EOT. |
| STATISTICAL METHODOLOGY | The statistical evaluation of the safety, tolerability, and exploratory efficacy endpoints will be carried out descriptively.<br><br>Safety and tolerability analysis will be based in combination with data from the AC-055-305 / MAESTRO study. More precisely, the analysis will be based on the All-treated DB + OL set, which includes the union of (i) all subjects who received at least one dose of macitentan in this AC-055-308 / MAESTRO-OL study, AND (ii) all subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study and did not enter the OL study. The observation period for the individual subject 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).<br><br>Efficacy exploratory analyses will be conducted both:<br>• Taking as baseline the last value obtained prior to or on the day of first administration of macitentan during this AC-055-308 OL study (All-enrolled set),<br>and<br>• Taking as baseline the baseline of the AC-055-305 / MAESTRO study and including data from the start of AC-055-305 / MAESTRO up to Month 12 in this AC-055-308 OL study, only for subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study (restricted All-enrolled set). |
| STUDY COMMITTEES | • A Steering Committee is involved in the design of the study and may be consulted prior to and during the study for any relevant medical issues and protocol-related questions.<br>• In order to ensure subjects' safety, an independent Data |

| | |
|---|---|
| | Monitoring Committee (DMC) will review the data from the AC-055-308 / MAESTRO-OL study on a regular basis until the end of the double-blind AC-055-305 / MAESTRO study (i.e., OL data will be reviewed only in combination with the data of the double-blind study). |

## Table 1 Visit and assessment schedule

| **PERIODS** | | **TREATMENT** | | | | | | **FOLLOW-UP** | |
|---|---|---|---|---|---|---|---|---|---|
| **VISITS** | **Number** | **1** | **2** | **Monthly Lab & Safety Monitoring[5]** | **3, 4** | **5, 6, etc.** | **EOT** | **Safety follow-up / EOS** | **U1, 2,…** |
| | **Name** | **Enrollment[2]** | **Month 1** | | **Month 6, Month 12** | **Month 18, Month 24, etc.** | | | **Unscheduled visits[6]** |
| | **Time** | **Day 1** | **Month 1 ± 1 week** | **Month 2 & every month thereafter up to EOT ± 1 week** | **Month 6 & Month 12 ± 2 weeks** | **Month 18 & every 6 months thereafter ± 2 weeks** | **Within 7 days after study drug disc.** | **30–33 days after study drug disc.** | **Anytime during the study** |
| **Informed consent / assent** | | X | | | | | | | |
| **Vital signs, Body Weight, Physical examination** | | X | X | | X | X | X | | X[6] |
| **Concomitant medications** | | X | X | X | X | X | X | X | X[6] |
| **$SpO_2$** | | X | | | X | | X | | X[6] |
| **WHO functional class / 6MWT/Borg dyspnea index** | | X | | | X | | X | | X[6] |
| **Complete laboratory tests**[1] | | X[3] | | | X | X | X | | X[6] |
| **Serum pregnancy test / methods of contraception** *(if applicable)*[4] | | X[3, 8] | X | X | X[8] | X[8] | X[8] | X | X[6] |
| **Hemoglobin**[7] | | X[3, 8] | X | X[7] | X[8] | X[8] | X[8] | X | X[6] |
| **LT** | | X[3, 8] | X | X | X[8] | X[8] | X[8] | X | X[6] |
| **Study drug dispensing** | | X | | X[11] | X | X | | | |
| **Study drug return** | | | | | X | X | X | | |
| **AEs**[9] | | X | X | X | X | X | X | X | X[6] |
| **SAEs**[9] | | X | X | X | X | X | X | X[10] | X[6] |

**1.** Complete laboratory tests: hematology (including hemoglobin), blood chemistry (including LTs), and serum pregnancy test. Laboratory samples at all visits will be sent to and analyzed by the central laboratory.

**2.** The enrollment visit is combined with the Week 16 (i.e., Visit 6 for subjects who complete the 16 weeks of double-blind treatment, or Visit 6a for subjects who prematurely discontinue double-blind treatment) in the AC-055-305 study. Tests are not to be repeated if performed for the Visit 6 or Visit 6a of the AC-055-305 study but are to be reported in the eCRF of both studies (if applicable).

**3.** In order to check the eligibility of the subject on the day of Enrollment, local laboratory results are required in addition to the sample sent to the central laboratory for analysis.

**4.** Only concerns females of childbearing potential.

**5.** Whenever possible, the monthly laboratory samples will be collected at site and analyzed centrally. Site staff should take this opportunity to meet the subject to discuss any (S)AEs that could have occurred since previous visit, and assess the concomitant medications and methods of contraception (if applicable). However, under specific circumstances (e.g., subject lives far away from the site and cannot return every month), monthly laboratory samples could be collected in a local laboratory close to where the subject lives and analyzed centrally; in these cases, the assessment of (S)AEs should be done via a telephone call.

**6.** At any time during the study (between Enrollment and End-of-Study visit) unscheduled site visits may be performed (based on investigator discretion). These include (but are not limited to) visits performed in case of safety concerns (e.g., new (S)AE, worsening of symptoms/assessment of 6MWD, adequate follow-up of any safety issues). Any study-specific procedures/assessments may be performed at an unscheduled visit, in which case the data will be collected in the eCRF.

**7.** Hemoglobin concentration will be measured every month during the first 6 months, every 3 months thereafter up to the EOT visit, and 30 days after study drug discontinuation (EOS visit).

**8.** Measured as part of the complete laboratory tests panel.

**9.** All new SAEs and AEs occurring from first dose of OL study drug up to 30 day after study drug discontinuation must be reported in this OL study.

**10.** New SAEs occurring after the 30-day follow-up period must be reported to the Actelion drug safety department, within 24 hours of the investigator's knowledge of the event, if considered causally related to previous exposure to the study medication by the investigator. They are reported on an SAE form but not on the eCRF.

**11.** Study drug may be dispensed on a monthly basis during monthly lab and safety monitoring.

6MWT = 6-minute walk test; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic Case Report Form; EOS = end-of-study; EOT = end-of-treatment; LT = liver test (liver aminotransferases [AST/ALT], alkaline phosphatase, total and direct bilirubin); MLA = marked laboratory abnormality(ies); OL = open-label; SAE = serious adverse event; $SpO_2$ = saturation of peripheral oxygen.

# 1 BACKGROUND AND RATIONALE

## 1.1 Eisenmenger Syndrome

Eisenmenger Syndrome (ES) belongs to group 1.4.4 of the Dana Point clinical classification of pulmonary hypertension [Simonneau 2009; see Appendix 1]. ES represents the most advanced form of congenital heart disease (CHD)-induced pulmonary arterial hypertension (PAH) [Beghetti 2009]. It is characterized by elevated pulmonary vascular resistance and right-to-left shunting through a systemic-to-pulmonary circulation connection. The disease is a progressive, multi-organ disorder, the symptoms and complications of which include dyspnea, cyanosis, syncope, fatigue, hemoptysis, erythrocytosis, cerebrovascular accidents, brain abscesses, arrhythmias and eventually right heart failure [Baumgartner 2010, Diller 2007]. Due to advances in surgery and pediatric cardiology, the prevalence of ES in the Western world has been reduced by an estimated 50% in the past 50 years. It is now estimated that more than 50% of patients with ES reach their fifth decade [Moons 2009]. Nevertheless, it remains a devastating condition with high mortality and considerable impact on patients' lives [Diller 2005, Diller 2006].

The most common cardiac defects leading to pulmonary vascular disease include ventricular septal defects (VSDs), atrial septal defects (ASDs), atrioventricular septal defects, and patent ductus arteriosus [Diller 2007]. Approximately 50% of all patients with unrepaired VSDs, approximately 10% of patients with large unrepaired ASDs, and almost all patients with unrepaired truncus arteriosus are at risk of developing ES [Vongpatanasin 1998].

The starting point in the development of ES is a left-to-right shunt, which generates an increased pulmonary blood flow and in turn induces severe pulmonary vascular disease and PAH. Eventually, this results in reversal of the shunt direction and central cyanosis [Baumgartner 2010]. The underlying mechanisms leading to PAH are not fully understood but involve blood flow-induced shear stress and circumferential stress, vasoconstriction, inflammation, thrombosis, cell proliferation and fibrosis [Humbert 2004a]. Molecular mediators of these phenomena include endothelin-1 (ET-1), prostacyclin, nitric oxide, angiopoietin-1 and thromboxane $A_2$ [Beghetti 2009, Morrell 2009].

Available treatment options for patients with ES have been limited to empirical palliative measures including oxygen, warfarin, diuretics, high-dose calcium channel blockers, and long-term continuous intravenous epoprostenol [Galiè 2008], until the BREATHE-5 placebo-controlled trial and the following open-label (OL) study revealed beneficial effects of bosentan-mediated dual endothelin receptor blockade in this patient population [Galiè 2006, Gatzoulis 2008]. Currently, patients with ES are usually treated with the endothelin receptor antagonist (ERA) bosentan or other PAH-specific therapies

(e.g., phosphodiesterase-5 inhibitors, prostanoids), but only bosentan has demonstrated efficacy in a controlled, multi-center trial. Lung transplant with repair of the cardiac defect or heart-lung transplantation is the final treatment option for patients with markers of poor prognosis, but has offered limited survival benefit [Baumgartner 2010, Moons 2009, Trulock 2001].

## 1.2 Endothelin-1 and pulmonary hypertension

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 [Galiè 2004].

There are 2 distinct receptors for ET-1: endothelin receptor A ($ET_A$) and endothelin receptor B ($ET_B$). The 2 receptors have unique binding locations and affinities for the endothelin peptide [Benigni 1995, Masaki 2004].The $ET_A$ receptors are expressed on pulmonary vascular smooth muscle cells, whereas $ET_B$ receptors are present both on pulmonary vascular endothelial smooth muscle cells and adventitial fibroblasts.

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. Both the $ET_A$ and $ET_B$ receptors 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 over-expressed 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 pulmonary hypertension of various etiologies [Stewart 1991, Giaid 1993]. Plasma levels of ET-1 correlate with pulmonary hemodynamics [Giaid 1993], PAH severity and prognosis [Rubens 2001]. The introduction of the ERA bosentan has represented a major advance in the treatment of PAH [Rubin 2002, Channick 2004, Humbert 2004b].

As in other forms of PAH, ET-1 is overexpressed in patients with CHD and shunt-associated PAH [Beghetti 2009, Tutar 1999, Yoshibayashi 1991, Cacoub 1993, Giaid 1993]. In the first double-blind study performed in patients with ES (BREATHE-5), blockade of the endothelin signaling system by bosentan was shown to improve exercise capacity and hemodynamic parameters without compromising peripheral oxygen saturation [Galiè 2006]. Further studies, including the BREATHE-5 OL extension and a long-term survival study (median follow up of

4.0 years), have supported the beneficial effects of ERA administration in this patient population [Gatzoulis 2008, Dimopoulos 2010].

## 1.3 Macitentan

### 1.3.1 Macitentan – Preclinical information

Macitentan / ACT-064992 is an 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 endothelin (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. In preclinical safety studies, no effects on normal physiological functions or electrocardiogram (ECG) variables, including cardiac repolarization, were observed, with the exception of a decrease in arterial blood pressure (BP) 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 levels (NOAEL) 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 (PK) profile consistent with once-daily dosing
- Lipophilic physicochemical properties facilitating the crossing of cell membranes
- A good safety and tolerability profile
- Low potential for drug-drug interactions

[redacted]

## 1.3.2 Macitentan – Clinical information

### *1.3.2.1 Phase 1 studies*

During the Phase 1 program, more than 200 healthy subjects and about 30 patients (with renal and hepatic impairment) were treated with macitentan. 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, subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others) than subjects receiving placebo. 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 (SBP and DBP, respectively), heart rate, or ECG intervals or morphology.

Eight cases of asymptomatic increases in aminotransferases were observed in the Phase 1 program (6 received macitentan, 2 received placebo). Of these increases, only 3 (all 3 subjects received macitentan) were > 3 × upper limit of normal (ULN), and none exceeded 4 × ULN. The increase in aminotransferases was not reported as an AE in any of the cases, and all cases resolved within 14 days of observation.

In healthy male subjects, the plasma concentration-time profile of macitentan (capsule formulation) can be described as slow absorption with maximum plasma concentrations achieved approximately 8 h after dosing. The apparent elimination half-life was approximately 16 h. After multiple dosing, the 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. Two metabolites were identified in plasma: one pharmacologically active metabolite (ACT-132577) and one metabolite (ACT-373898) that showed no effect on ET receptors. ACT-132577 reached steady state by Day 7 and had an apparent elimination half-life of about 2 days. The accumulation factor was approximately 8.5. The PK of ACT-132577 were dose-proportional after multiple dose administrations. 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, a dose-dependent increase in plasma ET-1 concentrations was observed with doses from 1 to 10 mg, with no further increases noted for the 30 mg dose. Therefore it was concluded that 10 mg once daily would be the dose that would produce the maximum effect on the ET system for this indication.

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 were no clinically relevant effects of sildenafil 20 mg 3 times daily 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).

Exposure to macitentan increased by approximately a factor of 2 after concomitant treatment with ketoconazole, a potent cytochrome P-450 (CYP) 3A4 inhibitor. Ketoconazole treatment reduced ACT-132577 exposure by 26%. The magnitude of the interaction is not considered to be clinically relevant and, therefore, macitentan may be concomitantly administered with CYP3A4 inhibitors.

Concomitant treatment with cyclosporine was well tolerated and did not have any clinically relevant effect on the exposure to macitentan or its metabolites ACT-132577 and ACT-373898 at steady-state. Concomitant treatment with rifampicin was well tolerated, but significantly reduced the exposure to macitentan and its metabolite ACT-373898 at steady-state. Exposure to the metabolite ACT-132577 was not affected to a clinically relevant extent by rifampicin. Reduced efficacy of macitentan in the presence of rifampicin should be considered.

The plasma concentrations of macitentan and ACT-132577 were generally lower in subjects with hepatic impairment than in healthy subjects. No correlation between the severity of hepatic impairment and the mean plasma concentrations of macitentan and ACT-132577 were apparent. Minor clinically non-relevant differences between PK parameters of macitentan, ACT-132577, and ACT-373898 were observed between healthy subjects and subjects with mild, moderate, and severe liver impairment.

Minor differences in the PK parameters of macitentan and ACT-132577 were noted between healthy subjects and subjects with severe renal impairment. However, marked differences in the PK parameters of the pharmacologically inactive metabolite, ACT-373898, were noted between healthy subjects and subjects with severe renal impairment. The safety profile of macitentan was similar in healthy subjects and subjects with severe renal impairment.

[redacted]

### *1.3.2.2 Phase 2 study in patients with essential hypertension*

A Phase 2 dose-finding study was conducted over 8 weeks in 379 patients with mild to moderate essential hypertension. Four doses of macitentan (0.3 mg, 1 mg, 3 mg, 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 (SiDBP) at trough (i.e., 24 h post dose).

This study demonstrated that macitentan is efficacious in reducing BP in patients with mild to moderate essential hypertension. Treatment with the 10 mg dose showed a statistically significant reduction versus placebo in SiDBP and sitting SBP (SiSBP) at trough, and a dose-related effect was indicated. The 2 highest doses of macitentan tested in the study were estimated to have a greater treatment effect than 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 4 dose levels. The overall frequency of AEs was similar to that observed in the placebo group. The numbers of patients 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 5 cases of increased liver enzymes > 3 × ULN. These 5 cases occurred in the macitentan groups, without obvious dose relationship (one, 2, one, and one in the 0.3 mg, 1 mg, 3 mg, and 10 mg dose groups, respectively). In 3 cases, there were other plausible reasons for increased liver enzymes (pancreatic cancer, surgery with general anesthesia, and concomitant antibiotic therapy, respectively). Most of the episodes of liver enzyme elevations resolved without sequelae within 2–3 weeks of observation. An episode of liver enzyme increase in a patient with pancreatic cancer resolved 48 days after surgery for pancreatic cancer.

[redacted]

### *1.3.2.3 Phase 2 study in patients with idiopathic pulmonary fibrosis*

A double-blind, randomized, placebo-controlled, multi-center, parallel group Phase 2 study to evaluate the efficacy and safety of a 10 mg dose of macitentan in 178 patients with idiopathic pulmonary fibrosis (IPF) has recently been completed. The primary endpoint (change in forced vital capacity) was not met, but it was shown that macitentan treatment with 10 mg dose was well tolerated. Overall, the safety profile was similar in the macitentan 10 mg and placebo groups. The overall incidence of

treatment-emergent AEs was similar in both groups. Dyspnea, peripheral edema, anemia, pneumonia and nausea occurred at a higher incidence in patients on macitentan than on placebo. The incidences of cough and pulmonary hypertension were lower on macitentan than on placebo.

An equal proportion of patients in the 2 treatment groups experienced SAEs and died during the study. The most frequently reported SAEs and causes of death were associated with lung disorders (worsening of IPF, hypoxia, respiratory failure, acute respiratory failure and pulmonary embolism), all known consequences of the underlying disease. Mean changes in laboratory variables were generally small and unremarkable in both groups. Seven patients treated with macitentan had a decrease in hemoglobin levels to ≤ 10 g/dL at some point during the study. Of these patients, 5 experienced transient decreases, one showed improvement by the time of treatment discontinuation, and one died due to pulmonary embolism prior to resolution of the hemoglobin decrease.

The overall incidence of elevations in liver aminotransferases was similar to placebo (3.4% and 5.1% incidence of alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 × ULN in the macitentan and placebo groups, respectively).

[redacted]

#### *1.3.2.4 Phase 3 study in patients with pulmonary arterial hypertension*

A randomized, placebo-controlled, event-driven Phase 3 study (AC-055-302 / SERAPHIN) has recently been completed to assess the effects of 3 mg and 10 mg of macitentan on morbidity and mortality in patients with symptomatic PAH. Global enrollment was completed in December 2009 with a total of 742 patients randomized. 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% ($p = 0.0108$).

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 × 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). A decrease in hemoglobin – reported as an AE – was observed more frequently on macitentan than placebo, with no difference in treatment discontinuation between groups.

[redacted]

### 1.3.3 Macitentan – Summary of potential risks and risk management

Preclinical studies with macitentan did not identify important risks of likely relevance to humans except for teratogenicity, a class effect of ERAs. The protocol includes stringent requirements for pregnancy testing and reliable contraception for female subjects of child-bearing potential.

In the SERAPHIN study, macitentan 10 mg once daily was well-tolerated and associated with a lower incidence of SAEs and AEs leading to study drug discontinuation than placebo. Of note, macitentan was not associated with a definite signal of adverse hepatic effects, and edema / fluid retention, an adverse effect reported with other endothelin antagonists, was reported with similar incidence across macitentan and placebo treatment groups.

Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with other ERAs. The liver safety data observed in clinical trials with macitentan are described in previous sections of this protocol [redacted]. Subjects with serum AST and/or ALT > 3 × ULN and those with severe hepatic impairment will be excluded from the proposed clinical trial, and liver tests (LTs) will be assessed every month during the treatment period and 30 days after study drug discontinuation.

Treatment with ERAs has been associated with increased incidences of anemia / hemoglobin decrease. This is ascribed to plasma volume expansion and is reversible upon treatment discontinuation. Overall, the findings with macitentan in this respect are very similar to those for the approved ERAs. Importantly, the incidence of SAEs of anemia in macitentan-treated patients in SERAPHIN was low, and anemia did not lead to an excess of study treatment discontinuation with macitentan. Patients with hemoglobin or hematocrit < 75% of the lower limit of normal will be excluded from the proposed clinical trial. The protocol also includes clear instructions regarding work-up and criteria for treatment discontinuation in the case of clinically relevant anemia.

Due to the vasodilatory effects of macitentan, effects on BP might occur. Hypotension is therefore considered to be a potential risk associated to treatment with macitentan, and patients with SBP < 85 mmHg will be excluded from the proposed study.

Reductions from baseline in leukocyte and platelet counts may be observed with macitentan. In the SERAPHIN study, macitentan was associated with modest and non-dose-dependent decreases in mean leukocyte count from baseline to End-of-Treatment (EOT). A small proportion of PAH patients, in both placebo and

macitentan groups, showed markedly reduced platelet counts, with or without bleeding complications, at some time during the study. Resolution during continued treatment with macitentan was observed, as well as absence of recurrence after treatment re-initiation, findings that make a specific, causal relationship to macitentan unlikely.

In the SERAPHIN study, menstrual disorder AEs (mainly menorrhagia, metrorrhagia, dysfunctional bleed) were reported at a low incidence overall, but more frequently on macitentan than placebo. None of the events led to discontinuation of study drug, there was no consistent drug-dose or drug-exposure pattern, and resolution of menstrual disorder during ongoing treatment was reported in the majority of cases. Confounding factors were present in the majority of these cases. A causal relationship to macitentan remains uncertain and further information will be collected during the study [see Section 4.2.4].

In clinical trials, a higher reporting rate of upper respiratory tract infections was seen with macitentan versus placebo. It is likely that many such events may represent symptoms of congestion due to local vasodilatation, rather than actual infection. For the clinically more relevant lower respiratory tract infections, especially pneumonia, there was no relevant difference between macitentan and placebo.

To further ensure trial participant safety, an independent Data Monitoring Committee (DMC) will review safety and tolerability data from the AC-055-308 / MAESTRO-OL study on a regular basis until the end of the double-blind AC-055-305 / MAESTRO study.

Given the extensive and long-term controlled data available with macitentan in PAH and the careful follow-up of subjects mandated by the protocol, the benefit/risk assessment supports the conduct of the study in patients with ES.

## 1.4 Study rationale

### 1.4.1 Medical and regulatory background

The ERA bosentan was the first drug showing efficacy in patients with ES in a controlled clinical trial, demonstrating improvement in cardiac hemodynamics and exercise capacity. Endothelin receptor antagonism has thus emerged as an important therapeutic strategy in pulmonary vasculopathy associated with ES. In the recently completed AC-055-302 / SERAPHIN study, macitentan demonstrated efficacy in PAH patients by improving clinical outcomes, functional status and exercise capacity.

The present OL study aims to assess the long-term safety and tolerability of macitentan in subjects with ES beyond the treatment of the double-blind AC-055-305 study, and to assess the long-term effect of macitentan on exercise capacity in this patient population.

### 1.4.2 Subject population

The subject population will consist of subjects with ES who have completed the double-blind AC-055-305 / MAESTRO study as scheduled, i.e., subjects who remained in the double-blind study up to Week 16 (whether or not they were still taking study drug at the end of this period), unless the double-blind treatment was discontinued for a safety issue.

### 1.4.3 Study design

This trial is an OL, non-comparative, multi-center, Phase 3 extension study of protocol AC-055-305, which aims to assess the long-term safety, tolerability and efficacy of macitentan in subjects with ES.

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

### 1.4.4 Dose selection

The proposed dose of macitentan (10-mg tablet once daily) for this OL study is the same dose as that used in the double-blind AC-055-305 / MAESTRO study.

### 1.4.5 Treatment duration

Study treatment duration for each subject will last from his/her enrollment (Visit 1) until the EOT, i.e., until the earliest of (i) the commercial availability of macitentan in this indication in the subject's country, or (ii) the sponsor decides to stop this OL study (e.g., request from the DMC [see Section 3.1] for safety reasons, or if results of AC-055-305 / MAESTRO do not show a statistically favorable effect of macitentan in this subject population), or (iii) the subject or the investigator decides to discontinue the study drug.

### 1.4.6 Primary endpoint

No primary 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

The present OL study aims to assess the long-term safety and tolerability of macitentan in subjects with ES beyond the treatment of the double-blind AC-055-305 study, and to assess the long-term effect of macitentan on exercise capacity in this patient population.

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall study design and plan

This trial is a multi-center, OL, non-comparative, Phase 3 extension study to assess the long-term safety, tolerability and efficacy of macitentan in subjects with ES.

The study will be conducted in approximately 90 centers in approximately 30 countries. Up to 220 subjects (males or females) from the double-blind AC-055-305 study will be enrolled in this OL study [see Section 1.4.2]. Subjects will be rolled over from the AC-055-305 study to this OL study without knowledge of their previous study drug (macitentan or placebo).

The sample size may be increased up to 330 subjects based on the interim blind sample size review during the double-blind AC-055-305 / MAESTRO study [redacted].

Enrollment in the AC-055-308 OL study (OL Visit 1) will be combined with the Week 16 visit (i.e., Visit 6 [Week 16 / EOT], or Visit 6a [Week 16 / premature EOT], if applicable) of the double-blind AC-055-305 / MAESTRO study [see Figure 1].

After the enrollment visit, subjects will come to the site at Month 1 (Visit 2), Month 6 (Visit 3), and every 6 months thereafter (Visits 4, 5, 6…), up to the EOT visit. In addition, subjects will undergo monthly lab and safety monitoring site visits.

A post-treatment safety follow-up period (30 days) will follow the permanent study drug discontinuation [see Figure 1]. At the end of this safety follow-up period, the safety follow-up / End-of-Study (EOS) visit will be performed.

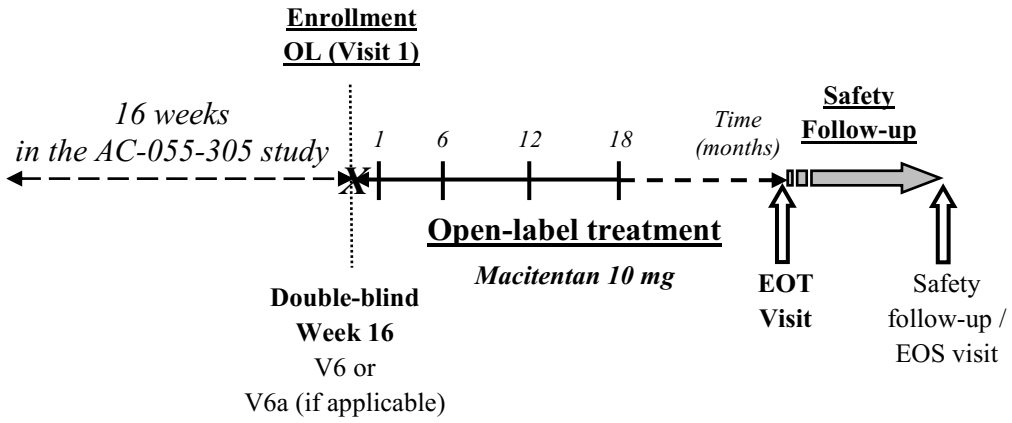
The study drug, 10-mg tablet of macitentan, will be taken orally, once daily in the morning, irrespective of food intake. Subjects will receive 6 medication bottles at enrollment (Visit 1), and thereafter every 6 months up to the EOT visit.

Note: Alternatively, if the subject comes to the investigational site every month for the monthly lab and safety monitoring, then it is possible to dispense one medication bottle on a monthly basis.

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

In order to ensure subjects' safety, an independent DMC will review the data from the AC-055-308 / MAESTRO-OL study on a regular basis until the end of the double-blind AC-055-305 / MAESTRO study (i.e., OL data will be reviewed only in combination with the data of the double-blind study).

**Figure 1 Study design**




## 3.2 Study population

### 3.2.1 Subject population

The subject population will consist of subjects with ES who have completed the double-blind AC-055-305 / MAESTRO study as scheduled, i.e., who have remained in the double-blind study up to Week 16 (whether or not they were still taking study drug at the end of this period), unless the double-blind treatment was discontinued for a safety issue.

### 3.2.2 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria:

1. Written informed consent/assent to participate in the study must be obtained from the subject or a parent / legal representative, and from the caregiver, where applicable, according to local regulations, prior to initiation of any study-mandated procedure.
2. Subjects with ES (including those with DS) who completed the double-blind AC-055-305 / MAESTRO study as scheduled, i.e., who remained in the double-blind study up to Week 16 (whether or not they were still taking study drug at the end of this period).
3. Females of childbearing potential must have a negative serum pregnancy test prior to first intake of OL study drug, and must use 2 reliable methods of contraception at the same time from enrollment and up to at least 30 days after study treatment discontinuation.

- A female is considered to have childbearing potential unless she meets at least one of the following criteria:
  - Previous bilateral salpingo and/or oophorectomy, or hysterectomy.
  - Premature ovarian failure confirmed by a specialist.
  - Pre-pubescence, XY genotype, Turner syndrome, uterine agenesis.
  - Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.
- Of the 2 contraceptive methods that must be used, one must be from Group 1, and one must be from Group 2, defined as follows:
  - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, intrauterine devices, female sterilization (tubal ligation or non-surgical sterilization, e.g., permanent contraception with Essure procedure), or partner's sterilization (vasectomy). If a hormonal contraceptive is chosen from this group, it must be taken for at least one month prior to enrollment. Alternatively, if the Essure procedure is chosen as a contraceptive method, a hysterosalpingogram must have been performed to confirm correct location of the microinserts and tubal occlusion (as per manufacturer's recommendations).
  - Group 2: Female or male condoms, diaphragm or cervical cap, any of them in combination with a spermicide.
- True abstinence from intercourse with a male partner is considered as an acceptable method of contraception for this study (not requiring a second reliable method of contraception) only when this is in line with the preferred and established lifestyle of the subject (e.g., homosexual females, females in religious order [e.g., nuns]), or when hormonal contraception is contraindicated.
- Sexual abstinence not meeting the above definition, rhythm methods, or contraception by the partner alone are not considered as acceptable methods of contraception for this study.
- The methods of contraception will be collected in the electronic Case Report Form (eCRF).

### 3.2.3 Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria:

**1.** Subjects who prematurely discontinue double-blind study drug during the AC-055-305 (MAESTRO) study due to:
- an AE assessed as related to the use of study drug, or
- LTs (related or unrelated to study drug).

2. Subjects with Down Syndrome (DS) who are not fully independent and need help to perform daily activities, and who do not have a caregiver or family member who agrees to accompany them to all visits, provide information about the participant as required by the protocol, and ensure compliance with study medication schedule.
3. SBP < 85 mmHg.
4. Hemoglobin or hematocrit < 75% of the lower limit of normal.
5. Serum AST and/or ALT > 3 × ULN.
6. Severe hepatic impairment according to National Cancer Institute organ dysfunction working group criteria, defined as total bilirubin > 3 × ULN accompanied by any AST elevation above the ULN.
7. Any known factor or disease that may interfere with treatment compliance or interpretation of the results, or that may influence the ability to comply with any of the study requirements.
8. Known hypersensitivity to drugs of the same class as macitentan, or any of the excipients.
9. Females who are pregnant or plan to become pregnant during the study or are lactating.

### 3.2.4 Concomitant medications

***Prohibited concomitant medications:***

- Any ERA or any investigational drug other than macitentan.
- CYP3A inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifapentin, rifabutin, St. John's wort).

Note: Study drug must be permanently discontinued if an ERA and/or another investigational drug is started during the treatment period.

## 3.3 Study drug

All subjects will receive macitentan 10-mg film-coated tablets once daily.

### 3.3.1 Administration of the study drug

If the subject is eligible, the first administration of OL study drug will take place during the enrollment visit after successful completion of all assessments.

Thereafter, one tablet should be administered orally, once daily, every morning, irrespective of food intake. On the day of study visits, the tablet should be taken from the bottle that is being returned to the site.

### 3.3.2 Study drug storage and dispensing

The investigator is responsible for 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 the subjects enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked room or a locked cupboard in a restricted access room, which can be accessed only by the pharmacist, the investigator, or another duly designated person as specified on the Delegation of Authority (DoA). The study drug must be stored below 25°C (77°F) and must be protected from moisture. Unopened, sealed study medication bottles may be stored in refrigerators (between the temperature range of +2°C [36°F] to 25°C [77°F]). If the temperature at a patient's home exceeds 25°C (77ºF), the patient should be instructed to store the unopened bottles of study drug in his/her refrigerator. Frozen storage (below +2°C [36°F]) is not permitted. Opened bottles must not be stored in the refrigerator.

A temperature log must be maintained and temperature control should occur at least on a weekly basis.

Actelion will provide a temperature log. However, the use of the log is not mandatory if the site has an acceptable means of recording the temperature. Any temperature recording system used at site can be used as long as all required information is included and certification of calibration is provided. If the temperature is captured electronically, a print-out should be made available to the monitor during each on-site visit.

In case a deviation from the defined temperature range is identified by the site, the deviation is to be reported to the monitor, preferably in writing and with supportive documentation (e.g., copy of the temperature log showing data for all excursion days). The monitor should immediately notify Actelion for further advice.

The study drug affected by a deviation will not be used (e.g., segregated physically at the investigational site) until confirmation by Actelion that it is safe to be used. In case the temperature deviation is defined as acceptable, a corresponding message is returned to the site via the monitor.

In case the temperature deviation is defined as not acceptable and the quality of the study drug might be affected, the study drug is to be kept segregated at the investigational site and returned to Actelion following internal drug return processes. New study drug supplies will be provided to the site.

Site temperature deviations correspondence must be kept in the Investigator Site File (ISF).

The study centers will be supplied with study drug according to the centers' needs, depending on the number of subjects enrolled.

Medication bottles will be allocated through the Interactive Voice or Web Response System (IXRS). Subjects will receive 6 medication bottles at the enrollment visit (Visit 1) and at each 6-monthly visit thereafter (Visits 3, 4, 5…) up to the EOT visit. Each childproof bottle contains study drug for one month (each bottle contains 36 tablets). Alternatively, if the subject comes to the investigational site every month for the monthly lab and safety monitoring, then it is possible to dispense one medication bottle on a monthly basis.

Once a subject has been enrolled and Investigational Medicinal Product (IMP) assigned, the corresponding bottles must NOT be used for another subject. If a subject has been allocated a bottle in error (one that has not been allocated yet to another subject), the IXRS helpdesk must immediately be contacted to advise of the misallocation of bottle numbers in all cases.

At the time study drug is dispensed, the subject should be educated on the proper storage conditions at their home.

Study drug dispensing must be performed only upon written confirmation by an authorized study physician listed on the DoA form.

### 3.3.3 Study drug up- and down-titration

Not applicable.

## 3.4 Study drug discontinuation and study withdrawal

### 3.4.1 Study drug interruption or discontinuation

The investigator must temporarily 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 subject.

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), withdrawal of the subject's consent, or might be due to administrative reasons.

Interruptions should be no longer than 2 consecutive weeks. Longer interruptions should lead to permanent discontinuation of study drug. All interruptions of study drug (including reason for interruption) should be recorded on the study drug log in the eCRF.

In case a subject discontinues study drug permanently, the EOT has to be registered in the IXRS in a timely manner to avoid any automatic study drug re-supply. Date entered into the system should be the date of the last study drug intake.

The reason for premature discontinuation from study drug (e.g., death, lost to follow-up, physician's decision / adverse event, subject's (or legal representative's) withdrawal of consent or withdrawal from treatment only, sponsor's decision to discontinue study) must be documented in the eCRF.

### 3.4.2 Subject's follow-up after study drug discontinuation

All enrolled subjects who received study drug must be followed up for at least 30 days after permanent discontinuation of study drug (safety follow-up period).

### 3.4.3 Withdrawal of consent and lost to follow-up

A subject will be considered as withdrawn from the study if, and only if, he/she has withdrawn his/her consent to participate in the study, or is lost to follow-up after unsuccessful and exhaustive attempts by the investigator to contact him/her.

If a subject is lost to follow-up, all reasonable means of contact must be used and all the attempts (at least 3 by telephone) must be recorded in the subject's chart. This information will be collected in the eCRF. In addition, a certified letter must be sent to the subject and a copy filed in the subject's medical record.

The potential follow-up of subjects after their withdrawal of consent will depend upon local regulations or specific agreement with the subjects.

The reason(s) for discontinuing the study and the decision owner (if applicable), must be documented in the eCRF.

### 3.4.4 Replacement policy

#### *3.4.4.1 Subjects*

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

#### *3.4.4.2 Centers*

Not applicable.

## 3.5 Treatment exposure, compliance and drug accountability

Adequate records of study drug received, dispensed, used, lost, returned and intervals between visits are to be kept during the study. Study drug accountability is to be performed on an ongoing basis by the study staff and an IMP Dispensing and Accountability Log is to be completed on an ongoing basis for each subject who has received study drug. The IMP Dispensing and Accountability Log will be checked by the

monitor during site visits and at completion of the study. Information from this log will be entered by the site into the Drug Accountability eCRF page. Treatment exposure will be calculated (by the sponsor) from this data.

Subjects should be instructed to return used and unused study drug (including empty bottles) at each visit. Study drug accountability must be performed each time the subject returns study drug to the study site by counting the number of remaining tablets in the returned bottles in order to evaluate the compliance. Prior to each new dispensation, the visit compliance must be evaluated by the site staff (as per formula below), who should then discuss any compliance issue with the subject and re-educate them on correct administration of study drug.

Compliance = (N° of Tablets taken / Total N° of Tablets that should have been taken during the period) × 100

If the compliance is < 80% or > 120%, a comment must be documented on the IMP Dispensing and Accountability log.

At the conclusion of the study, all remaining drug supplies, used and unused, shall be collected and returned to the sponsor for destruction by the sponsor's representative. Destruction must be documented.

## 3.6 Treatment assignment

All subjects will receive macitentan 10 mg tablets. All drug bottle numbers must be assigned through the IXRS.

### 3.6.1 Blinding

Not applicable.

### 3.6.2 Emergency procedure for unblinding

Not applicable.

## 3.7 Study drug packaging and labeling

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

### 3.7.1 Study drug packaging

Actelion will provide macitentan as tablets in childproof bottles containing 36 tablets each.

### 3.7.2 Study drug labeling

Each medication bottle will have a label with a tear-off part specifying the study protocol number, the batch number and the bottle number. When the medication is issued to the subject, the investigator, pharmacist (if applicable), or designee must remove the tear-off part and attach it to the IMP Label Dispensing Log.

## 3.8 Study endpoints

### 3.8.1 Efficacy exploratory endpoints

Change from baseline of the OL* to Month 6 and Month 12 in:

- Exercise capacity, as measured by the 6-minute walk distance (6MWD),
- World Health Organization (WHO) functional class,
- Dyspnea (assessed by the Borg dyspnea index),
- Oxygen saturation, assessed by pulse oximetry: saturation of peripheral oxygen ($SpO_2$) at rest before the 6-minute walk test (6MWT).

* Baseline is defined as the last value obtained prior to or on the day of first administration of macitentan during this AC-055-308 OL study.

For subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study:

Change from baseline** of AC-055-305 / MAESTRO to Month 6 and Month 12 in:

- Exercise capacity, as measured by the 6MWD,
- WHO functional class,
- Dyspnea (assessed by the Borg dyspnea index),
- Oxygen saturation, assessed by pulse oximetry: $SpO_2$ at rest before the 6MWT.

** Baseline is defined as the last value obtained prior to or on to the day of first administration of macitentan in the double-blind AC-055-305 / MAESTRO study.

### 3.8.2 Safety and tolerability endpoints

- Treatment-emergent AEs up to 30 days after study drug discontinuation.
- AEs leading to premature discontinuation of study drug.
- Treatment-emergent SAEs up to 30 days after study drug discontinuation.
- Treatment-emergent marked laboratory abnormalities (MLAs) up to EOT.
- Proportion of subjects with treatment-emergent ALT and/or AST abnormality ($> 3$ and $\leq 5 \times$ ULN; $> 5$ and $\leq 8 \times$ ULN; $> 8 \times$ ULN) associated or not with total bilirubin $> 2 \times$ ULN, up to EOT.

## 3.9 Study assessments

All on-site study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff.

Site team members conducting the 6MWT must be instructed on the Actelion 6MWT guideline [Appendix 2] and a training log must be collected upon completion.

Site team members must be specially trained on the management of subjects with DS and on the study-specific considerations in this patient population, and a training log must be collected upon completion of the training. The training material will be provided separately by the sponsor.

The investigator or designated physician will review laboratory reports, AEs or other safety information as soon as possible (but no later than 3 calendar days for laboratory reports, and 5 days for AEs / safety information) after receipt/acknowledgment, and have the corresponding documents signed and dated (if applicable).

The following order of assessments is recommended:

- Vital signs
- WHO functional class
- $SpO_2$ (at rest prior to 6MWT)
- 6MWT
- Borg dyspnea index

### 3.9.1 Safety and tolerability assessments

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

#### *3.9.1.1 Vital signs*

Vital signs (SBP and DBP, pulse rate) will be measured at enrollment, Month 1, each 6-monthly visit, and EOT. The data will be recorded in the eCRF.

#### *3.9.1.2 Body Weight*

Body weight will be measured at enrollment, Month 1, each 6-monthly visit, and EOT. The data will be recorded in the eCRF.

#### *3.9.1.3 Physical examination*

Physical examination will be performed at enrollment, Month 1, each 6-monthly visit, and EOT. The data will be recorded in the eCRF. Clinically relevant findings found after study drug initiation and meeting the definition of an AE must be recorded on an AE page of the eCRF.

The following could be examined during such an assessment:

general appearance; head, ears, eyes, nose, throat; neck; heart; lungs; abdomen; lymph nodes; genitourinary system; extremities; neurological system; skin; musculoskeletal system.

#### *3.9.1.4 Laboratory assessments*

##### *3.9.1.4.1 Type of laboratory*

A **central** laboratory (see Investigator Laboratory Manual for contact details) will be used for the analysis of blood samples described in the protocol.

Whenever possible, all blood samples will be collected at site and sent for analysis to the central laboratory.

However, under specific circumstances (e.g., the subject lives far away from the site and cannot return every month), laboratory samples could be collected at a local laboratory close to where the subject lives, and analyzed by the central laboratory. In that event, the site should provide the local laboratory with the central laboratory kits that will be used for blood collection. The blood samples collected locally will be shipped by the local laboratory to the central laboratory for analysis. Such local laboratory shall be identified as soon as possible, and whenever possible, no later than upon enrollment of the subject in MAESTRO-OL.

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

In the exceptional event that a local laboratory is utilized for the collection **and** analysis of blood samples (e.g., the subject is hospitalized in a hospital other than the site), laboratory certification / reference ranges / laboratory director's CV will be collected retrospectively by Actelion. Local laboratory results* and reference ranges will be collected in the eCRF.

*As a minimum, the following local laboratory results (i.e., results from samples collected and analyzed locally) will be collected in the eCRF:

- Any local laboratory result related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of ALT and/or AST elevations of > 3 × ULN. In such cases, the minimum data to be analyzed and entered in the eCRF are ALT, AST, alkaline phosphatase, and total and direct bilirubin.
- Any local laboratory result related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of hemoglobin decrease from baseline (i.e., last value obtained prior to first intake of OL study treatment) of > 2.0 g/dL, a value of hemoglobin < 8.0 g/dL, or a hemoglobin decrease requiring transfusion.
- Any local laboratory test documenting the result of an assessment requested per protocol and for which no central laboratory result is available (e.g., in the case that no sample was sent to the central laboratory at a planned visit because the subject was hospitalized at another hospital, or in the case that the sample sent to the central laboratory is uninterpretable [because, for example, the sample was hemolyzed]).

- Any local laboratory result related to the documentation or follow-up of an AE or an SAE, including clinically significant abnormal laboratory results and their follow-up.

In the event that several local laboratory samples have been collected on the same day, or if the sample was tested several times, the "worst" value (e.g., highest value for ALT / AST) should be reported in the eCRF (together with the local laboratory reference ranges).

Central laboratory reports will be transmitted to the investigator by fax.

In the case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor and the site concerned. Alert flags that will trigger such notifications are displayed in Appendix 6.

All laboratory reports (from central and local laboratories) must be reviewed, signed and dated by the Principal Investigator or other qualified study personnel at the study site as soon as possible (but no later than 3 calendar days) after receipt, and filed with the source documentation.

Any clinically significant laboratory abnormalities (including ALT/AST abnormalities $> 3 \times$ ULN) occurring after study drug initiation must be reported by the investigator as an AE and/or SAE, as appropriate [see Section 4], and must be followed by additional laboratory evaluations until they return to normal range, stabilize, or until the change is no longer clinically relevant except when otherwise specified (e.g., in the case of ALT/AST abnormalities, see Section 3.9.1.4.3). Further laboratory analysis should be performed as indicated and according to the judgment of the investigator.

Any pregnancy occurring during the treatment period and up to 30 days after study drug discontinuation must be reported immediately to the Actelion Global Drug Safety department using the Actelion Pregnancy Form [see Section 4.4].

*3.9.1.4.2 Laboratory parameters*

Complete laboratory parameters (i.e., standard hematology tests [including hemoglobin], blood chemistry tests [including LTs], and serum pregnancy tests [if applicable]) will be measured at enrollment (Visit 1), each 6-monthly visit, and EOT.

In addition,

- LTs will be monitored monthly up to 30 days after study drug discontinuation;
- Serum pregnancy tests (if applicable) will be performed monthly up to 30 days after study drug discontinuation;
- Hemoglobin will be monitored every month up to Month 6, every 3 months thereafter up to the EOT visit, and 30 days after study drug discontinuation (EOS visit).

**Hematology**

- Hemoglobin
- Hematocrit
- Erythrocyte count
- Leukocyte count with differential
- Platelet count

**Blood chemistry**

- LTs: liver aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin
- Creatinine
- Urea or blood urea nitrogen (BUN)
- Uric acid
- Glucose
- Sodium
- Potassium
- Magnesium
- Calcium
- Albumin

**Serum pregnancy test**

For females of childbearing potential, a serum pregnancy test must be performed at enrollment (Visit 1), and monthly thereafter up to at least 30 days after study drug discontinuation.

Each month, it must be verified whether the methods of contraception previously used are still valid, in accordance with the protocol [see Section 3.2.2], and correctly used by the subject. Documentation on the discussion with the subject must be available in the subject's source documents.

For pre-pubescent females, childbearing potential must be assessed each month, and the subject must be requested to use 2 reliable methods of contraception as soon as childbearing potential has been established.

In the event of pregnancy, a Pregnancy Form must be completed [see Section 4.4.2].

*3.9.1.4.3 Liver function monitoring and study treatment adjustments*

Liver function monitoring: LTs (liver aminotransferases [AST/ALT], alkaline phosphatase, and total and direct bilirubin) must be measured at enrollment (Visit 1), at

Month 1, each monthly lab monitoring, each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and at the 30-day safety follow-up / EOS visit.

Study treatment adjustment in case of ALT and/or AST elevations

| ALT and/or AST | Treatment and monitoring recommendations |
|---|---|
| **> 3 and ≤ 8 × ULN** | Interrupt study medication. Perform a re-test of aminotransferases, total and direct bilirubin and alkaline phosphatase within one week of the previous blood collection. If AST and/or ALT elevation is confirmed, continue to monitor aminotransferases, total and direct bilirubin and alkaline phosphatase levels weekly until values return to pre-treatment* levels or to normal ranges. If the aminotransferase values return to pre-treatment levels or to normal ranges, reintroduction of study treatment can be considered. Interruptions should be for less than 2 consecutive weeks; longer interruptions should lead to permanent discontinuation of study drug.<br><br>Reintroduction 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 or within normal ranges. The advice of a hepatologist is recommended.<br><br>Liver aminotransferase levels must then be checked within 3 days after reintroduction, then again after a further 2 weeks and thereafter according to the recommendations above (i.e., at monthly intervals). |

* Pre-treatment level: level prior to first intake of open-label study treatment.
ALT =alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

In case of aminotransferases > 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), in case of aminotransferases > 3 × ULN and associated increase in total bilirubin > 2 × ULN, or in case of aminotransferases > 8 × ULN, study drug must be stopped and its reintroduction is not to be considered. Aminotransferase, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study drug discontinuation until values return to pre-treatment levels or to normal ranges.

Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (e.g., acetaminophen-related liver toxicity) should be considered and ruled out by performing the appropriate tests.

Whenever possible, all laboratory testing performed to confirm and/or monitor ALT and/or AST elevations of > 3 × ULN, will be collected at site and sent to the central laboratory. For other cases see Section 3.9.1.4.1.

Note: If an abnormal ALT/AST value is observed, the sponsor may request additional assessments to be performed on a case by case basis (e.g., acetaminophen concentration to rule out an acetaminophen-related liver toxicity). This additional analysis would be performed using samples that have already been collected.

All LT abnormalities leading to study drug interruption or discontinuation must be recorded as AEs [see Section 4.2].

An independent Liver Safety Data Review Board (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any hepatic events that may require further evaluation.

In order to ensure the proper and comprehensive evaluation of cases of ALT and/or AST increase > 3 × ULN, additional subject data will be collected in the LT questionnaire of the eCRF.

*3.9.1.4.4 Hemoglobin concentration monitoring*

Hemoglobin will be measured at Visit 1 (enrollment) as part of the blood hematology tests, Visit 2 (Month 1), then monthly thereafter during the first 6 months, followed by every 3 months until the EOT visit, and 30 days after study drug discontinuation (EOS visit).

In case of a decrease from baseline* of > 2.0 g/dL, a retest should be performed with additional laboratory evaluations that may include, but are not limited to, any of the following: red blood cell cellular indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity [TIBC], transferrin saturation), lactate dehydrogenase [LDH], indirect bilirubin.

This work-up should be performed within 10 days of the previous blood collection (additional re-tests may be performed at the discretion of the investigator), but should not result in study drug interruption or discontinuation, unless clinically mandated based on the investigator's judgment or in the following situation:

A decrease in hemoglobin to < 8.0 g/dL (< 4.9 mmol/L), a decrease in hemoglobin from baseline* of > 5.0 g/dL, or the need for transfusion should result in temporary interruption of study medication. Reintroduction of study medication can be considered if hemoglobin recovery, defined as a return of hemoglobin to within 1.0 g/dL of the baseline* value, is achieved. Interruption of study medication should last no longer than 2 consecutive weeks; longer interruption should lead to permanent discontinuation of study drug.

All of the above re-test/work-up/follow-up laboratory samples for hemoglobin monitoring should be collected at the site and sent to the central laboratory.

* Baseline hemoglobin: last value obtained prior to first intake of OL study treatment.

#### *3.9.1.5 General management of Eisenmenger Syndrome*

In addition to the study-specific safety assessments listed above, it is recommended that standard of care for the management of ES and clinical practice guidelines [ACC/AHA 2008] are considered in the light of each subject's individual circumstances.

### 3.9.2 Efficacy exploratory assessments

#### *3.9.2.1 WHO functional class*

The WHO functional class [see Appendix 4] is assessed at enrollment (Visit 1), Month 6 (Visit 3), Month 12 (Visit 4), and EOT visit.

#### *3.9.2.2 Six-minute walk test and Borg dyspnea index*

The 6MWT is performed at enrollment (Visit 1), Month 6 (Visit 3), Month 12 (Visit 4) and EOT visit.

It is a non-encouraged test, which measures the distance walked in 6 minutes. However, for subjects with DS, standardized encouragement and positive reinforcement should be given according to the "Actelion guidelines for 6MWT", provided in Appendix 2.

Details on the correct execution of these tests are provided in Appendix 2. Minor deviations from these guidelines (such as corridor length 25–30 m [instead of 30 m], corridor marked every 5 m [instead of every 3 m]) will be first discussed with the sponsor, and formal approval should be obtained from the sponsor before performing any study-specific 6MWT in the corresponding corridor.

It is important that, for each individual subject, the 6MWT is conducted under the same conditions throughout the study (e.g., same corridor). In addition, if possible, for each individual subject, the 6MWT should be conducted by the same tester and preferably at the same time at each visit in this OL study. Moreover, as much as possible, the same conditions as in the AC-055-305 / MAESTRO study should be used. A trained tester must assess the reliability of each visit.

The 6MWT may be invalidated due to environmental factors, or other factors unrelated to the cardiopulmonary status resulting from the physical exertion required by the test. If the test is determined to be invalid by the trained tester, it may be repeated only once, either on the same day, at least 2 h later, or on another day provided it is still within the time window for the particular study visit.

If the 6MWT is repeated, then all the 6MWT-related assessments (i.e., Borg dyspnea index, and $SpO_2$) must be repeated as well. Any 6MWT-related assessments already performed for the first (invalid) 6MWT will be recorded in the source notes, but not entered in the eCRF, except for the date of the invalidated test and reason for considering the test to be invalid, which will be captured in the eCRF.

The Borg dyspnea index is evaluated after each 6MWT. It rates dyspnea on a scale from '0' to '10' [see Appendix 3].

#### *3.9.2.3 Oxygen saturation ($SpO_2$)*

$SpO_2$ is measured at rest prior to each 6MWT, i.e., at enrollment (Visit 1), Month 6 (Visit 3), Month 12 (Visit 4) and EOT visit.

Oxygen saturation will be assessed by pulse oximetry ($SpO_2$). As much as possible, for each individual subject, oxygen saturation measurements will be performed based on which location has the best pulsatile vascular bed (finger, earlobe). The same part of the body (e.g., finger) and the same pulse oximeter as in the AC-055-305 / MAESTRO study should be used throughout this OL study.

For subjects with patent ductus arteriosus, oxygen saturation during Visit 1 (Enrollment) will be measured on a toe. All subsequent oxygen saturation measurements will be performed based on which location has the best pulsatile vascular bed (right hand or earlobe).

### 3.9.3 Baseline parameters and concomitant medications

#### *3.9.3.1 Baseline demographics and disease characteristics*

Baseline demographic and disease characteristics of interest for this OL study will be taken from the AC-055-305 database.

#### *3.9.3.2 Concomitant medications*

Concomitant medications will be reviewed at all visits.

All concomitant medications taken from enrollment (Visit 1) up to 30 days after study drug discontinuation (EOS visit) will be recorded on the Concomitant Medication page of the eCRF. Generic name, start/end date of administration, route, dosage, frequency, and indication will be collected.

## 3.10 Visit and assessment schedule

Table 1 provides a summary of all visits and assessments described in the following sections.

### 3.10.1 Enrollment visit (Visit 1)

This visit is to be combined with Visit 6 of the AC-055-305 study for subjects who completed the 16-week double-blind treatment, or with Visit 6a of the AC-055-305 study for subjects who prematurely discontinued double-blind study treatment but came back at Week 16 [see Figure 1].

It is the responsibility of the investigator to obtain written informed consent/assent [as per Section 6.2.3] from each subject and/or from parent(s) / legal representative(s) (if applicable), and from caregivers (if applicable) after adequate face-to-face explanation of the methods and objectives of the study.

The informed consent/assent form must be signed and dated at the clinic/hospital, during the enrollment visit at the latest, and prior to any study-related assessment or procedure.

This visit includes:

- Subject / parent(s) / legal representative(s) / caregiver information and consent/assent form signature
- Physical examination
- Measurement of vital signs and body weight
- Recording of concomitant medications
- Recording of methods of contraception
- WHO functional class
- Measurement of oxygen saturation ($SpO_2$) at rest, prior to the 6MWT
- 6MWT
- Borg dyspnea index, after the 6MWT
- Complete laboratory tests including:
  - Hematology (including hemoglobin),
  - Blood chemistry (including LT),
  - Serum pregnancy test (for females of childbearing potential)
- After completion of all enrollment assessments and procedures and verification of all entry criteria: dispensing of study drug (enough for a 1 or 6-month treatment period).
- Recording of AEs and SAEs:
  - All AEs occurring from the initiation of the OL study drug must be recorded in the OL eCRF.

– All SAEs (except for those already reported in the AC-055-305 / MAESTRO study) occurring from signature of the consent/assent form to first OL drug administration must be recorded in the OL eCRF and on an SAE form.

**Note 1**: Tests are not to be repeated if performed for the Visit 6 or Visit 6a of the AC-055-305 study, but are to be reported in the eCRF of both studies.
**Note 2:** in order to check the eligibility of the subject on the day of Enrollment, local laboratory results are required in addition to the sample sent to the central laboratory.
**Note 3**: The first administration of OL study drug should take place during this visit after the successful completion of all assessments. Subsequently, the site staff should instruct the subject to take one tablet irrespective of food intake every morning.

### 3.10.2 Treatment period

#### *3.10.2.1 Month 1 visit (Visit 2)*

This visit is scheduled one month (± 1 week) from the day of enrollment.

This visit includes:

- Physical examination
- Measurement of vital signs and body weight
- Recording of changes in concomitant medications
- Recording of methods of contraception (for females of childbearing potential)
- Laboratory tests consist of:
  - Hemoglobin,
  - LT,
  - Serum pregnancy test (for females of childbearing potential)
- Recording of AEs and SAEs

#### *3.10.2.2 Monthly Lab and Safety Monitoring*

<u>All blood samples will be collected at site and sent for analysis to the central laboratory, whenever possible.</u>

LTs and serum pregnancy test (for females of childbearing potential) must be assessed monthly ± 1 week after initiation of the OL study drug and up to at least 30 days after study drug discontinuation.

Hemoglobin must be assessed monthly ± 1 week during the first 6 months, every 3 months thereafter up to the EOT visit, and 30 days after study drug discontinuation (EOS visit).

If the monthly laboratory samples are collected at the study site, site staff should take this opportunity to meet the subject to monitor their safety (i.e., assessment of AEs and SAEs), and assess the concomitant medications and methods of contraception (if

applicable). Study drug may be dispensed at this time as an alternative to 6-monthly dispensing. In the specific cases where the monthly laboratory samples are not collected at the site, the safety monitoring (AEs, SAEs, concomitant medications, methods of contraception if applicable) should be done via a telephone call that should be documented in the subject's file.

All AEs and SAEs occurring from the initiation of the OL study drug up to 30 days after permanent study drug discontinuation must be recorded.

Note: At any time during the study, unscheduled site visits may be performed, as necessary, at the discretion of the investigator [see Section 3.10.3]. These include (but are not limited to) visits performed in the case of safety concerns (e.g., new (S)AE, worsening of symptoms / assessment of 6MWD, adequate follow-up of any safety issues).

#### *3.10.2.3 Month 6 and Month 12 visits (Visits 3 and 4, respectively)*

These visits are scheduled 6 months (± 2 weeks) and 12 months (± 2 weeks) from the day of enrollment.

These visits include:

- Physical examination
- Measurement of vital signs and body weight
- Recording of changes in concomitant medications
- Recording of methods of contraception (for females of childbearing potential)
- WHO functional class
- Measurement of oxygen saturation ($SpO_2$) at rest, prior to the 6MWT
- 6MWT
- Borg dyspnea index, after the 6MWT
- Complete laboratory tests including:
  - Hematology (including hemoglobin),
  - Blood chemistry (including LT),
  - Serum pregnancy test (for females of childbearing potential)
- Recording of AEs and SAEs
- Return of unused medication including all empty bottles
- Dispensing of study drug (enough for a 1 or 6-month treatment period)

Note: On the day of these visits, the morning dose of study drug should be taken as usual; this tablet should be taken from the bottle that is being returned to the site.

### *3.10.2.4 Visits at 6-monthly intervals (Visits 5, 6 etc.)*

These 6-monthly visits are scheduled every 6 months ± 2 weeks, from the day of enrollment.

These visits include:

- Physical examination
- Measurement of vital signs and body weight
- Recording of changes in concomitant medications
- Recording of methods of contraception (for females of childbearing potential)
- Complete laboratory tests including:
  - Hematology (including hemoglobin),
  - Blood chemistry (including LT),
  - Serum pregnancy test (for females of childbearing potential)
- Recording of AEs and SAEs
- Return of unused medication including all empty bottles
- Dispensing of study drug (enough for a 1 or 6-month treatment period)

Note: On the day of these visits, the morning dose of study drug should be taken as usual; this tablet should be taken from the bottle that is being returned to the site.

### *3.10.2.5 EOT visit*

Actelion will notify all concerned sites when an EOT visit should be planned (upon commercial availability of macitentan in this indication in the respective country, or in case the sponsor decides to stop the study; see Section 1.4.5).

At the end of the OL study, the EOT visit is scheduled for all subjects still participating in this OL study. Any visit formerly scheduled within 2 weeks of the EOT will not be performed.

Subjects prematurely discontinuing macitentan treatment must also undergo the EOT visit. Permanent study drug discontinuation has to be reported in the IXRS in a timely manner to avoid any automatic study drug re-supply. Date entered into the system should be the date of the last study drug intake.

The EOT visit should be performed as soon as possible after permanent discontinuation of study drug and, whenever possible, no later than 7 days after the last dose of study drug.

The EOT visit includes:

- Physical examination
- Measurement of vital signs and body weight
- Recording of changes in concomitant medications

- Recording of methods of contraception (for females of childbearing potential)
- WHO functional class
- Measurement of oxygen saturation ($SpO_2$) at rest, prior to the 6MWT
- 6MWT
- Borg dyspnea index, after the 6MWT
- Complete laboratory tests including:
  - Hematology (including hemoglobin),
  - Blood chemistry (including LT),
  - Serum pregnancy test (for females of childbearing potential)
- Recording of AEs and SAEs
- Return of unused medication including all empty bottles

### 3.10.3 Unscheduled visit(s)

At any time during the study, unscheduled site visits may be performed, as necessary, at the discretion of the investigator.

These include (but are not limited to) visits performed in the case of safety concerns (e.g., new (S)AE, worsening of symptoms / assessment of 6MWD, adequate follow-up of any safety issues). The reason why such visits are performed will be recorded in the eCRF.

If any of the following assessments are performed, the corresponding data will be collected in the eCRF:

- Physical examination
- Measurement of vital signs and body weight
- Recording of changes in concomitant medications
- Recording of methods of contraception (for females of childbearing potential)
- WHO functional class
- Measurement of oxygen saturation ($SpO_2$) at rest, prior to the 6MWT
- 6MWT
- Borg dyspnea index, after the 6MWT
- Assessment of AEs and SAEs

If a laboratory sample is collected, it should be sent to the central laboratory for analysis (using the laboratory kits for “unscheduled” visits).

### 3.10.4 30-day safety follow-up / EOS visit

For an individual subject, the end of this OL study corresponds to the 30-day safety follow-up / EOS visit.

All attempts should be made to have this visit performed 30 to 33 days after the permanent discontinuation of study drug.

This visit includes:

- Recording of changes in concomitant medications
- Recording of methods of contraception (for females of childbearing potential)
- LTs, hemoglobin, and serum pregnancy tests (for females of childbearing potential)
- Reporting of any AE and/or SAEs occurring up to 30 days after permanent discontinuation of study drug in the eCRF and on an SAE form.

For all subjects, the reason for discontinuing the study and (if applicable) the decision owner (physician, subject, or sponsor) must be documented in the eCRF.

# 4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

## 4.1 Summary table

| Periods | Prior to start of treatment | Treatment | Follow-up | After follow-up |
|---|---|---|---|---|
| **Time frame** | From signing the ICF to first OL drug administration | During study drug administration | 30 days after study drug discontinuation | After 30 days |
| **AE/SAE reporting on eCRF AE page** | All SAEs (except for those already reported in the AC-055-305 / MAESTRO study) | All AEs / SAEs | All AEs / SAEs | None |
| **SAE reporting on SAE form** | All SAEs (except for those already reported in the AC-055-305 / MAESTRO study) | All SAEs | All SAEs | All SAEs related to previous study drug exposure |
| **Reconciliation** [1] | Yes | Yes | Yes | Not applicable |
| **Clinical study report** | Analyzed | Analyzed | Analyzed | Might be described |

[1] Reconciliation between clinical and drug safety databases.

AE = adverse event; eCRF = electronic Case Report Form; ICF = Informed Consent Form; OL = open-label; SAE = serious adverse event

## 4.2 Adverse events

### 4.2.1 Definitions of adverse events

An AE is any adverse change from the subject'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.

* Subject's condition prior to initiating the OL 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.

AEs 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., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities 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.
- Overdose, medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

AEs 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 present at baseline that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.

### 4.2.2 Intensity of adverse events

The intensity of clinical AEs is graded on a 3-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

The 3 categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not influence daily activities, and does not usually require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

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

A mild, moderate, or severe AE may or may not be serious [see Section 4.3.1]. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance 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.

### 4.2.3 Relationship to study drug

Each AE must be assessed by the investigator 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 (whether 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 down-titrated, interrupted, or discontinued.
- The event reoccurred when treatment was reintroduced.
- 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 (whether 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 new adverse events

All AEs occurring from initiation of the OL study drug and up to 30 days after study drug discontinuation are defined as treatment-emergent AEs and must be recorded on specific AE pages of the OL eCRF.

These AEs must be documented in the corresponding subject medical records. Data such as evaluation of maximum intensity and evaluation of possible relationship to study drug are also to be documented in the source documents. The investigator who performed the AE assessment should be identifiable in the source documents.

Additional safety information will be collected for AEs related to menstrual disorders (e.g., menorrhagia, increased menstrual bleeding) and ovarian cysts, in order to better characterize these events, in compliance with the EU Risk Management Plan for Opsumit®. This additional information will be entered in the drug safety database only.

### 4.2.5 Follow-up of ongoing adverse events

AEs still ongoing 30 days after study drug discontinuation must be followed up until they are no longer clinically significant.

## 4.3 Serious adverse events

### 4.3.1 Definitions

#### *4.3.1.1 Serious adverse events*

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring inpatient 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 was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, 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, Ethics Committees / Institutional Review Boards (ECs/IRBs) and investigators in an expedited fashion is the IB [redacted].

#### *4.3.1.2 Hospitalization – prolongation of existing hospitalization*

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition (present at baseline) that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition (present at baseline) that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example, if a complication prolongs hospitalization).

#### *4.3.1.3 Serious adverse events related to study-mandated procedures*

An SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such a procedures (other than administration of study drug). Examples of study-mandated procedures include discontinuation of a subject's previous treatment during a washout period, complication of a mandated invasive procedure such as blood sampling or heart catheterization, car accident on the way to the hospital for a study visit, etc.

### 4.3.2 Reporting of new serious adverse events

#### *4.3.2.1 Prior to start of OL treatment period*

All SAEs occurring from signing the Informed Consent Form to first drug administration in the OL are to be reported in the eCRF and on an SAE form, except for those already reported in the AC-055-305 / MAESTRO study.

#### *4.3.2.2 Treatment and follow-up periods*

All SAEs, including those related to study-mandated procedures and regardless of causal relationship, must be reported. Those SAEs occurring from the initiation of the OL study drug and up to 30 days after study drug discontinuation are defined as treatment-emergent SAEs.

These treatment-emergent SAEs are reported on SAE forms and also on AE pages in the eCRF. They are therefore entered into both the drug safety and clinical databases, and must be reconciled before study closure.

#### *4.3.2.3 After Follow-up period*

New SAEs occurring at any time after the 30-day follow-up period after study drug discontinuation must be reported to the Actelion Global Drug Safety department within 24 hours of the investigator's knowledge of the event, if considered causally related to previous exposure to the study medication by the investigator. These SAEs are only entered in the drug safety database, and hence will not affect study closure.

#### *4.3.2.4 Reporting procedures*

All SAEs (whether or not considered by the investigator to be related to study drug) must be reported by the investigator or designee to the Actelion Global Drug Safety department within 24 hours of the investigator's first knowledge of the event. The initial reporting of the SAE should not be delayed if some information is unavailable at time of first knowledge of the event.

The Principal Investigator or designee must complete the SAE form in English (unless otherwise specified), and must assess the relationship of the event to study drug. Only a site team member authorized for this task as per the DoA should sign off the SAE form, thus confirming that the assessment of the events, especially causality, has been made by a physician. The completed SAE form must be faxed to the Actelion Global Drug Safety department (see contact details on page 2).

Actelion Global Drug Safety will confirm receipt of the initial SAE report, or any update provided thereafter, by sending an acknowledgement of receipt (via email). If an email acknowledging the receipt is not received within 2–3 working days, the site should contact the monitor to clarify if the fax SAE form was received by Actelion Global Drug Safety.

Such preliminary reports will be followed by detailed descriptions that may include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable.

The Actelion Global Drug Safety department may contact the investigator to obtain further information and may email/fax a Data Clarification Form (DCF) to the site. The

Principal Investigator or designee should complete the DCF as soon as possible and fax it to the fax number specified on the form. The original DCF should be filed at site with the appropriate SAE form.

Once an SAE form is faxed, no additional information must be added to the existing form. In case of new information, a new SAE form must be completed and 'follow-up' ticked and faxed again to Actelion Global Drug Safety. Follow-up information about a previously reported SAE must also be reported within 24 hours of the investigator's first knowledge of the new information.

The eCRF entries must be consistent with the event term, relationship to study drug, seriousness, onset/resolution date and outcome recorded on the SAE form(s), DCF and in the corresponding subject's source documents.

SAEs must be reported to the ECs/IRBs according to the site- and country-specific reporting requirements. Copies of all communication regarding the SAE to the ECs/IRBs and to the sponsor must be appropriately filed in the ISF.

Investigational New Drug Safety Updates or CIOMS reports must be submitted to ECs/IRBs as per local requirements.

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

*SAEs that are expected due to underlying disease:*

The following events that are expected to occur in subjects with pulmonary hypertension or PAH will be considered as 'disease-related' and 'expected' for regulatory reporting purposes in this population: signs and symptoms of PAH worsening/exacerbation/progression, 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.

For expedited reporting purposes, these SAEs will be treated as 'disease-related' and expected, and will therefore not require systematic unblinding and will not require expedited reporting to Health Authorities, ECs/IRBs, and investigators.

However, all safety data (including these events) obtained in this AC-055-308 / MAESTRO-OL study until the end of the double-blind AC-055-305 / MAESTRO study will be monitored during the study by the DMC.

### 4.3.3 Follow-up of ongoing serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided (e.g., fatal outcome).

## 4.4 Pregnancy

### 4.4.1 Teratogenicity

Due to the potential teratogenicity of macitentan, appropriate precautions must be taken by females of childbearing potential. Females must not become pregnant during the study and up to 30 days after study drug discontinuation.

If pregnancy is suspected, the subject must immediately stop taking the study drug. If the pregnancy is confirmed, the subject must be discontinued from the study, and Actelion Global Drug Safety must be notified within 24 hours. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

### 4.4.2 Reporting of pregnancy

Any pregnancy occurring during study drug administration or during the 30 days following study drug discontinuation must be reported to Actelion Global Drug Safety within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion Global Drug Safety department (see contact details provided on the pregnancy form), and on an AE page of the eCRF. All reporting requirements and timelines specified in Section 4.3.2.4 (Reporting Procedures for SAEs) also apply to the reporting of a pregnancy.

### 4.4.3 Follow-up of pregnancy

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

Such follow-up information will only be entered in 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, data displays, and algorithms to be used for data derivations.

The SAP will include the definition of the protocol deviations and the link between protocol deviations and the analysis sets. The protocol deviations will be identified by trained staff before study closure.

All the listings will be presented by previous treatment group during AC-055-305 (i.e., former placebo and former macitentan), site, subject number, and assessment date, where appropriate. Where appropriate, all the summaries and graphics will be presented by previous treatment group during AC-055-305 (i.e., former placebo and former macitentan) and all subjects pooled together.

## 5.2 Analysis sets

Three different analysis sets are defined.

- **All-enrolled set**

This analysis set comprises all subjects enrolled in this AC-055-308 OL study, whether or not they took at least one dose of macitentan during the OL study.

- **Restricted all-enrolled set**

This analysis set comprises all subjects in the All-enrolled set who received macitentan during the AC-055-305 / MAESTRO study.

- **All-treated DB + OL set**

This analysis set comprises the union of (i) all subjects who received at least one dose of macitentan in this AC-055-308 OL study AND (ii) all subjects who received macitentan during the AC-055-305 / MAESTRO study and did not participate in the OL study.

## 5.3 Exploratory efficacy endpoints

For a detailed description of the exploratory efficacy endpoints, see Section 3.8.1.

The All-enrolled set is used to perform the efficacy analyses, except otherwise specified.

Each endpoint is analyzed descriptively and displayed depending on its nature as follows:

*For numerical variables:*

- Mean and 95% confidence limits (CLs) for the absolute values at selected time-points will be plotted over time including data from the start of AC-055-305/MAESTRO up to Month 12 in this AC-055-308 OL study. These graphs will serve to draw the pattern of the raw data for subjects included in this OL study.
- Mean and 95% CLs for the changes from baseline to selected time-points will be plotted over time:

- Taking as baseline the last value obtained prior to or on the day of first administration of macitentan during this AC-055-308 OL study. These graphs will serve to draw the pattern of the data during the OL phase alone.
- Taking as baseline the baseline of the AC-055-305 / MAESTRO study and including data from the start of AC-055-305 / MAESTRO up to Month 12 in this AC-055-308 OL study, only for subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study. These graphs will serve to draw the pattern of the data for subjects who received macitentan during the entire study (double-blind and OL phase). The restricted All-enrolled set is used to perform this analysis.

All the graphics will be accompanied by summary tables displaying descriptive summary statistics (i.e., number of observations [n], mean, median, standard deviation, standard error, quartiles, minimum, maximum and 95% 2-sided CLs of mean and median).

*For categorical variables:*

A shift table will be computed and displayed. The proportions of subjects in each category at the different time points will be displayed, as well as the proportion of subjects having an improvement/worsening together with the 95% CLs.

## 5.4 Safety and tolerability endpoints

For a detailed description of the safety endpoints, see Section 3.8.2.

The All-treated DB + OL set is used to perform safety analyses, unless otherwise specified.

The observation period for each individual subject starts at the time of the first administration of macitentan and ends with the permanent discontinuation of macitentan, regardless of administration type (i.e., double-blind or open-label).

Unless otherwise specified, the baseline is defined as the baseline of the AC-055-305 study for the subjects who received macitentan during the double-blind AC-055-305 / MAESTRO study, or as the last value obtained prior to first administration of macitentan during this AC-055-308 OL study, for the subjects who received placebo during the double-blind AC-055-305 / MAESTRO study.

Numerical safety and tolerability endpoints will be displayed using descriptive statistics (i.e., number of observations [n], mean, median, standard deviation, quartiles, minimum, maximum) at the different time points of assessment (if available).

### 5.4.1 Adverse events, serious adverse events, reasons for death, and premature discontinuation

All AEs and SAEs as well as reasons for death are coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percentage of subjects who experienced treatment-emergent SAEs up to 30 days after study drug discontinuation will be tabulated:

- by system organ class (SOC), and individual preferred terms within each SOC (in descending order according to the overall incidence)
- by frequency of terms coded with the same preferred term (in descending order according to the overall incidence).

Additionally, the following will be summarized in a similar manner to that used for treatment-emergent SAEs:

- AEs and AEs leading to premature discontinuation of study drug
- Reasons for death
- Reasons for premature discontinuation from study drug
- Reasons for premature discontinuation from the study

### 5.4.2 Laboratory parameters

The sponsor's internal guidelines will be used for the definition of MLAs. In rare cases when a local laboratory performs the analysis, normalization of local laboratory data will be done by the sponsor based on the central laboratory ranges [see Appendix 5].

The number and percentage of subjects with treatment-emergent MLAs up to EOT will be tabulated for each laboratory assessment by treatment group.

The number and percentage of subjects with treatment-emergent ALT and/or AST abnormalities ($> 3$ and $\leq 5 \times$ ULN; $> 5$ and $\leq 8 \times$ ULN; $> 8 \times$ ULN), associated or not with total bilirubin $> 2 \times$ ULN, up to EOT will be tabulated providing their incidence and frequency.

## 5.5 Exposure to study drug

Exposure to macitentan will be described in terms of duration and compliance. The duration of exposure is defined as the time elapsing between the first administration of macitentan (included) and permanent discontinuation of macitentan (included) regardless of administration type (i.e., double-blind or open-label). Duration of exposure to macitentan during this AC-055-308 OL study only will be also evaluated. The exposure time will be summarized as a numerical variable using descriptive statistics. It will be also summarized as categorical variable: the cumulative distribution of exposure time by

different class intervals (e.g., at least 4 weeks, at least 8 weeks, and at every interval of 4 weeks thereafter) will be tabulated to show counts and percentages of subjects in each class interval.

Compliance is defined as the total number of tablets taken divided by the total number of tablets that should have been taken, in percentage, for the time period under consideration. Overall compliance and compliance at each visit will be summarized using descriptive statistics.

## 5.6 Baseline parameters and concomitant medications

Baseline demographic (except for age) and disease characteristics are those collected in the double-blind AC-055-305 / MAESTRO study.

Continuous/numerical demographic characteristics (e.g., age, height, weight, body mass index, etc.) and baseline disease characteristics (e.g., time from ES, 6MWD and Borg dyspnea index, $SpO_2$, etc.) will be summarized displaying descriptive statistics.

Qualitative demographic characteristics (e.g., sex, race, etc.) and baseline disease characteristics (e.g., WHO functional class etc.) will be summarized displaying counts and percentages.

Inclusion/exclusion checklist will only be listed for subjects in the All-enrolled set.

Concomitant medications will be coded according to the latest available version of the WHO drug code and the Anatomic Therapeutic Chemical class code. They will be summarized by type in a similar manner to that used for treatment-emergent AEs (i.e., by treatment class and individual preferred terms within each class, and by frequency of preferred term).

Distributions of these parameters will only be compared descriptively between the treatment groups. No statistical inference will be performed.

## 5.7 Exploratory analyses

Not applicable.

## 5.8 Interim analyses

No interim efficacy analysis is planned.

# 6 PROCEDURES AND GOOD CLINICAL PRACTICE

## 6.1 Procedures

### 6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore 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, and must be reviewed by the Coordinating/Principal Investigator or Steering Committee, as appropriate.

Changes to the Core Information Leaflet and Informed Consent/Assent Form requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

#### *6.1.1.1 Non-substantial amendment*

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

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

#### *6.1.1.2 Substantial amendment*

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of subjects, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Information Leaflet and Informed Consent/Assent Form.

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

#### *6.1.1.3 Urgent amendment*

An urgent amendment might become necessary to preserve the safety of the subjects included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or Actelion in the best interests of the subjects. If

deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases 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 prepared and submitted by Actelion to the appropriate ECs/IRBs and Health Authorities within 10 working days of receiving the notification.

### 6.1.2 Monitoring

The monitor will contact and visit the investigator regularly and, on request, must be permitted to have access to all source documents needed to verify the entries on the eCRF and other protocol-related documents, provided that subject confidentiality is maintained in accordance with local regulations.

Prior to or at the latest at initiation, the monitor must have verified which type of source documents are used at the site and confirm adequate access to these documents to allow Source Data Verification (SDV) as required per monitoring guidelines upon the first monitoring visit. In case electronic source documents are used, the requirements described in Section 6.1.4 must be adhered to.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. Actelion monitoring standards require full verification that informed consent has been provided, and verification of 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 will be performed according to the study-specific monitoring plan. Any protocol violation identified will be discussed with the site and notified to the ECs/IRBs, as required per local regulation. No protocol waivers are allowed in this study.

The investigator must ensure that subject anonymity is maintained on all documents submitted to Actelion. On these documents, subjects must be identified only by study-specific subject number, and never by name, initials, or hospital subject number. The investigator must keep a subject identification code list showing the subject number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed informed consent forms) should not be sent to Actelion, and must be kept in strict confidence by the investigator.

Adequate workspace, including Internet access for verification of eCRF, should be provided to the monitor and to any Actelion representative during an on-site visit. The monitor(s) and any Actelion representative must have access to the study drug storage

and the laboratory sample collection facility, as appropriate. The required site personnel must be available during the on-site visit and allow adequate time to meet with the monitor(s) and any Actelion representative to discuss study-related issues. The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

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

An initiation visit will be performed before the first subject is included in this OL study. 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.

### 6.1.3 Data management

#### *6.1.3.1 Data collection*

CRF data will be captured via electronic data capture using the Rave system provided by Medidata Solutions, Inc., a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (ref. to 21 CFR Part 11), and this approval is used to confirm accuracy of the data recorded.

Site team members who obtained access to the eCRF in the AC-055-305 study will use the same account to access to the eCRF of the OL study.

For a new user to obtain access to the eCRF the following information should be verified and confirmed:

- Personal email account for collection of log-in details for every user
- Completion of eLearning for every user requiring access

At least one site team member must have access to the system prior to or at the latest at site initiation visit.

The eCRF information need to be completed as soon as possible after each subject's visit (but no later than 5 days after the subject's visit), and all eCRF entries must be supported by the site source documents. An eCRF will be completed for each enrolled subject.

#### *6.1.3.2 Database management and quality control*

eCRFs will be used for all subjects. The investigator will have access to the data throughout the trial life cycle. The eCRF must be kept current to reflect subject status at any time point during the course of the trial.

While entering the data, the investigator will be prompted by logical checks (error messages) built into the web-based data entry screens performed on the data. Other protocol specific validation programs will run routinely to perform more extensive data checks for accuracy and completeness. Additional data review will be processed in parallel by the Clinical Trial Team, to look for unexpected patterns in data, and other summaries needed for study monitoring. In case problematic data are detected, a query specifying the problem and requesting clarification will be issued and visible via the eCRF by the investigator, who will then respond and clarify directly onto the eCRF.

This process will continue until database closure.

After the database has been declared complete and accurate, the database will be locked.

### 6.1.4 Recording of data and retention of documents

The investigator must 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 are to be classified into 2 different categories: ISF, and subject clinical source documents.

- The ISF will be provided prior to or at the latest during the initiation visit and will contain all the essential documents that are required onsite.

  The ISF will contain the protocol and all protocol amendments, the FDA1572 form for studies conducted under an Investigational New Drug (IND; applicable for IND sites only), a financial disclosure form, the eCRFs together with all data changes made (CD_ROM provided after database closure), EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff CVs and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations. The ISF must be stored in a secure area during and after the study.

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

  If the site source documents are available on an electronic hospital/office database, it is requested to print out the complete set of source data needed for the SDV prior to the monitoring visit, unless the site confirmed that they are 21 CFR part 11 compliant

and provide access (personal user ID and password) to the monitor and/or any other Actelion representative during an on-site visit to verify electronic source documents with eCRF. The print-outs should be numbered, stapled, if possible, but at least kept together with a coversheet, signed and dated by the investigator or designee to confirm the accuracy and completeness of the subject's data. After monitoring the source documents, the monitor will sign and date the coversheet stating that attached source documents have been used for SDV. The coversheet should contain the following information: total number of pages, signature and date of Principal Investigator or designee, signature and date of monitor. Any new source data information added after sign off of the initial cover sheet should be initialed and dated by the responsible site team member and information updated on the cover sheet by all parties involved. Any new print-outs will be added, following the same process and information will be added on the same cover page.

Any changes of critical data in the source documents should be attributable to the site personnel doing the changes and if several source documents are available for the same assessment, the site must clearly state which source document is used for the data reported in the eCRF.

Source documents and investigator's file must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval, of the investigational drug). 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 in writing.

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

Copies of the eCRFs together with all data changes made will be supplied to the investigator at the end of the trial (CD-ROM provided after database closure). The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

### 6.1.5 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 a Health Authority, the investigator must inform Actelion immediately that such a request has been made.

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

### 6.1.6 Handling of study drug

Actelion will supply study drug 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 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 dispensed to each subject must be available for inspection at any time.

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

### 6.1.7 Publication and reporting of study results

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the Coordinating Investigator.

In accordance with standard editorial and ethical practice, the 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 Coordinating Investigator and the Steering Committee 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 must 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.

### 6.1.8 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by Actelion in strict confidence, and to request similar confidentiality from his or her staff

and the EC/IRB. Study documents provided by Actelion (including IBs, protocols, eCRFs 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 who wish to participate in the trial.

### 6.1.9 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 reasons for the termination or suspension.

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

In addition, if the investigator terminates or suspends a study without prior agreement from Actelion, the investigator must promptly inform Actelion and the EC/IRB, and must provide Actelion 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 must 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 Steering Committee, as appropriate.

## 6.2 Good Clinical Practice

### 6.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh and Seoul), 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 to each investigational site.

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

For any site staff member responsible for performing a critical task as confirmed on the DoA and/or listed on the FDA1572 form, ICH GCP experience and training must be documented on the CV. Actelion will train any site staff member not familiar with or having conducted an ICH GCP training more than one year prior to initiation or start of involvement in the study.

If an investigator is moving to a new site location, an on-site visit by the monitor is required, to assess if the new facility(ies) are compliant with study-specific requirements. If a new Principal Investigator takes over a site, an assessment of the new Principal Investigator's credentials needs to be performed. In both cases, regulatory documents will need to be updated to reflect the correct and current situation.

In accordance with laws and regulations of the country and as per EC/IRB requirements, the updated information will be submitted for approval/notification, as appropriate.

### 6.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an EC or IRB. Approval from the committee must be obtained before starting the study, and must 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 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 6.1.1].

### 6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study as well as from the parent(s) / legal representative(s) (if applicable), and from caregivers (if applicable), after adequate explanation of the methods, objectives and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason. The subject / parent(s) / legal representative(s) / caregiver should have ample time to review the information obtained and sign an informed consent.

The ICF/Assent must be obtained in person at the site and the subject and/or parent(s) / legal representative(s) / caregiver must sign, personally date and time the ICF/Assent before any study-related procedure begins. The ICF/Assent must also be signed, personally dated and timed by the person who conducted the informed consent

discussion. The whole consenting process must be clearly documented in the subject's medical record.

If the person conducting the informed consent discussion is a non-physician, all medical questions must be addressed and answered by a physician. The investigator performing the informed consent discussion must be listed on the FDA1572 and DoA forms.

The Information Leaflet and ICF will be provided in the local language. A special ICF (assent) will be provided for subjects who are minors and for subjects with DS who are not able to personally read and sign the informed consent (if needed according to the local regulations).

Appropriate forms for documenting informed consent will be provided to the sites prior to the study. The original Information Leaflet-ICF/Assent is to be filed on-site, and a copy must be given to the subject and/or legal representative / caregiver.

The Subject Identification Log must be maintained for all patients who consented to participate in the study, whether or not they were enrolled.

### 6.2.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both 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 in the event of study-related injuries will comply with applicable regulations.

### 6.2.5 DoA, FDA1572, CV, GCP Declaration Form and Financial Disclosure Form

The DoA must be available at the site initiation visit with all sections completed by the site according to instructions on the form.

The Principal Investigator may delegate some of his/her responsibilities to the appropriate site personnel. The DoA must be completed by all site personnel delegated by the Principal Investigator to perform any procedures before performing any study-related tasks, and filed in the ISF.

The DoA will list the critical tasks, which may only be delegated to a physician. However, the 6MWT may be delegated to a qualified non-physician.

For the delegated tasks, there must be evidence that the person has been sufficiently trained to carry out the task (CV / training records must be available at site). Training must be given and documented before the task is performed.

The Principal Investigator must authorize the assignment of the task and confirm appropriate training is received by the site team member by signing and dating the

approval column for each individual site member. The Principal Investigator's approval date must be prior to or on the study involvement start date of the corresponding site personnel. If there is any discrepancy between the Principal Investigator approval date and the site personnel start date, a comment must be provided by the Principal Investigator.

The DoA must be updated on an ongoing basis and any change must be dated and signed by the Principal Investigator.

It is recommended that each task be assigned to at least 2 persons. Several tasks may be assigned to one person.

The Principal Investigator must sign and date the DoA at the end of the study.

If site personnel listed on the DoA are responsible for a critical task, s/he must be listed on the form FDA1572 (IND sites only) and must provide a signed and dated CV, professional license (if applicable), authorization for data use and data transfer form, GCP training declaration form and Financial Disclosure Form before performing any task associated with the protocol. In case of changes in site personnel performing critical tasks, the FDA1572 (IND sites only) must be updated, and if necessary other required documents must be collected and appropriate training given and documented.

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## Appendix 1 Clinical Classification of Pulmonary Hypertension

Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008) [Simonneau 2009]

1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
***1.4.4 Congenital heart diseases***
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2 Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease

3 Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension (CTEPH)

5 Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

## Appendix 2 Actelion Guidelines for 6MWT

**6-Minute Walk Test (6MWT)**

### ➢ General instructions

The American Thoracic Society (ATS) published an official statement on the 6MWT in 2002 **[ATS Guidelines 2002]**. Only a brief summary of these guidelines is included here. Where applicable, adaptations (indicated by an asterisk and footnote) have been made for subjects with Down Syndrome.

- **The 6MWT should be performed** indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The use of treadmill is forbidden.
- **The walking distance used for the test should be 30 meters (100 feet) in length.** This distance should be marked every 3 meters (10 feet). The turnaround point should be marked with a cone. A starting line, which marks the beginning and the end of each 60-m lap, should be marked on the floor using brightly colored tape.
- **The study staff member administering the 6MWT** should stand near the starting line during the test and **must not walk with the subject!*** Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest, he/she may pause, lean against the wall or sit and should continue walking whenever he/she feels able. The timer must continue to run. The test can be stopped at any moment in case the subject complains of having chest pain, intolerable dyspnea, leg cramps, or has a pale or ashen appearance.

  ***For subjects with Down Syndrome** the tester may walk behind the subject, but must avoid body contact (e.g., holding hands).
- **The 6MWT is a non-encouraged test*.** No instructions or encouragement will be given during the test. Eye contact and body language signaling the subject to speed up should be avoided during the test.

  ***For subjects with Down Syndrome** standard encouragement should be given at each 1 minute interval, as per the dialogue provided below.
- **For an individual subject, repeat testing** should always be conducted under the same conditions throughout the study (e.g., same corridor). Whenever possible, repeat testing for an individual subject should be conducted by the same tester and preferably at about the same time of the day to minimize variability.

**Required equipment:**

- Countdown timer (or stop watch)

- Mechanical lap counter
- Two small cones for the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets on a clipboard
- Sphygmomanometer
- Automated electronic defibrillator
- Source of oxygen.
- Oximeter

## Subject preparation

- The subject should wear comfortable clothing and appropriate walking shoes.
- The meals preceding the test should be light, and the subject should not have exercised vigorously within 2 hours of beginning the test.
- The subject should sit at rest for at least 10 minutes before the test starts.
- Subjects should receive their usual medication on the day of the test. If the subject is used to taking bronchodilators before a walk, he/she should take them 5–30 min before the test.

➢ **Measurement of the 6-minute walk distance / 6-minute Walk Test – Instructions to the subject**

The person administering the test will use the following exact dialogue* with the subject:

> "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to.
>
> You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".
>
> (*The tester demonstrates the walking and pivots around a cone briskly).*
>
> "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"
"Please explain what you are going to do."
"Are you ready?"
"Start now, or whenever you are ready"

**As soon as the subject starts to walk, the tester will start the timer and write down start time.**

The tester will tell the subject the time elapsed by saying:
"You have 4 minutes to go."
"You have 2 minutes to go."

When the timer is 15 seconds from completion, the tester says:
"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you".

When the timer alarm rings the tester says:
"Stop!"

The tester walks over to the subject, marks the spot where the subject stopped, records the total distance walked in the worksheet and congratulates the subject on good effort.

*For Down Syndrome subjects the dialogue is modified to include standardized familiarization components in order to meet the needs of diverse learners and maintain focus for the entirety of the 6 minutes. This is meant to replace the above:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".

(*The tester demonstrates the walking and pivots around a cone briskly).*

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. I will talk to you during the test. Keep walking when I talk."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"
"Please explain what you are going to do."
"Are you ready?"
"Start now, or whenever you are ready"

**As soon as the subject starts to walk, the tester will start the timer and write down start time.**

The tester uses an even tone of voice when using the standard phrases of encouragement:

After the first minute, tell the patient the following:
*"You are doing well* INSERT FIRST NAME HERE. *You have 5 minutes to go."*

When the timer shows 4 minutes remaining, tell the patient the following:
*"Keep up the good work* INSERT FIRST NAME HERE. *You have 4 minutes to go."*

When the timer shows 3 minutes remaining, tell the patient the following:
*"Great effort. Keep it up* INSERT FIRST NAME HERE. *You are halfway done."*

When the timer shows 2 minutes remaining, tell the patient the following:
*"Keep up the good work* INSERT FIRST NAME HERE. *You have 2 minutes to go."*

When the timer shows 1 minute remaining, tell the patient the following:
*"You are doing well. You have only 1 minute to go."*

When the timer is 15 seconds from completion, the tester says:
"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you".

When the timer alarm rings the tester says:
"Stop!"

The tester walks over to the subject, marks the spot where the subject stopped, records the total distance walked in the worksheet and congratulates the subject on good effort.

**Borg dyspnea index**

As soon as possible following the walk test, the subject is asked to rate his/her dyspnea using the Borg Scale [Appendix 3]. The tester will use the following dialog:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg scale).

If there was no shortness of breath at all you would point to 0;

if the shortness of breath was not very great you would choose from 0.5 to 2;

if you were somewhat more short of breath you would select 3;

and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was;

10 represents the greatest shortness of breath you have ever experienced in your life."

**Appendix 3 Borg dyspnea index (Borg Scale) / Perceived Breathlessness**

| | |
|---|---|
| **0** | **NOTHING AT ALL** |
| **0.5** | **VERY, VERY SLIGHT (just noticeable)** |
| **1** | **VERY SLIGHT** |
| **2** | **SLIGHT (light)** |
| **3** | **MODERATE** |
| **4** | **SOMEWHAT SEVERE** |
| **5** | **SEVERE (heavy)** |
| **6** | |
| **7** | **VERY SEVERE** |
| **8** | |
| **9** | |
| **10** | **VERY, VERY SEVERE (maximal)** |

## Appendix 4 WHO functional classification of Pulmonary Hypertension

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

## Appendix 5 Central laboratory ranges

The ranges below are valid at the time of protocol finalization. Any changes to these ranges during the course of the study will be reflected in the ranges displayed in the laboratory reports sent from the central laboratory to the investigational sites.

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | Hematology | 5 | y | 14 | y | M/F | 11.4 | 15.1 | g/dL | 0.1 | 114 | 151 | g/L | | |
| Hemoglobin | Hematology | 15 | y | 999 | y | M | 13.5 | 17.5 | g/dL | 0.1 | 135 | 175 | g/L | | |
| Hemoglobin | Hematology | 15 | y | 999 | y | F | 12.0 | 16.0 | g/dL | 0.1 | 120 | 160 | g/L | | |
| Hematocrit | Hematology | 5 | y | 14 | y | M/F | 36 | 47 | % | 100 | 0.36 | 0.47 | L/L | | |
| Hematocrit | Hematology | 15 | y | 999 | y | M | 40 | 52 | % | 100 | 0.40 | 0.52 | L/L | | |
| Hematocrit | Hematology | 15 | y | 999 | y | F | 36 | 46 | % | 100 | 0.36 | 0.46 | L/L | | |
| Erythrocyte Count | Hematology | 5 | y | 14 | y | M/F | 4.0 | 5.6 | x10E6/uL | 1 | 4.0 | 5.6 | x10E12/L | | |
| Erythrocyte Count | Hematology | 15 | y | 999 | y | M | 4.6 | 5.8 | x10E6/uL | 1 | 4.6 | 5.8 | x10E12/L | | |
| Erythrocyte Count | Hematology | 15 | y | 999 | y | F | 4.1 | 5.2 | x10E6/uL | 1 | 4.1 | 5.2 | x10E12/L | | |
| MCV | Hematology | 5 | y | 14 | y | M/F | 78 | 95 | fL | 1 | 78 | 95 | fL | | |
| MCV | Hematology | 15 | y | 999 | y | M/F | 81 | 98 | fL | 1 | 81 | 98 | fL | | |
| MCH | Hematology | 5 | y | 999 | y | M/F | 27 | 34 | pg | 1 | 27 | 34 | pg | | |

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MCHC | Hematology | 5 | y | 999 | y | M/F | 32.0 | 37.0 | g/dL | 0.1 | 320 | 370 | g/L | | |
| Leukocyte Count | Hematology | 5 | y | 999 | y | M/F | 4.0 | 10.7 | x10E3/uL | 1 | 4.0 | 10.7 | x10E9/L | | |
| Neutrophils (%) | Hematology | 7 | y | 999 | y | M/F | 43 | 74 | % | 1 | 43 | 74 | % | | |
| Total Lymphs (%) | Hematology | 7 | y | 12 | y | M/F | 12 | 49 | % | 1 | 12 | 49 | % | | |
| Total Lymphs (%) | Hematology | 13 | y | 999 | y | M/F | 20 | 44 | % | 1 | 20 | 44 | % | | |
| Monocytes (%) | Hematology | 7 | y | 999 | y | M/F | 3 | 10 | % | 1 | 3 | 10 | % | | |
| Eosinophils (%) | Hematology | 7 | y | 12 | y | M/F | 0 | 6 | % | 1 | 0 | 6 | % | | |
| Eosinophils (%) | Hematology | 13 | y | 999 | y | M/F | 0 | 7 | % | 1 | 0 | 7 | % | | |
| Basophils (%) | Hematology | 31 | d | 999 | y | M/F | 0 | 2 | % | 1 | 0 | 2 | % | | |
| Neutrophils (Abs) | Hematology | 7 | y | 999 | y | M/F | 1.6 | 7.4 | x10E3/uL | 1 | 1.6 | 7.4 | x10E9/L | | |
| Total Lymphs (Abs) | Hematology | 7 | y | 12 | y | M/F | 1.0 | 3.9 | x10E3/uL | 1 | 1.0 | 3.9 | x10E9/L | | |
| Total Lymphs (Abs) | Hematology | 13 | y | 999 | y | M/F | 1.0 | 4.0 | x10E3/uL | 1 | 1.0 | 4.0 | x10E9/L | | |
| Monocytes (Abs) | Hematology | 7 | y | 999 | y | M/F | 0.1 | 0.9 | x10E3/uL | 1 | 0.1 | 0.9 | x10E9/L | | |
| Eosinophils (Abs) | Hematology | 7 | y | 12 | y | M/F | 0.0 | 0.5 | x10E3/uL | 1 | 0.0 | 0.5 | x10E9/L | | |
| Eosinophils (Abs) | Hematology | 13 | y | 999 | y | M/F | 0.0 | 0.7 | x10E3/uL | 1 | 0.0 | 0.7 | x10E9/L | | |

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Basophils (Abs) | Hematology | 31 | d | 999 | y | M/F | 0.0 | 0.2 | x10E3/uL | 1 | 0.0 | 0.2 | x10E9/L | | |
| Platelets count | Hematology | 5 | y | 14 | y | M/F | 175 | 420 | x10E3/uL | 1 | 175 | 420 | x10E9/L | | |
| Platelets count | Hematology | 15 | y | 999 | y | M/F | 150 | 350 | x10E3/uL | 1 | 150 | 350 | x10E9/L | | |
| Reticulocytes (%) | Hematology | 12 | y | 17 | y | M/F | 0.7 | 2.5 | % | 1 | 0.7 | 2.5 | % | | |
| Reticulocytes (%) | Hematology | 18 | y | 999 | y | M/F | 0.7 | 2.5 | % | 1 | 0.7 | 2.5 | % | | |
| Reticulocytes (Abs) | Hematology | 12 | y | 17 | y | M/F | 25 | 115 | x10E3/uL | 1 | 25 | 115 | x10E9/L | | |
| Reticulocytes (Abs) | Hematology | 18 | y | 999 | y | M/F | 30 | 110 | x10E3/uL | 1 | 30 | 110 | x10E9/L | | |
| Iron | Hematology | 0 | y | 999 | y | M | 59 | 178 | ug/dL | 5.58 | 11 | 32 | umol/L | 5 | 1 |
| Iron | Hematology | 0 | y | 999 | y | F | 37 | 173 | ug/dL | 5.58 | 7 | 31 | umol/L | 5 | 1 |
| Ferritin | Hematology | 0 | y | 999 | y | M | 22 | 322 | ug/L | 1 | 22 | 322 | ug/L | | |
| Ferritin | Hematology | 0 | y | 999 | y | F | 10 | 291 | ug/L | 1 | 10 | 291 | ug/L | | |
| Transferrin Saturation | Hematology | 0 | y | 999 | y | M/F | 20 | 55 | % | 1 | 20 | 55 | % | | |
| TIBC | Hematology | 0 | y | 999 | y | M/F | 250 | 452 | ug/dL | 5.58 | 45 | 81 | umol/L | | |

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sodium | Chemistry | 0 | y | 999 | y | M/F | 135 | 148 | mmol/L | 1 | 135 | 148 | mmol/L | | |
| Potassium | Chemistry | 0 | y | 999 | y | M/F | 3.5 | 5.3 | mmol/L | 1 | 3.5 | 5.3 | mmol/L | | |
| BUN (Urea) | Chemistry | 10 | y | 15 | y | M/F | 5 | 18 | mg/dL | 2.801 | 1.8 | 6.4 | mmol/L | 2.0 | 0.9 |
| BUN (Urea) | Chemistry | 16 | y | 18 | y | M/F | 5 | 20 | mg/dL | 2.801 | 1.8 | 7.1 | mmol/L | 2.0 | 0.9 |
| BUN (Urea) | Chemistry | 19 | y | 999 | y | M/F | 6 | 25 | mg/dL | 2.801 | 2.1 | 8.9 | mmol/L | 2.0 | 0.9 |
| Creatinine | Chemistry | 4 | y | 12 | y | M/F | 0.24 | 0.77 | mg/dL | 0.0113 | 21 | 68 | umol/L | 0.20 | 18 |
| Creatinine | Chemistry | 13 | y | 18 | y | M | 0.35 | 1.20 | mg/dL | 0.0113 | 31 | 106 | umol/L | 0.20 | 18 |
| Creatinine | Chemistry | 13 | y | 18 | y | F | 0.46 | 1.00 | mg/dL | 0.0113 | 41 | 88 | umol/L | 0.20 | 18 |
| Creatinine | Chemistry | 19 | y | 999 | y | M | 0.70 | 1.20 | mg/dL | 0.0113 | 62 | 106 | umol/L | 0.20 | 18 |
| Creatinine | Chemistry | 19 | y | 999 | y | F | 0.50 | 0.91 | mg/dL | 0.0113 | 44 | 80 | umol/L | 0.20 | 18 |
| Uric Acid | Chemistry | 10 | y | 12 | y | M/F | 2.2 | 5.8 | mg/dL | 16.8 | 0.13 | 0.34 | mmol/L | 0.2 | 0.01 |
| Uric Acid | Chemistry | 13 | y | 15 | y | M | 3.1 | 7.0 | mg/dL | 16.8 | 0.18 | 0.42 | mmol/L | 0.2 | 0.01 |
| Uric Acid | Chemistry | 13 | y | 15 | y | F | 2.2 | 6.4 | mg/dL | 16.8 | 0.13 | 0.38 | mmol/L | 0.2 | 0.01 |
| Uric Acid | Chemistry | 16 | y | 59 | y | M | 4.0 | 8.5 | mg/dL | 16.8 | 0.24 | 0.51 | mmol/L | 0.2 | 0.01 |
| Uric Acid | Chemistry | 16 | y | 999 | y | F | 2.5 | 7.5 | mg/dL | 16.8 | 0.15 | 0.45 | mmol/L | 0.2 | 0.01 |

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Uric Acid | Chemistry | 60 | y | 999 | y | M | 3.4 | 8.7 | mg/dL | 16.8 | 0.20 | 0.52 | mmol/L | 0.2 | 0.01 |
| Albumin | Chemistry | 0 | y | 999 | y | M/F | 3.2 | 5.5 | g/dL | 0.1 | 32 | 55 | g/L | | |
| Total Bilirubin | Chemistry | 8 | d | 999 | y | M/F | 0.1 | 1.2 | mg/dL | 0.0585 | 2 | 21 | umol/L | 0.1 | 2 |
| Direct Bilirubin | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.4 | mg/dL | 0.0585 | 0 | 7 | umol/L | 0 | 0 |
| indirect Bilirubin | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.7 | mg/dL | 0.0585 | 0 | 12 | umol/L | | |
| AST | Chemistry | 7 | y | 999 | y | M/F | 0 | 41 | U/L | 1 | 0 | 41 | U/L | 4 | 4 |
| ALT | Chemistry | 10 | y | 18 | y | M | 5 | 30 | U/L | 1 | 5 | 30 | U/L | 4 | 4 |
| ALT | Chemistry | 10 | y | 18 | y | F | 5 | 20 | U/L | 1 | 5 | 20 | U/L | 4 | 4 |
| ALT | Chemistry | 19 | y | 999 | y | M/F | 0 | 45 | U/L | 1 | 0 | 45 | U/L | 4 | 4 |
| AP (Alk Phos) | Chemistry | 1 | y | 12 | y | M/F | 0 | 299 | U/L | 1 | 0 | 299 | U/L | 1 | 1 |
| AP (Alk Phos) | Chemistry | 13 | y | 17 | y | M | 0 | 389 | U/L | 1 | 0 | 389 | U/L | 1 | 1 |
| AP (Alk Phos) | Chemistry | 13 | y | 17 | y | F | 0 | 186 | U/L | 1 | 0 | 186 | U/L | 1 | 1 |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | M | 40 | 129 | U/L | 1 | 40 | 129 | U/L | 1 | 1 |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | F | 35 | 104 | U/L | 1 | 35 | 104 | U/L | 1 | 1 |
| LDH | Chemistry | 7 | y | 12 | y | M | 145 | 325 | U/L | 1 | 145 | 325 | U/L | 5 | 5 |

| Test Name Full | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conv. Ref. Interval Low | Conv. Ref. Interval High | Conv. Unit | Conv. Factor SI to Conv | SI Ref. Interval Low | SI Ref. Interval High | SI Unit | Conv. Report limit Low | SI Report limit Low |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDH | Chemistry | 7 | y | 12 | y | F | 140 | 280 | U/L | 1 | 140 | 280 | U/L | 5 | 5 |
| LDH | Chemistry | 13 | y | 15 | y | M | 120 | 290 | U/L | 1 | 120 | 290 | U/L | 5 | 5 |
| LDH | Chemistry | 13 | y | 15 | y | F | 100 | 275 | U/L | 1 | 100 | 275 | U/L | 5 | 5 |
| LDH | Chemistry | 16 | y | 999 | y | M | 100 | 242 | U/L | 1 | 100 | 242 | U/L | 5 | 5 |
| LDH | Chemistry | 16 | y | 999 | y | F | 100 | 220 | U/L | 1 | 100 | 220 | U/L | 5 | 5 |
| Glucose | Chemistry | 0 | y | 999 | y | M/F | 70 | 140 | mg/dL | 18.01477 | 3.9 | 7.8 | mmol/L | | |
| Calcium | Chemistry | 0 | y | 999 | y | M/F | 8.6 | 10.5 | mg/dL | 4.0 | 2.14 | 2.62 | mmol/L | | |
| Magnesium | Chemistry | 0 | y | 999 | y | M/F | 1.8 | 2.4 | mg/dL | 2.43 | 0.74 | 0.99 | mmol/L | 0.1 | 0.03 |
| Pregnancy (serum) | Immunochemistry | 0 | y | 999 | y | F | 0 | 9 | mIU/mL | 1 | 0 | 9 | IU/L | 2 | 2 |

# Appendix 6 Alert flags

## Exclusionary (TE) Alert Value - At Enrollment (V1)

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | 5 | y | 14 | y | M/F | < 75 % LLN | < 8.6 | g/dL | < 86 | g/L |
| Hemoglobin | 15 | y | 999 | y | M | < 75 % LLN | < 10.2 | g/dL | < 102 | g/L |
| Hemoglobin | 15 | y | 999 | y | F | < 75 % LLN | < 9.0 | g/dL | < 90 | g/L |
| Hematocrit | 5 | y | 14 | y | M/F | < 75% LLN | < 27 | % | < 0.27 | L/L |
| Hematocrit | 15 | y | 999 | y | M | < 75% LLN | < 30 | % | < 0.30 | L/L |
| Hematocrit | 15 | y | 999 | y | F | < 75% LLN | < 27 | % | < 0.27 | L/L |
| AST | 7 | y | 999 | y | M/F | >3 ULN | > 123 | U/L | > 123 | U/L |
| ALT | 10 | y | 18 | y | M | >3 ULN | > 90 | U/L | > 90 | U/L |
| ALT | 10 | y | 18 | y | F | >3 ULN | > 60 | U/L | > 60 | U/L |
| ALT | 19 | y | 999 | y | M/F | >3 ULN | > 135 | U/L | > 135 | U/L |
| Pregnancy (serum) | 0 | y | 999 | y | F | | >9 | mIU/mL | >9 | IU/L |

### Exclusionary (TY) Alert Value - At Enrollment (V1)

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| total bilirubin | 0 | y | 999 | y | M/F | > 3 ULN | > 3.6 | mg/dL | > 63 | umol/L | |
| AST | 7 | y | 18 | y | M/F | > ULN | > 41 | U/L | > 41 | U/L | |

### Total Bilirubin flag (TB) Alert Value - All visits

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| total bilirubin | 0 | y | 999 | y | M/F | > 2 x ULN | > 2.4 | mg/dL | > 42 | umol/L |

**Study medication stop (TM) Alert Value - All visits except enrollment visit (V1)**

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| AST | 7 | y | 999 | y | M/F | > 8 x ULN | > 328 | U/L | > 328 | U/L |
| ALT | 10 | y | 18 | y | M | > 8 x ULN | > 240 | U/L | > 240 | U/L |
| ALT | 10 | y | 18 | y | F | > 8 x ULN | > 160 | U/L | > 160 | U/L |
| ALT | 19 | y | 999 | y | M/F | > 8 x ULN | > 360 | U/L | > 360 | U/L |
| Pregnancy (serum) | 0 | y | 999 | y | F | | >9 | mIU/mL | >9 | IU/L |

**Repeat (TR) Alert value - All visits except enrollment visit (V1)**

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| AST | 7 | y | 999 | y | M/F | > 3 x ULN | > 123 | U/L | > 123 | U/L |
| ALT | 10 | y | 18 | y | M | > 3 x ULN | > 90 | U/L | > 90 | U/L |
| ALT | 10 | y | 18 | y | F | > 3 x ULN | > 60 | U/L | > 60 | U/L |
| ALT | 19 | y | 999 | y | M/F | > 3 x ULN | > 135 | U/L | > 135 | U/L |

### Notable (T) Alert Values – All Visits

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | 0 | y | 999 | y | M/F | | < 7.0 and > 20.0 | g/dL | < 70 and > 200 | g/L |
| Leucocyte Count | 0 | y | 999 | y | M/F | | < 2.0 and > 35.0 | x10E3/uL | < 2.0 and > 35.0 | x10E9/L |
| Platelets count | 0 | y | 999 | y | M/F | | < 50 and > 1000 | x10E3/uL | < 50 and > 1000 | x10E9/L |
| ALT | 0 | y | 999 | y | M/F | | >2000 | U/L | >2000 | U/L |
| Calcium | 0 | y | 999 | y | M/F | | <6.0 and >12.0 | mg/dL | <1.50 and >3.00 | mmol/L |
| Sodium | 0 | y | 999 | y | M/F | | < 125 and > 155 | mmol/L | < 125 and > 155 | mmol/L |
| Potassium | 0 | y | 999 | y | M/F | | < 2.5 and > 6.5 | mmol/L | < 2.5 and > 6.5 | mmol/L |
| Creatinine | 0 | y | 999 | y | M/F | | > 3.39 | mg/dL | > 300 | umol/L |
| Glucose | 0 | y | 999 | y | M/F | | < 40 and > 500 | mg/dL | < 2.2 and > 27.8 | mmol/L |

**Notable (TF) alert Values - All visits except enrollment visit (V1)**

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | 0 | y | 999 | y | M/F | | > 2.0 decrease from baseline | g/dL | > 20 decrease from baseline | g/L |

**Notable (TG) alert Values - All visits except enrollment visit (V1)**

| Test Name Full | Age Low | Age Low Unit | Age High | Age High Unit | Sex | xULN | Alert Range Conventional | Conventional Unit | Alert Range SI | SI Unit |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | 0 | y | 999 | y | M/F | | < 8.0 | g/dL | < 80 | g/L |
| Hemoglobin | 0 | y | 999 | y | M/F | | > 5.0 decrease from baseline | g/dL | > 50 decrease from baseline | g/L |

| Flag | Legend |
|---|---|
| **H** | The result is above the upper limit of the reference range for normal subjects. |
| **L** | The result is below the lower limit of the reference range for normal subjects. |
| **TE** | The result is outside the study specific defined limit for inclusion in the study. |
| **TY** | Subject should be excluded only if the TY flag is appearing for both AST and bilirubin. |
| **TB** | In combination with TR (ALT and/or AST) on the report, study medication should be stopped. |
| **TM** | Please refer to the study protocol; study medication must be stopped. |
| **TR** | In case there is no TM flag a repeat testing is needed. |
| **TF** | Repeat testing is needed. |
| **TG** | Please refer to the study protocol; study medication should be interrupted. |
| **T** | Notable value. |

## Appendix 7 List of protocol amendments

| Document Date | Global Amendment | Changes |
|---|---|---|
| 3 Apr 2013 | Amendment 1, and resulting Global Protocol Version 2 | – A summary of the potential risks associated with macitentan and the methodology for risk management were added.<br>– Group 1 contraceptive methods were revised to add non-surgical sterilization methods (e.g., the Essure procedure)<br>– Measures to be taken with the study medication in the event of significantly decreased hemoglobin (to < 8.0 g/dL, of more than 0.5 g/dL from baseline, or requiring transfusion) were added, including a temporary interruption-re-introduction schedule or permanent discontinuation.<br>– Sections related to liver function monitoring and study treatment adjustments were slightly modified to:<br>(a) consider other etiologies (e.g., acetaminophen -related liver toxicity) by performing appropriate tests.<br>(b) ensure that all local laboratory data used to monitor ALT and/or AST > 3× ULN were collected in the eCRF along with the normal ranges. In addition, the corresponding total and direct bilirubin values were required to be entered into the eCRF.<br>– Sections related to study assessments (for e.g., review of the documents, order of assessments, 6MWT and Borg dyspnea index, etc.) were slightly modified in order to clarify the instructions relevant to the investigators.<br>– References to "major and minor" protocol deviations were removed.<br>– The "risks" section of the ICF was revised to account for the possibility of interruption or permanent discontinuation of study medication based on specific decreases in hemoglobin levels.<br>– The ICF was revised to include additional information about the potential risk of macitentan to align with updates to the Macitentan IB for non-oncology indications. The ICF was also updated to clarify the duties of the trial subjects following a change in the sponsor's insurance company. |

| | | |
|---|---|---|
| 19 Sep 2013 | Amendment 2, and resulting Global Protocol Version 3 | – The number of study sites was increased to improve the rate of recruitment.<br>– Results of all protocol-mandated laboratory assessments to be collected in the database. A Central Laboratory was to be used for the analysis of all laboratory variables requested in the protocol.<br>– Results of all assessments requested for the purpose of the study were to be collected in the clinical database.<br>– Monthly laboratory and safety monitoring at a site visit was added in order to improve sponsor oversight.<br>– Analysis of all laboratory samples in a central laboratory within confirmation of eligibility via local laboratory were added.<br>– The reason for permanent discontinuation was now documented in the eCRF.<br>– Throughout the protocol, upper limits for liver abnormality were updated to reflect the FDA guidance on DILI (i.e., > 3 × ULN, rather than ≥ 3 × ULN for ALT/AST and > 2 × ULN rather than ≥ 2 × ULN for total bilirubin).<br>– For hemoglobin monitoring, clarification on re-tests for assessing hemoglobin change was provided.<br>– Assessment and recording of methods of contraception was changed to occur at each visit.<br>– Collection of information on concomitant medication was extended to all visits.<br>– Instructions for collection and handling of local laboratory samples and, where applicable, reporting of results within the eCRF of local analyses of local laboratory samples were added.<br>– Instructions on performing and recording unscheduled visits were added.]<br>– Updated definitions of alert flags for abnormal laboratory values were included in the appropriate appendix.<br>– The ICF was updated to reflect the increased number of planned study sites.<br>– The ICF was updated to reflect the assessment and recording of methods of contraception was changed to occur at each visit.<br>– The ICF was updated to reflect the expanded instructions for unscheduled visits.<br>– The risk section of the ICF was updated to account for the latest results of controlled studies. |

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| 16 May 2014 | Amendment 3, and resulting Global Protocol Version 4 | – The recruitment period was made consistent with the updated study planned duration of the AC-055-305 / MAESTRO-DB study.<br>– The SBP exclusion criterion was lowered to SBP < 85 mmHg.<br>– The hepatic exclusion criterion was updated to exclude "severe hepatic failure"<br>– Eligibility criteria was opened up to females of childbearing potential truly abstinent and to subjects with DS (if they had support from a caregiver or family member).<br>– To address anticipated difficulties in DS subjects, adaptations were made to the 6MWT to accommodate these subjects and to safeguard study outcome.<br>– The schedule of visits and assessments was updated to mention the monthly assessment of methods of contraception. Unscheduled visits were re-labeled from A to U.<br>– The number of study centers selected for the AC-055-305 / MAESTRO-DB study was increased to improve recruitment speed. The same change was implemented in the MAESTRO-OL protocol.<br>– Clarification regarding which prohibited concomitant treatments must lead to study treatment discontinuation was added.<br>– To be consistent with section 3.9.1.4.4, "Hemoglobin concentration monitoring", a correction was made to the examples of local laboratory results that were collected in the eCRF.<br>– Clarifications were added on when to perform the requested laboratory re-tests for hemoglobin monitoring.<br>– The timeline to review the laboratory report was shortened in order to identify any potential clinically significant abnormality as early as possible. The measurement of peripheral oxygen saturation in subjects with patent ductus arteriosus is unstable on upper extremities. For baseline, the lower extremities are used. For assessment in the context of 6MWTs, the best pulsatile vascular bed is chosen.<br>– Information collected in the eCRF for each concomitant medication includes the frequency. Methods of contraception and changes in concomitant medications are assessed and reported in the eCRF at each visit.<br>– Clarifications on medication errors and pre-existing medical conditions were added.<br>– The sponsor Global Drug Safety department collected AEs related to menstrual disorders to comply with the EU RMP for the marketed compound.<br>– The ICF was updated to reflect the protocol changes. |

6MWT = 6-minute walk test; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; DS = Down Syndrome; eCRF = electronic Case Report Form; FDA = (US) Food and Drug Administration; IB = Investigator's Brochure; ICF = Informed Consent Form; LFT = liver function test; LT = liver test; RMP = risk management plan; SBP = systolic blood pressure; ULN = upper limit of normal; VHP = Voluntary Harmonisation Procedure.